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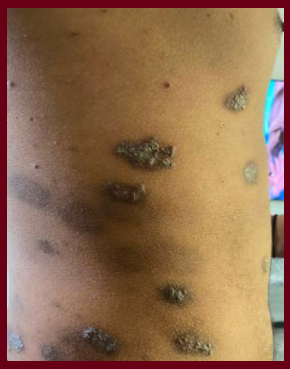

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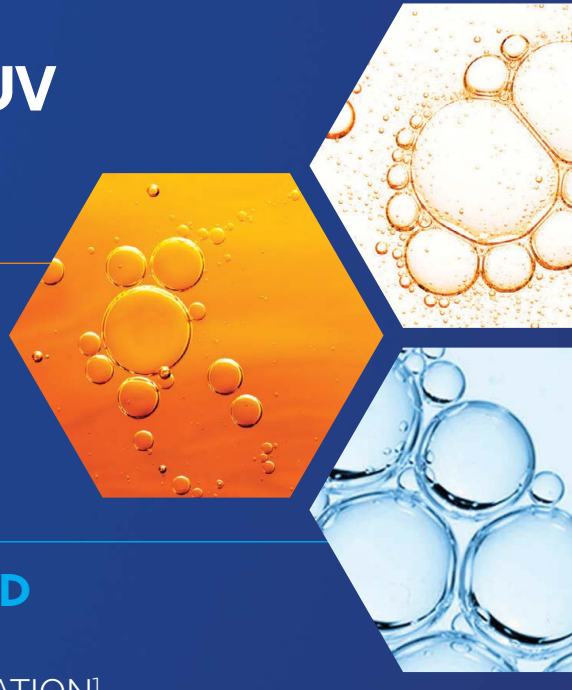

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Journal of Drugs in Dermatology (JDD) (ISSN 1545-9616) is published monthly for $300 per year US Individual subscriptions/$600 per year International Individual subscriptions/(Corporate and Institutional rates contact Sales for a quote) by the *SanovaWorks*, c/o WebMD, 283 - 299 Market St, 2 Gateway Center, 4th Floor, Newark, NJ 07102. Periodicals postage paid at New York, NY and additional mailing offices.

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POSTMASTER: Send address changes to the Journal of Drugs in Dermatology,
PO Box 2008, Cedar Rapids IA 52406-2008

Journal of Drugs in Dermatology (JDD)
is indexed in MEDLINE®/PubMed® and is published monthly by the
***SanovaWorks*, c/o WebMD**
283 - 299 Market St, 2 Gateway Center, 4th Floor, Newark, NJ 07102
telephone: 212-213-5434 | JDDonline.com

doi:10.36849/JDD.8246

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ORIGINAL ARTICLE

Journal of Drugs in Dermatology

Safety of Bimekizumab for Plaque Psoriasis: An Expert Consensus Panel

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ABSTRACT

Background: Plaque psoriasis is a chronic, relapsing systemic illness that has a significant effect on quality of life. Bimekizumab is the first monoclonal antibody to target both interleukin (IL)-17A and IL-17F, and recently received Food and Drug Administration (FDA) approval for moderate to severe plaque psoriasis. Guidance is necessary regarding the safety of bimekizumab.

Methods: A comprehensive literature search of PubMed, Scopus, and Google Scholar was completed for English-language original research articles on the safety of bimekizumab for moderate to severe psoriasis. A panel of 9 dermatologists and 1 rheumatologist with significant expertise in the treatment of psoriasis gathered to review the articles and create consensus statements on this new medication. A modified Delphi process was used to approve each statement, and strength of recommendation was assigned using the Strength of Recommendation Taxonomy criteria.

Results: The literature search produced 110 articles that met the criteria. A thorough screening of the studies for relevance to the research question resulted in 15 articles. These were distributed to all panelists for review prior to a roundtable discussion. The panel unanimously voted to adopt 5 consensus statements and recommendations, all of which were given a strength of "A."

Conclusion: Bimekizumab has a safety profile consistent with other biologics, except for a higher risk of oral candidiasis. Its hepatic safety profile is comparable with other currently FDA-approved biologics for plaque psoriasis. In addition, the data do not support an association of bimekizumab with suicide, and the incidence of inflammatory bowel disease is not greater than the incidence of other IL-17 blockers.

J Drugs Dermatol. 2024;23(8):592-599. doi:10.36849/JDD.8246

INTRODUCTION

Plaque psoriasis is a chronic, relapsing systemic illness that has a significant effect on quality of life.[1-3] New biologic therapies targeting tumor necrosis factor (TNF), interleukin (IL)-12/23, IL-17, and IL-23 have demonstrated efficacy and safety for the treatment of plaque psoriasis.[4] The IL-17 class of biologic therapies includes secukinumab and ixekizumab, which target IL-17A,[5,6] and brodalumab, which targets IL-17RA.[7] Bimekizumab, the first monoclonal IgG antibody to target both IL-17A and IL-17F, was recently approved by the Food and Drug Administration (FDA) for the treatment of plaque psoriasis.[8] Clinical trial data as well as real-world studies have revealed bimekizumab's rapid and long-lasting clinical efficacy for moderate to severe plaque psoriasis.[9–15]

The safety profile of bimekizumab has been extensively studied, demonstrating consistent adverse events to other biologics, apart from an increased incidence of oral candidiasis.[16] Several important safety considerations for bimekizumab include its effects on the liver, rates of oral candidiasis, relationship with suicidal ideation and behavior (SIB), and rates of inflammatory bowel disease (IBD) (specifically Crohn's disease). As bimekizumab has been recently approved in the United States for plaque psoriasis and clinicians will begin prescribing it, a thorough evaluation of these safety considerations is vital. The purpose of this study was for a panel of experts in psoriasis to evaluate the current literature and provide consensus statements on the safety of bimekizumab.

MATERIALS AND METHODS

Literature Search and Study Selection

A comprehensive literature search of PubMed, Scopus, and Google Scholar was completed on November 15, 2023, using the keywords "psoriasis," "bimekizumab," and "safety" along with the Boolean term "AND" for English-language original research articles, systematic reviews, and meta-analyses without date restrictions. This study did not require Institutional Review Board (IRB) approval. Articles were screened for relevance to the safety of bimekizumab for the treatment of moderate to severe psoriasis.

A 10-person consensus panel was selected for their expertise in the management of plaque psoriasis. The articles that met inclusion criteria were distributed to the panelists, and each member of the panel reviewed the selected studies and assigned them a level of evidence based on the Strength of Recommendation Taxonomy (SORT) criteria.[17] These levels include level 1 (good-quality patient-oriented evidence), level 2 (limited-quality patient-oriented evidence), or level 3 (other evidence such as consensus guidelines, usual practice, opinion, or disease-oriented evidence).[17]

Development of Consensus Statements

The panel consisted of 9 dermatologists and 1 rheumatologist with expertise in the treatment of psoriasis. The panel convened on November 30, 2023, to review and discuss the studies and create consensus statements with guidance on the safety of bimekizumab for the treatment of plaque psoriasis. To reach a consensus for each statement, a modified Delphi process was used.[18] This process requires supermajority approval for the adoption of a recommendation through multiple rounds of real-time voting and is a regularly used method to create expert recommendations in dermatology.[19–22]

RESULTS

Literature Search and Study Selection

The literature search resulted in 110 articles that met the search criteria. After a comprehensive screening process, 15 articles were selected as relevant to the research questions. These articles were distributed to the panelists for evaluation prior to the roundtable discussion.

Levels of Evidence Designation

The panel assigned level 1 evidence to all articles that were evaluated (Table 1).

Consensus Statements

The panel developed 5 consensus statements regarding the safety of bimekizumab for the treatment of plaque psoriasis. Of the 5 statements, all received a unanimous (10/10) vote for adoption. SORT criteria were used to assign a strength to each statement and recommendation (Table 2).

Statement 1: *Compared with traditional oral systemic therapies like methotrexate, cyclosporine, and acitretin for plaque psoriasis, biologic agents exhibit a favorable hepatic safety profile. Bimekizumab has a comparable hepatic safety profile to other currently FDA-approved biologics for plaque psoriasis. (SORT Level A).*

Traditional oral systemic therapies for plaque psoriasis, including methotrexate (MTX), cyclosporine, and acitretin, are known to have harmful effects on the liver.[23] A systematic review of clinical trials demonstrated that MTX increases the risk of total adverse liver events and both minor (≤3 upper limit of normal (ULN)) and major (>3 ULN) liver enzyme abnormalities.[23,24] Hepatic adverse events of MTX range from elevation in liver function tests (LFTs) to fatty liver disease, fibrosis, and cirrhosis.[25] Cyclosporine also has a risk of abnormal LFTs and hepatotoxicity, though lower than MTX.[23,26] In addition, acitretin is associated with abnormal LFT findings and hepatitis.[27] The psoriasis patient population has a high rate of metabolic syndrome, obesity, and level of alcohol consumption, each of which can have adverse effects on a patient's liver function.[28,29] Non-alcoholic fatty liver disease is also more prevalent in psoriasis patients, occurring in up to 66% of patients, and can contribute to elevation in LFTs.[30]

Biologic agents for plaque psoriasis have consistently demonstrated a lower rate of adverse effects on the liver compared with MTX, cyclosporine, and acitretin.[12,14,31-34,30] The hepatic safety data of bimekizumab have been reported throughout multiple randomized clinical trials. In a pooled analysis of phase II and phase III data, the overall exposure-adjusted incidence rate (EAIR) of elevated liver enzyme levels was 3.6 (3.0-4.4) per 100 person-years (PY).[16] Clinical trials demonstrate a comparable safety profile to other FDA-approved biologics for plaque psoriasis. After 24 weeks of bimekizumab every 4 weeks and then every 8 weeks, EAIR for elevated LFTs was 5.5 (1.5-14.1) per 100 PY, whereas for adalimumab alone it was higher at 15.8 (7.9-28.3) per 100 PY.[31] The hepatic adverse event rate declined with time and was not cumulative, EAIR at 1 year was 2.2 (0.3-8.0) per 100 PY for bimekizumab vs 6.9 (2.5-15.0) per 100 PY for those who received adalimumab followed by bimekizumab (ADA/BKZ).[31] At year 1, there was a similar number of patients with elevated LFTs for bimekizumab compared with ADA/BKZ (1.3% vs 4.0%, respectively).[34] At year 2, EAIR continued to decrease, 1.6 (0.2-5.9) per 100 PY for bimekizumab vs 6.1 (2.4-12.5) per 100 PY for ADA/BKZ.[31] In a phase III trial for adalimumab, LFT elevation occurred at a rate of 1.2% compared with 1.8% in placebo after 16 weeks.[35] Of note, many patients who are onTNF-blockers such as adalimumab are concurrently taking MTX.

TABLE 1.

SORT Criteria Level of Evidence for Articles Pertaining to the Safety of Bimekizumab

Article	Level of Evidence
Blauvelt A, Armstrong A, Merola JF, et al. Bimekizumab in patients with moderate to severe plaque psoriasis: analysis of mental health and associated disorders. *SKIN J Cutan Med.* 2023;7(6):s300. doi:10.25251/skin.7.supp.300	1
Reich K, Nestle FO, Papp K, et al. Infliximab induction and maintenance therapy for moderate-to-severe psoriasis: a phase III, multicentre, double-blind trial. *Lancet.* 2005;366(9494):1367-1374. doi:10.1016/S0140-6736(05)67566-6	1
Menter A, Gordon KB, Leonardi CL, Gu Y, Goldblum OM. Efficacy and safety of adalimumab across subgroups of patients with moderate to severe psoriasis. *J Am Acad Dermatol.* 2010;63(3):448-456. doi:10.1016/j.jaad.2009.09.040	1
UCB, Inc. BIMZELX (bimekizumab-bkzx) [package insert]. *US Food Drug Adm.* Published online 2023. Accessed December 10, 2023. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/761151s000lbl.pdf	--
Abbott Laboratories. Humira [package insert]. *US Food Drug Adm.* Published online 2007. Accessed December 10, 2023. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/125057s410lbl.pdf	--
Centocor Inc. Remicade [package insert]. *US Food Drug Adm.* Published online 2006. Accessed December 10, 2023. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/103772s5401lbl.pdf	--
Gordon KB, Langley RG, Warren RB, et al. Bimekizumab safety in patients with moderate to severe plaque psoriasis: pooled results from phase 2 and phase 3 randomized clinical trials. *JAMA Dermatol.* 2022;158(7):735-744. doi:10.1001/jamadermatol.2022.1185	1
Gordon KB, Foley P, Krueger JG, et al. Bimekizumab efficacy and safety in moderate to severe plaque psoriasis (BE READY): a multicentre, double-blind, placebo-controlled, randomised withdrawal phase 3 trial [published correction appears in Lancet. 2021;27;397(10280):1182]. *Lancet.* 2021;397(10273):475-486.	1
Kokolakis G, Warren RB, Strober B, et al. Bimekizumab efficacy and safety in patients with moderate-to-severe plaque psoriasis who switched from adalimumab, ustekinumab or secukinumab: results from phase III/IIIb trials. *Br J Dermatol.* 2023;188(3):330-340. doi:10.1093/bjd/ljac089	1
Reich K, Papp KA, Blauvelt A, et al. Bimekizumab versus ustekinumab for the treatment of moderate to severe plaque psoriasis (BE VIVID): efficacy and safety from a 52-week, multicentre, double-blind, active comparator and placebo controlled phase 3 trial [published correction appears in Lancet. 2021;397(10275):670]. *Lancet.* 2021;397(10273):487-498. doi:10.1016/S0140-6736(21)00125-2	1
Reich K, Papp KA, Blauvelt A, et al. Bimekizumab versus ustekinumab for the treatment of moderate to severe plaque psoriasis (BE VIVID): efficacy and safety from a 52-week, multicentre, double-blind, active comparator and placebo controlled phase 3 trial. *Lancet.* 2021;397(10273):487-498. doi:10.1016/S0140-6736(21)00125-2	1
Reich K, Warren RB, Lebwohl M, et al. Bimekizumab versus secukinumab in plaque ssoriasis. *N Engl J Med.* 2021;385(2):142-152. doi:10.1056/NEJMoa2102383	1
Strober B, Tada Y, Mrowietz U, et al. Bimekizumab maintenance of response through 3 years in patients with moderate-to-severe plaque psoriasis: results from the BE BRIGHT open-label extension trial. *Br J Dermatol.* 2023;188(6):749-759. doi:10.1093/bjd/ljad035	1
Strober B, Paul C, Blauvelt A, et al. Bimekizumab efficacy and safety in patients with moderate to severe plaque psoriasis: two-year interim results from the open-label extension of the randomized BE RADIANT phase 3b trial [published online ahead of print, 2023 May 12]. *J Am Acad Dermatol.* 2023;S0190-9622(23)00782-X.	1
Thaci D, Vender R, de Rie MA, et al. Safety and efficacy of bimekizumab through 2 years in patients with moderate-to-severe plaque psoriasis: longer-term results from the BE SURE randomized controlled trial and the open-label extension from the BE BRIGHT trial. *Br J Dermatol.* 2023;188(1):22-31. doi:10.1093/bjd/ljac021	1
Warren RB, Blauvelt A, Bagel J, et al. Bimekizumab versus adalimumab in plaque psoriasis. *N Engl J Med.* 2021;385(2):130-141. doi:10.1056/NEJMoa2102388	1

Comparator trials demonstrate the head-to-head hepatic adverse event rates. For ustekinumab, year 1 EAIR for elevated LFTs was 2.6 (0.7-6.6) per 100 PY compared with 1.7 (0-9.7) per 100 PY for bimekizumab;[12] and the number of patients with total hepatic events was also similar (3% vs 3%), respectively.[32] Clinical trial data also demonstrate comparable hepatic adverse events to secukinumab. One year EAIR for bimekizumab was 1.6 (0.2-5.6) per 100 PY compared with 5.9 (3.5-9.2) per 100 PY for secukinumab;[12] and the number of patients with elevated LFTs was 5.6% vs 5.1%, respectively.[33] Other biologics have LFT elevation rates similar to or greater than bimekizumab: infliximab (9%),[36] ixekizumab (3%),[37] and brodalumab (1%).[38]

In a phase IIIb trial, year 1 EAIR for LFT elevation more than 3 times the ULN was 3.0 (1.4-5.5) per 100 PY for continuous bimekizumab and 4.6 (2.6-7.6) per 100 PY for secukinumab followed by bimekizumab (SEC/BKZ).[14] At year 2, EAIR for >3xULN for LFT elevation was 1.9 (0.8-3.9) per 100 PY for continuous bimekizumab vs 2.0 (0.8-4.2) per 100 PY for SEC/BKZ.[14] Furthermore, in a phase III clinical trial of bimekizumab for patients with psoriatic arthritis, the majority of whom were concurrently taking MTX, elevated LFTs only occurred in 2% of patients,[39] further substantiating the hepatic safety of bimekizumab.

TABLE 2.

Consensus Statements and Recommendations for the Safety of Bimekizumab

Consensus Statement/Recommendation	Strength of Recommendation	Consensus Vote
Compared with traditional oral systemic therapies like methotrexate, cyclosporine, and acitretin for plaque psoriasis, biologic agents exhibit a favorable hepatic safety profile. Bimekizumab has a comparable hepatic safety profile to other currently FDA-approved biologics for plaque psoriasis.	A	10/10
There is no evidence to support more frequent monitoring of hepatic function tests in patients on bimekizumab compared with other biologics.	A	10/10
The risk of oral candidiasis is higher with bimekizumab than with other biologics and is dose dependent. Most cases are mild to moderate, easily managed, and did not result in discontinuation.	A	10/10
The risk of suicidality with bimekizumab is rare and not greater than what is seen in the psoriasis population. The data do not support an association of bimekizumab with suicide.	A	10/10
The prevalence of Crohn's disease is increased in patients within psoriasis. The incidence of IBD, including Crohn's disease, in patients treated with IL-17 blockers, including bimekizumab, is very low. The incidence of IBD in patients treated with bimekizumab is not higher than the incidence for other IL-17 blockers.	A	10/10

FDA, Food and Drug Administration; IBD, inflammatory bowel disease; IL, interleukin.

In the summary basis of approval for bimekizumab, the FDA concluded that there was no clear drug-induced liver injury (DILI) phenotype for the 10 at least possible DILI cases.[40] These cases had a median latency of 164 days (range 28-338 days) to elevated liver enzymes.[40] No cases were very likely or certain to be DILI by the FDA and/or the Hepatic Adjudication Committee (HAC) of UCB Pharma.[40] Five cases were considered probably or possibly related to bimekizumab, and the FDA and HAC only agreed on 2 of 5 cases (Table 3). All but 1 of the patients with adverse hepatic events had an additional component of their medical history that could also contribute to the elevation of hepatic enzymes.[40] Of these 5 cases, 2 had a history of alcohol use, 4 were obese, 2 were taking concomitant medications known to cause liver damage, and 2 had a history of elevated LFTs (Table 3).

The association between bimekizumab dosing and the rate of hepatic adverse events may also provide insight into this relationship. In phase III trials, bimekizumab dosing of 320 mg every 8 weeks had a 24-week EAIR of 5.5 (1.5-14.1) per 100 PY for elevated LFTs compared with 4.2 (0.9-12.2) per 100 PY for 320mg every 4 weeks.[31] At year 1 this relationship was maintained, 2.2 (0.3-8.0) per 100 PY vs 1.1 (0-5.9) per 100 PY, respectively.[31] These findings demonstrate that, when dosing was raised, the rate of elevated LFTs decreased, indicating that there is no dose-dependent relationship. And, the adverse events may not be entirely related to bimekizumab.

Statement 2: *There is no evidence to support more frequent monitoring of hepatic function tests in patients on bimekizumab compared with other biologics. (SORT Level A).*

Given the reports of adverse hepatic events for bimekizumab, the frequency of monitoring is an important consideration. The FDA package insert for bimekizumab states, "Test liver enzymes, alkaline phosphatase, and bilirubin at baseline, periodically during treatment with BIMZELX, and according to routine patient management".[8]

TABLE 3.

Cases of Possible or Probable DILI Due to Bimekizumab[56]

Case	History of Alcohol Use	History of Obesity	Concomitant Medications[1]	History of Elevated LFTs	Likelihood that the Liver Problem was Caused by DILI[2]
1	No	Yes	Yes	Yes	HAC: Possible FDA: Possible
2	No	No	No	No	HAC: Possible FDA: Possible
3	No	Yes	No	No	HAC: Possible FDA: Probable
4	Yes	Yes	No	No	HAC: Probable FDA: Possible
5	Yes	Yes	Yes	Yes	HAC: Probable FDA: Possible

[1]Concomitant medications with known adverse effects on the liver.
[2]According to the FDA definitions for whether a liver issue was caused by drug-induced liver injury (DILI): "unlikely" = 5-25%, "possible" = 25-50%, "probable" = 50-75%, "very likely" = 75-95%, "certain, definite" = >95%.
DILI, drug-induced liver injury; HAC, Hepatic Adjudication Committee of UCB; FDA, Food and Drug Administration; LFTs, Liver Function Tests.

There is currently no consensus on the meaning of "routine patient management". For many biologic therapies, common approaches are to obtain baseline hepatic function tests for all patients and, if normal, to subsequently monitor at 6-month intervals or once within the first year, and none thereafter.[41,42] All participants in this expert consensus panel for bimekizumab recommend obtaining baseline hepatic function tests for all patients being initiated on bimekizumab. If normal at baseline, and unless there is any suggestion of liver injury, 7/10 participants would routinely check hepatic function tests at least once within the first year of treatment. Although there is no published clinical evidence to support the timing of routine monitoring, the phrasing in the FDA package insert guided these participants to choose this monitoring schedule. The package insert does not provide a recommended monitoring timeline, but participants felt monitoring is necessary as there may be medical/legal implications if it is not performed.

If the hepatic function tests continue to be within the normal range after 1 year of bimekizumab treatment, 3/10 participants would routinely re-check them. These participants would do so as they routinely check hepatic function tests after 1 year for all other biologics for plaque psoriasis. Given the higher rates of hepatic adverse events for infliximab and adalimumab, recommended routine monitoring is more frequent than for other biologics.[41-44]

If hepatic function tests are abnormal, consultation with a hepatic expert may be necessary to exclude other causes, and cessation of the drug may be required if DILI is suspected.[45] If the cause of LFT elevation is thought to be DILI and drug administration is suspended, LFTs typically return to normal within days to several weeks.[46]

As the rates of LFT elevation with bimekizumab are consistent with or lower than other biologics, this expert panel found no evidence to support more frequent monitoring of hepatic function tests for bimekizumab compared with other biologics.

Statement 3: *The risk of oral candidiasis is higher with bimekizumab than with other biologics and is dose-dependent. Most cases are mild to moderate, easily managed, and do not result in discontinuation. (SORT Level A).*

Blockage of IL-17 has been associated with candida infections in both animal models and humans.[47] Oral candidiasis was one of the most common treatment-related adverse events reported with bimekizumab.[14,16,31] The overall bimekizumab EAIR for oral candidiasis throughout phase II and phase III clinical trials was 12.6 (11.3-14.0) per 100 PY.[16] Comparator trials to other biologics demonstrated bimekizumab's higher rate of oral candidiasis. After 24 weeks of treatment, oral candidiasis EAIR for bimekizumab was 21.9 (12.2-36.0) per 100 PY compared with 0 for adalimumab.[31] When compared at year 1, the EAIR was 0.6 (0.0-3.6) per 100 PY for ustekinumab vs 23.7 (12.6-40.6) per 100 PY for bimekizumab, and 3.4 (1.7-6.0) per 100 PY for secukinumab vs 9.5 (4.9-16.7) per 100 PY for bimekizumab.[12] The number of cases in the head-to-head trials also follows this trend: secukinumab 3% vs bimekizumab 19.3%, adalimumab 0 vs bimekizumab 9.5%, and ustekinumab 1% vs bimekizumab 15%.[32–34]

Other IL-17 blockers have had lower rates of oral candidiasis compared with bimekizumab. In a comprehensive summary of safety outcomes, ixekizumab had an EAIR for oral candidiasis of 0.8 (0.7-0.9) per 100 PY and was present in 2.1% of patients.[48] In a pooled data analysis, brodalumab had 0 cases of oral candidiasis.[38]

Most cases of oral candidiasis with bimekizumab were mild or moderate, many patients with an infection only had 1 occurrence, and the majority of infections resolved with treatment.[16] Treatment regimens commonly included nystatin and/or fluconazole,[16] which is consistent with prior infections due to IL-17 blockers.[49,50] Of all patients, only 3 (0.2%) discontinued bimekizumab due to oral candidiasis.[16]

Statement 4: *The risk of suicidality with bimekizumab is rare and not greater than what is seen in the psoriasis population. The data do not support an association of bimekizumab with suicide. (SORT Level A).*

Patients with psoriasis are more likely to exhibit suicidal behaviors, attempt suicides, and complete suicides than those without psoriasis.[51] Clinical trial data for bimekizumab demonstrate that the risk of suicidality is rare. Overall EAIR for adjudicated suicidal ideation and behavior (SIB) was 0.1 (0-0.3) per 100 PY[16]; and in head-to-head trials SIB was similar to other biologics: ustekinumab 1% vs bimekizumab <1%, secukinumab 0 vs bimekizumab 0.3%, and ADA/BKZ 0 vs bimekizumab 0.[32–34] In pooled safety analyses of bimekizumab and ADA/BKZ, EAIR of SIB was 0 for both groups through year 2.[31] In addition, patients who switched from adalimumab, ustekinumab, or secukinumab to bimekizumab also had EAIR of 0 for SIB through 1 year.[12] There was also no pattern of SIB events according to treatment initiation or dosing of bimekizumab.[16]

In an analysis of mental health for patients taking bimekizumab, mean Patient Health Questionnaire (PHQ)-9 scores with bimekizumab were lower than placebo and similar to active comparators.[52] Low PHQ-9 scores were maintained over 3 years of treatment (mean score of 1.2).[52] This study also showed that over 7,166 PY of bimekizumab treatment, rates of adjudicated SIB (0.13 per 100 PY), suicidal behavior (0.06 per 100 PY), and completed suicides (0.01 per 100 PY) were on par with rates from other IL-17A blockers and IL-23 blockers for psoriasis.[52] The

risk of adjudicated SIB is also similar to the general psoriasis population, which has an EAIR of 0.09-0.54 per 100 PY.[53–55]

In 2015, the FDA completed a clinical review of SIB across all psoriasis biologics at the time. Regarding suicidal ideation, brodalumab had a rate of 240 per 100,000 PY, followed by apremilast with 135 per 100,000 PY, adalimumab with 74 per 100,000 PY, etanercept with 72 per 100,000 PY, secukinumab with 31 per 100,000 PY, and infliximab, ixekizumab, and ustekinumab each with 0.[56] More specifically for brodalumab, an analysis of all clinical trials found an overall SIB rate of 0.20 (0.08-0.41) per 100 PY, which was similar to ustekinumab with 0.60 (0.12-1.74) per 100 PY.[57] Of interest, brodalumab, which blocks IL-17RA, was given a boxed warning and Risk Evaluation and Mitigation Strategy program for suicides even though no causal association was made between the drug and suicides.[57] Since its introduction to the American market, there have not been any completed suicides in the US.[58] The data demonstrate that bimekizumab does not have a causal association with suicide and is similar to other currently FDA-approved biologics for plaque psoriasis.

Statement 5: *The prevalence of Crohn's disease is increased in patients with psoriasis. The incidence of IBD, including Crohn's disease, in patients treated with IL-17 blockers, including bimekizumab, is very low. The incidence of IBD in patients treated with bimekizumab is not higher than the incidence for other IL-17 blockers. (SORT Level A).*

Inflammatory bowel disease (IBD), including Crohn's disease, has been associated with an increased prevalence in the psoriasis population.[59,60] Multiple systematic reviews/meta-analyses found no statistically significant differences in risk of new or recurrent IBD for patients treated with IL-17 blockers (secukinumab, ixekizumab, and brodalumab) compared with placebo.[61,62] New cases of IBD with secukinumab or ixekizumab occurred at an EAIR of 0.23 per 100 PY in patients with psoriasis.[61] Specifically for ixekizumab, IBD occurred at EAIR of 0.1 per 100 PY[48] and Crohn's at 1.1 per 1,000 PY,[63] which was similar to brodalumab at 0.2 per 100 PY.[38]

In bimekizumab trials, patients with IBD were excluded from enrollment; therefore, incident cases of IBD were recorded. The overall EAIR of IBD for bimekizumab was 0.1 per 100 PY, with a total of 4 incident cases (3 which led to bimekizumab discontinuation).[16] In a phase IIIb trial, EAIR of IBD after 1 year of treatment with bimekizumab was 0.3 per 100 PY, which decreased to 0 after 2 years.[14] In another trial, IBD EAIR for adalimumab, ustekinumab, and bimekizumab were 0, whereas for secukinumab EAIR was 0.3 per 100 PY.[12] In addition, there were comparable IBD rates throughout all comparator trials: bimekizumab <1% vs ustekinumab 0, bimekizumab 0.3% vs secukinumab 0.3%, bimekizumab 0 vs ADA/BKZ 0.[32–34] The data demonstrate similar rates of incident IBD for bimekizumab when compared with other IL-17 blockers, as well as other biologics for plaque psoriasis.

CONCLUSION

Bimekizumab is the first monoclonal antibody to target both IL-17A and IL-17F and recently received FDA approval for moderate to severe plaque psoriasis. An expert consensus panel completed a comprehensive review of the literature and developed 5 consensus statements related to the safety of bimekizumab. Bimekizumab has a hepatic safety profile comparable to other currently FDA-approved biologics for plaque psoriasis, and there is no evidence to support more frequent monitoring of hepatic function tests. There is a higher risk of oral candidiasis, but most cases are mild to moderate and easily managed. In addition, the data do not support an association of bimekizumab with suicide and the incidence of IBD is not greater than the incidence for other IL-17 blockers. This expert panel concluded that bimekizumab has a safety profile consistent with other biologics, and the consensus statements will help guide clinicians in their management of plaque psoriasis with bimekizumab.

DISCLOSURES

This study was funded in part by an unrestricted educational grant from UCB Pharma. Joshua Burshtein MD, Milaan Shah MD, and Danny Zakria MD MBA have no conflicts to disclose. April W. Armstrong MD MPH has served as a research investigator, scientific advisor, or speaker to AbbVie, Almirall, Arcutis, ASLAN, Beiersdorf, BI, BMS, EPI, Incyte, Leo, UCB, Janssen, Lilly, Nimbus, Novartis, Ortho Dermatologics, Sun, Dermavant, Dermira, Sanofi, Regeneron, and Pfizer. Alexandra K. Golant MD has received consulting or speaker fees from Regeneron, Sanofi, Abbvie, Incyte, Dermavant, Eli Lilly, Arcutis, Janssen, Amgen, and Pfizer. Alice B. Gottlieb MD PhD has received research/educational grants from AnaptypsBio, Highlights Therapeutics, Moonlake Immunotherapeutics AG, Novartis, Bristol-Myers Squibb, Janssen, and UCB Pharma (all paid to Mount Sinai School of Medicine); and has received honoraria as an advisory board member and consultant for Amgen, AnaptypsBio, Avotres Therapeutics, Boehringer Ingelheim, Bristol-Myers Squibb, Dice Therapeutics, Eli Lilly, Highlights Therapeutics, Janssen, Novartis, Sanofi, UCB, and Xbiotech. Jeffrey M. Weinberg MD has received speaking and research funds from Abbvie, Amgen, Arcutis, Dermavant Sciences, Eli Lilly, Incyte, Janssen, Pfizer, Sanofi-Regeneron, and UCB, Inc., and is a consultant for Castle Biosciences. Leon Kircik MD is or has been an investigator, consultant/advisor, or speaker for Abbott Laboratories, Abbvie, Allergan, Inc., Almirall, Amgen, Inc., Arcutis, Biogen-Idec, BMS, Boehringer-Ingleheim, Breckinridge Pharma, Celgene, Centocor, Inc., Cellceutix, Cipher, Combinatrix, Connetics Corporation, Coria, Dermavant, Dermira, Dow Pharmaceutical Sciences, Inc., Dr. Reddy's Lab, Eli Lilly, Galderma, Genentech, Inc., GlaxoSmithKline, PLC, Idera, Johnson & Johnson, Leo,

Maruho, Merck, Medicis Pharmaceutical Corp., Nimbus, Novartis AG, Promius, PharmaDerm, Pfizer, Serono (Merck Serono International SA), Stiefel Laboratories, Inc., Sun Pharma, Taro, UCB, Valeant Pharmaceuticals Intl, Ventyx, and XenoPort. George Han MD PhD is or has been an investigator, consultant/advisor, or speaker for AbbVie, Amgen, Athenex, Boehringer Ingelheim, Bond Avillion, Bristol-Myers Squibb, Celgene, Eli Lilly, Novartis, Janssen, LEO Pharma, MC2, Ortho Dermatologics, PellePharm, Pfizer, Regeneron, Sanofi Genzyme, Sun Pharma, and UCB. Richard G. Langley MD FRCPC has received honoraria as a principal investigator, scientific advisor, or speaker for AbbVie, Amgen, Boehringer Ingelheim, Bristol-Myers-Squibb, Dermavant, Dermira, Eli Lilly, GlaxoSmithKline, Janssen, Leo Pharma, Novartis, Ortho Dermatologics, Pfizer, Sanofi -Genzyme, Sun Pharma, and UCB Pharma. Andrea L. Neimann MD has received honoraria from Ad Board for Janssen, UCB, BMS, and Sun Pharma within the last 1 to 2 years. Mark Lebwohl is an employee of Mount Sinai and receives research funds from Abbvie, Amgen, Arcutis, Avotres, Boehringer Ingelheim, Cara Therapeutics, Dermavant Sciences, Eli Lilly, Incyte, Inozyme, Janssen Research & Development, LLC, Ortho Dermatologics, Pfizer, Sanofi-Regeneron, and UCB, Inc., and is a consultant for Almirall, AltruBio Inc., AnaptysBio, Apogee, Arcutis, Inc., AstraZeneca, Atomwise, Avotres Therapeutics, Brickell Biotech, Boehringer-Ingelheim, Bristol-Myers Squibb, Castle Biosciences, Celltrion, Corevitas, Dermavant Sciences, EPI, Evommune, Inc., Facilitation of International Dermatology Education, Forte Biosciences, Foundation for Research and Education in Dermatology, Galderma, Genentech, Incyte, LEO Pharma, Meiji Seika Pharma, Mindera, Pfizer, Sanofi-Regeneron, Seanergy, Strata, Takeda, Trevi, and Verrica.

ACKNOWLEDGMENT

We would like to thank Jose U. Scher MD for his contributions to this manuscript.

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doi:10.36849/JDD.8128

August 2024 600 Volume 23 • Issue 8

ORIGINAL ARTICLE

Journal of Drugs in Dermatology

Efficacy and Safety of Secukinumab in the Treatment of Psoriasis in Patients With Skin Phototypes IV to VI

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ABSTRACT

Background: There is a paucity of data on the treatment of psoriasis in patients with skin of color – a diverse population among whom variations in clinical features and higher quality of life impact have been reported. This single-center, open-label clinical study evaluated the safety and efficacy of secukinumab in the treatment of moderate-to-severe plaque psoriasis in adults with Fitzpatrick skin types IV-VI.

Methods: A total of 20 male and female subjects (ages ≥ 18, BSA ≥10%, PASI Score ≥ 12, IGA ≥ 3) completed this study. The total study duration was 28 weeks. During the treatment period, subjects received secukinumab 300 mg subcutaneously at weeks 0, 1, 2, 3, and 4, then monthly through week 20.

Results: Seventy-three percent of patients achieved at least 90% improvement in PASI score (PASI90) at week 16 compared to baseline (P=0.0592). There was a statistically significant proportion of patients achieving PASI75, IGA of clear or almost clear, and a change from baseline in DLQI total score at weeks 12, 16, and 24. A statistically significant reduction in IGAxBSA-75 score was achieved between week 16 and baseline.

Limitations: The sample size was small and underpowered to detect statistically significant changes in some endpoints. Furthermore, the study period was interrupted by the COVID-19 pandemic, which contributed to numerous missing data points.

Conclusion: Secukinumab 300 mg administered monthly was safe, well-tolerated, and efficacious in treating skin of color patients with psoriasis and improving health-related quality of life. Larger studies involving skin of color populations with psoriasis are warranted.

J Drugs Dermatol. 2024;23(8):600-606. doi:10.36849/JDD.8128

INTRODUCTION

Psoriasis is a chronic inflammatory disorder primarily affecting the skin and joints. It affects different racial/ethnic groups worldwide with varying prevalence. Although psoriasis has historically been considered to predominately affect populations who self-identify as White, recent data show substantial rates of psoriasis in patients with skin of color.[1,2] The 2011 to 2014 National Health and Nutrition Examination Surveys estimate the prevalence of psoriasis to be 3.6% of White, 1.5% of African American, and 1.9% of Hispanic adults aged 20 to 59.[1] However, the true prevalence of psoriasis in Black/African American and Hispanic populations may be higher than suggested due to potential under-diagnosis and under-reporting.[3,4]

Classically, plaque psoriasis presents as well-demarcated erythematous plaques with an overlying micaceous scale. However, it is important to note nuances in the clinical presentation of psoriasis in patients of skin of color. Black patients with psoriasis tend to have less discernable erythema and/or erythema that appears more violaceous or hyperchromic, thicker plaques with more scale, and greater body surface area involvement compared to White patients, and increased incidence of postinflammatory pigmentary alteration, which may be more bothersome to patients than the disease itself.[5-10]

Psoriasis in skin of color patients has been linked to a greater psychosocial impact and worse quality of life (QOL) compared to psoriasis in White patients as evidenced by consistently

higher Dermatology Life Quality Index (DLQI) scores in Black and Hispanic populations compared with White populations, despite controlling for affected body surface area and severity of disease.[5-7, 11-12, 24]

Despite notable racial/ethnic differences in clinical presentation and QOL impact of psoriasis, there is a lack of data on the use of biologic medications for the treatment of psoriasis in patients with skin of color.[6,7] The aforementioned nuances in clinical presentation, disease severity, and pigmentary sequelae in skin of color populations are unique issues that necessitate studies dedicated to evaluating treatment options for the effective management of psoriasis in skin of color populations.

Secukinumab is an injectable monoclonal antibody against interleukin-17A (IL-17A) that has demonstrated efficacy in the treatment of moderate-to-severe plaque psoriasis at a dose of 300 mg.[13,14] Significant improvements in health-related QOL and psoriasis symptoms, including itch, pain, and scaling have also been noted with secukinumab.[15-18]

There is a paucity of data on the safety and efficacy of secukinumab in patients with skin of color. The pivotal phase III trials of secukinumab included a predominantly White population.[14,19] Sub-analyses of phase II and phase III trials in Asian and Hispanic groups have demonstrated improvements in moderate-severe plaque psoriasis consistent with the full multi-ethnic cohort data.[20-22] Despite this, given the small number of skin of color subjects included in the secukinumab clinical trials (especially those who self-identify as Black/African American), it is difficult to make meaningful comparisons between different racial and ethnic subgroups.

Given the above, we aimed to characterize additional data on the safety and efficacy of secukinumab in the treatment of patients with skin of color. This was a single-center, open-label clinical study to determine the safety and efficacy of secukinumab 300 mg in the treatment of moderate-to-severe plaque psoriasis in patients with Fitzpatrick skin types IV-VI. This study also included unique endpoints that are particularly relevant to patients with skin of color such as change in psoriasis-associated dyspigmentation during treatment and objective measurement of erythema using spectrophotometry.

MATERIALS AND METHODS

Patients

Eligible patients had Fitzpatrick skin phototype IV-VI, self-identified as having a non-White race/ethnicity, were ≥ 18 years of age at time of screening, and had a clinical diagnosis of moderate-to-severe chronic plaque-type psoriasis of the body for at least six months prior to randomization as defined by: psoriasis area and severity index (PASI) ≥12 and body surface area (BSA) ≥ 10% and Investigator's Global Assessment mod 2011 (IGA) ≥ 3. Patients were candidates for systemic therapy defined as having psoriasis inadequately controlled by topical treatments and/or phototherapy and/or previous systemic therapy, and were in general good health as judged by the Investigator.

Patients with Fitzpatrick Skin phototype I-III, White self-identity, or who had any form of diagnosed psoriasis other than chronic plaque psoriasis were excluded from the study. Patients were excluded if they had previous exposure to secukinumab or other biologic agents targeting IL-17A or IL-17RA or if they had received the following prohibited treatments prior to randomization: biologic drugs directly targeting IL-12/23 or IL-23, alefacept, and efalizumab within 6 months, other biologic or targeted therapies within 12 weeks, systemic psoriasis therapies including methotrexate, systemic steroids, retinoids, apremilast, or phototherapy within 4 weeks; topical psoriasis therapies within 2 weeks; UVA or UVB phototherapy within 2 weeks; and/or use of any other investigational drugs within 5 half-lives prior to randomization.

Other exclusion criteria included unwillingness to limit exposure to UV light, unwillingness to use appropriate designated method(s) of contraception, ongoing skin disease or infection that may interfere with treatment and/or examination of psoriasis lesions, current significant medical problems or laboratory abnormalities that would put the patient at risk by participating in the study, previous history of or current infection with hepatitis C, hepatitis B, HIV, active systemic infection 2 weeks prior to randomization, evidence of tuberculosis infection at screening, malignancy within the past 5 years with few exceptions, or history of allergy to any component of the IP.

A total of 20 subjects completed all study procedures. All patients provided written, signed, and dated informed consent prior to initiating any study-related activities.

Study Design

This was a single-center, open-label study conducted at Mount Sinai West in New York City. Twenty adult subjects were enrolled in a single treatment group. Subjects underwent a 4-week screening period. Subjects who successfully completed the screening period were then assigned to the 24-week treatment period, during which all patients received secukinumab 300 mg by subcutaneous injection at weeks 0, 1, 2, 3, and 4, followed by 300 mg every 4 weeks through week 20.

The protocol was approved by the institutional review board of the Icahn School of Medicine at Mount Sinai. This study was conducted in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki. The ClinicalTrials.gov identifier is NCT04571567.

Study Objectives and Endpoints

The primary objective was to determine the efficacy of secukinumab. The primary efficacy endpoint was the proportion of patients achieving PASI90 (≥90% improvement in Psoriasis Area Severity Index) at week 16 compared to baseline.

The 6 secondary endpoints were as follows:

1. Efficacy of secukinumab based on PASI75 and PASI100 at weeks 4, 12, 16, 24 and PASI90 at weeks 4, 12, 24 (defined as the proportion of patients achieving ≥75% or 100% improvement in PASI score at weeks 4, 12, 16, and 24 compared to baseline and the proportion of patients achieving ≥90% improvement in PASI score at weeks 4, 12, 24 compared to baseline), IGA treatment success defined as clear (0) or almost clear (1) at weeks 12, 16, 24, and ≥75% reduction in IGAxBSA score (IGAxBSA-75) at week 16 defined as a ≥75% improvement in PGAxBSA Composite Tool;
2. Change in melanin index (MI) of target lesion at weeks 12, 16, and 24 compared to week 4 and change in MI at week 24 compared to week 12;
3. Change in erythema index (EI) of target lesion at weeks 4, 12, 16, 24 compared to baseline;
4. Change in physician and patient-rated change in dyspigmentation of the target lesion(s) based on a numeric rating scale (NRS) and visual analog scale (VAS), respectively at weeks 12, 16, and 24 compared to week 4 and at week 24 compared to week 12;
5. Change in the Dermatology Life Quality Index (DLQI) total score from baseline and the proportion of subjects achieving DLQI 0 or 1 at weeks 12, 16, 24;
6. Clinical safety and tolerability of secukinumab based on measurement of vital signs, routine clinical laboratory evaluation, and adverse events monitoring from baseline through 24 weeks.

Assessments

All physician and patient assessments were performed according to schedule during site visits, including screening (visit 1), week 0/baseline (visit 2), week 4 (visit 3), week 12 (visit 4), week 16 (visit 5), and week 24 (visit 6).

The severity of psoriasis was assessed using the PASI score and the IGA mod 2011 using a five-point scale (clear, almost clear, mild, moderate, severe).

A skin spectrophotometer (Mexameter® M18 [Courage + Lhazaka electronic GmbH, Cologne, Germany]) was used to quantify the melanin index and erythema index of a representative target lesion selected at baseline by the investigator compared to a specified area of unaffected skin.

The physician dyspigmentation NRS was used to evaluate dyspigmentation ranging from 5 (severe dark brown pigmentation) to -5 (complete absence of pigment) compared to unaffected skin, with 0 being baseline skin pigmentation. The scale is as follows: 5 severe dark brown pigmentation (darkest imaginable color), 4 dark brown pigmentation, 3 medium brown pigmentation, 2 light brown pigmentation, 1 slight dark pigmentation (barely perceptible compared to surrounding skin), 0 baseline skin pigmentation, -1 slight hypopigmentation (barely perceptible compared to surrounding skin), -2 mild hypopigmentation (light brown), -3 moderate hypopigmentation (creme-colored skin), -4 severe hypopigmentation (almost complete absence of pigment), -5 depigmentation (complete absence of pigment).

Patient-reported outcomes included the DLQI (validated 10-question questionnaire developed to address quality of life in patients with dermatological disorders) and a patient VAS used to assess patients' perception of skin dyspigmentation. The VAS is a 10cm long line on which the subjects indicate the severity of their skin dyspigmentation from "0" (normal skin color) to "+10" (dyspigmentation of the skin).

Safety was assessed with vital sign monitoring, physical examination, local tolerability assessments, and monitoring for adverse events (AEs).

Statistical Analysis

Descriptive statistical analyses were conducted in accordance with the primary and secondary endpoints outlined in the study protocol.

RESULTS

Patients

Subjects with chronic plaque psoriasis, age ≥ 18 years, BSA ≥ 10%, PASI Score ≥ 12, IGA ≥ 3, with Fitzpatrick skin types IV-VI were recruited from the dermatology faculty practices and resident clinics in the Mount Sinai Health System.

Between October 2019 and August 2021, a total of 20 subjects consented and enrolled in the study and were included in the full analysis set. All subjects completed the study.

The total analysis population included 20 patients (7 Black or African American, 1 Asian, 12 other). Nine patients identified as Hispanic or Latino while 11 patients did not. There were 9 female and 11 male patients, mean age = 47.1 (±12.95). Participant demographics are displayed in Table 1.

Efficacy

Investigator Assessments

With regards to the primary endpoint, 73% of patients achieved

TABLE 1.

Baseline Patient Characteristics	
	Number of Participants
Age (years) - mean (SD)	47.1 (12.95)
Males	11
Females	9
Race: (N = 20)	
American Indian or Alaska Native	0
Asian	1
Native Hawaiian or Other Pacific Islander	0
Black or African American	7
White	0
More than one race	0
Unknown or Not Reported	12
Ethnicity: (N=20)	
Hispanic or Latino	9
Not Hispanic or Latino	11
Unknown or Not Reported	0

a ≥90% improvement in Psoriasis Area Severity Index (PASI) at week 16 compared to baseline (PASI90), *P*=0.06; 5 missing values.

With regards to secondary endpoints, 39% of patients achieved PASI75 at week 4 compared to baseline (*P*=0.88, 2 missing values); 92% achieved PASI75 at week 12 compared to baseline (*P*=0.002; 7 missing values), 93% achieved PASI75 at week 16 compared to baseline (*P*=0.001; 5 missing values) and 78% achieved PASI75 at week 24 compared to baseline (*P*=0.02; 2 missing values).

Eleven percent (11%) of patients achieved PASI90 at week 4 compared to baseline (*P*=0.99; 2 missing values), 69% achieved PASI90 at week 12 compared to baseline (*P*=0.13; 7 missing values), 73% achieved PASI90 at week 16 compared to baseline (*P*=0.06; 5 missing values), and 61% achieved PASI90 at week 24 compared to baseline (*P*=0.24; 2 missing values).

No patients achieved a PASI100 at week 4 compared to baseline (2 missing values). Forty-six percent of patients achieved PASI100 at week 12 compared to baseline (*P*=0.71; 7 missing values. Fifty-three percent of patients achieved PASI100 at week 16 compared to baseline (*P*=0.5; 5 missing values), and 44% of patients achieved PASI100 at week 24 compared to baseline (0.76; 2 missing values).

Eighty-five percent (85%) of patients achieved an Investigator Global Assessment score (IGA) of 0 (clear) or almost clear (1) at week 12 (*P*=0.01; 7 missing values), 87% achieved an IGA of 0 or 1 at week 16 (*P*=0.004; 5 missing values), and 72% achieved an IGA of 0 or 1 at week 24 (*P*<0.048; 2 missing values).

One hundred percent (100%) of patients achieved a ≥75% reduction in the IGAxBSA score (IGAxBSA-75) between week 16 and baseline.

Change in melanin index at week 12 compared to week 4: 6.17 (*P*=0.65; 8 missing values), at week 16 compared to week 4: 5.62 (*P*=0.47; 7 missing values), at week 24 compared to week 4: 12.69 (*P*=0.14; 4 missing values), and at week 24 compared to week 12: -5.73 (*P*=0.30; 9 missing values).

Change in erythema index at week 4 compared to baseline: -1.83 (*P*=0.86; 2 missing values), week 12 compared to baseline: -8.85 (*P*=0.38; 7 missing values), week 16 compared to baseline: -1.67 (*P*=0.85; 5 missing values), and week 24 compared to baseline: -0.61 (*P*=0.93; 2 missing values).

Change in physician-rated NRS at week 12 compared to week 4: -0.08 (*P*=0.75; 8 missing values), at week 16 compared to week 4: 0.15 (*P*=0.75; 7 missing values), at week 24 compared to week 4 (*P*=0.76; 4 missing values), and at week 24 compared to week 12: 0.0 (*P*=1.0; 9 missing values).

Of note, the number of missing values due to visit interruptions at the onset of the COVID-19 pandemic are included to provide context for the lack of statistical significance observed in many of the aforementioned endpoints.

Patient-Reported Outcomes

The difference in patient-rated change in dyspigmentation visual analog scale (VAS) at week 12 compared to week 4: 0.17 (*P*=0.81; 8 missing values), at week 16 compared to week 4: -1.54 (*P*=0.07; 7 missing values), at week 24 compared to week 4: -1.27 (*P*=0.11; 5 missing values), and at week 24 compared to week 12: -1.64 (*P*=0.01; 9 missing values).

Changes from in DLQI total score at week 12 compared to baseline: -11.46 (*P*<0.0001; 7 missing values), at week 16 compared to baseline: -11.4 (*P*<0.0001; 5 missing values), and at week 24 compared to baseline -10.94 (*P*<0.0001; 2 missing values).

Forty-six percent (46%) of subjects achieved a DLQI score of 0 or 1 at week 12 (*P*=0.71; 7 missing values), 47% of subjects achieved a DLQI score of 0 or 1 at week 16 (*P*=0.70; 5 missing values), and 44% of subjects achieved a DLQI score of 0 or 1 at week 24 (*P*=0.76; 2 missing values).

Again, the number of missing values due to visit interruptions at the onset of the COVID-19 pandemic are included to provide

TABLE 2.

Primary and Secondary Endpoints (Investigator- and Patient-Rated)				
	Result (SD)	95% CI	*P*-Value	# Values Missing
Primary endpoint:				
Proportion of patients achieving PASI90 at week 16 compared to baseline	0.73	[0.51 0.96]	0.0592	5
Secondary endpoints:				
Proportion of patients achieving PASI75 at week 4 compared to baseline	0.39	[0.16 0.61]	0.8811	2
Proportion of patients achieving PASI75 at week 12 compared to baseline	0.92	[0.78 1]	0.0017	7
Proportion of patients achieving PASI75 at week 16 compared to baseline	0.93	[0.81 1]	0.0005	5
Proportion of patients achieving PASI75 at week 24 compared to baseline	0.78	[0.59 0.97]	0.0154	2
Proportion of patients achieving PASI90 at week 4 compared to baseline	0.11	[0 0.26]	0.9999	2
Proportion of patients achieving PASI90 at week 12 compared to baseline	0.69	[0.44 0.94]	0.1334	7
Proportion of patients achieving PASI90 at week 16 compared to baseline	0.73	[0.51 0.96]	0.0592	5
Proportion of patients achieving PASI90 at week 24 compared to baseline	0.61	[0.39 0.84]	0.2403	2
Proportion of patients achieving PASI100 at week 4 compared to baseline	0	[0.0 0.0]	1	2
Proportion of patients achieving PASI100 at week 12 compared to baseline	0.46	[0.19 0.73]	0.7095	7
Proportion of patients achieving PASI100 at week 16 compared to baseline	0.53	[0.28 0.79]	0.5	5
Proportion of patients achieving PASI100 at week 24 compared to baseline	0.44	[0.21 0.67]	0.7597	2
Proportion of patients at week 12 who achieved IGA of clear (0) or almost clear (1)	0.85	[0.65 1]	0.0112	7
Proportion of patients at week 16 who achieved IGA of clear (0) or almost clear (1)	0.87	[0.69 1]	0.0037	5
Proportion of patients at week 24 who achieved IGA of clear (0) or almost clear (1)	0.72	[0.52 0.93]	0.0481	2
≥75% reduction in IGAxBSA score between week 16 and baseline	1	[1.0 1.0]	0	5
Change in melanin index (MI) at week 12 compared to week 4	6.17 (46.11)	[-23.13 35.46]	0.6522	8
Change in melanin index (MI) at week 16 compared to week 4	5.62 (27.58)	[-11.05 22.28]	0.4771	7
Change in melanin index (MI) at weeks 24 compared to week 4	12.69 (32.96)	[-4.87 30.25]	0.1444	4
Change in melanin index (MI) at week 24 compared to week 12	-5.73 (17.19)	[-17.27 5.82]	0.295	9
Change in erythema index (EI) at week 4 compared to baseline	-1.83 (42.94)	[-23.19 19.52]	0.8584	2
Change in erythema index (EI) at week 12 compared to baseline	-8.85 (35.28)	[-30.17 12.47]	0.3837	7
Change in erythema index (EI) at week 16 compared to baseline	-1.67 (33.16)	[-20.03 16.7]	0.8485	5
Change in erythema index (EI) at week 24 compared to baseline	-0.61 (29.34)	[-15.2 13.98]	0.9306	2
Change in physician-rated NRS at week 12 compared to week 4	-0.08 (0.9)	[-0.66 0.49]	0.7545	8
Change in physician-rated NRS at week 16 compared to week 4	0.15 (1.68)	[-0.86 1.17]	0.7463	7
Change in physician-rated NRS at week 24 compared to week 4	-0.12 (1.63)	[-0.99 0.74]	0.763	4
Change in physician-rated NRS at week 24 compared to week 12	0.0 (1.73)	[-1.16 1.16]	1	9
Change in VAS (patient-rated change in dyspigmentation) at week 12 compared to week 4	0.17 (2.37)	[-1.34 1.67]	0.8118	8
Change in VAS (patient-rated change in dyspigmentation) at week 16 compared to week 4	-1.54 (2.82)	[-3.24 0.16]	0.0725	7
Change in VAS (patient-rated change in dyspigmentation) at week 24 compared to week 4	-1.27 (2.89)	[-2.87 0.33]	0.1117	5
Change in VAS (patient-rated change in dyspigmentation) at week 24 compared to week 12	-1.64 (1.75)	[-2.81 -0.46]	0.0111	9
Change from baseline in DLQI total score at week 12	-11.46 (6.9)	[-15.63 -7.29]	<0.0001	7
Change from baseline in DLQI total score at week 16	-11.4 (7.51)	[-15.56 -7.24]	<0.0001	5
Change from baseline in DLQI total score at week 24	-10.94 (7.88)	[-14.86 -7.03]	<0.0001	2
Proportion of subjects achieving DLQI score of 0 or 1 at week 12	0.46	[0.19 0.73]	0.7095	7
Proportion of subjects achieving DLQI score of 0 or 1 at week 16	0.47	[0.21 0.72]	0.6964	5
Proportion of subjects achieving DLQI score of 0 or 1 at week 24	0.44	[0.21 0.67]	0.7597	2

context for the lack of statistical significance observed in many of the aforementioned endpoints. Primary and secondary endpoints (both investigator- and patient-rated) are noted in Table 2.

Safety and Tolerability

No serious adverse events (AEs) occurred during the course of this study. A total of 9 distinct adverse events occurred in the study population. All AEs were mild in severity. The most common AEs were gastrointestinal (constipation – 1 patient, diarrhea – 3 patients, nausea – 1 patient) and infectious (cold symptoms – 1 patient, runny nose – 1 patient, boil – 1 patient). The remainder of adverse events were deemed unrelated to treatment by investigators and included a dental procedure, intermittent numbness of right thumb and index finger, and bilateral knee pain, each of which occurred in one patient. Overall, secukinumab was well tolerated.

DISCUSSION

Monthly treatment with secukinumab 300 mg subcutaneously was overall safe and well tolerated in the treatment of moderate-to-severe plaque psoriasis in patients with skin of color. The primary efficacy endpoint was nearly met with 73% of patients achieving PASI90 at week 16 compared to baseline (P=0.592). However, five subjects were unable to complete their week 16 visit due to restrictions that occurred at the onset of the COVID-19 pandemic. We suspect that had these visits been completed, statistical significance would have been achieved in the primary endpoint.

While the proportion of patients achieving PASI75 at weeks 12, 16, and 24 compared to baseline was statistically significant, the proportion of patients achieving PASI90 and PASI100 was not statistically significant at any timepoint. Despite this, the proportion of subjects who achieved an IGA of clear or almost clear was statistically significant at all timepoints and the reduction in IGAxBSA-75 score at week 16 compared to baseline was also statistically significant.

The change in melanin indices, change in erythema indices, and change in physician-rated NRS were not found to be statistically significant at any timepoint. The change in the patient-rated change in dyspigmentation was found to be statically significant only when comparing week 24 and week 12.

The proportion of subjects achieving a DLQI score of 0 or 1 was not found to be statistically significant at any timepoint. However, the change from the baseline DLQI score was found to be statistically significant at every timepoint. This suggests that while 5 months of treatment was not sufficient to eliminate the effect of plaque psoriasis on patient dermatology life quality index, it did result in a significant improvement in patient quality of life as it pertains to psoriasis. Perhaps this is one of the largest takeaways: while not all endpoints were found to be statistically significant, the positive impact on the dermatology life quality index is observed as early as after completion of the loading doses of secukinumab.

Taken together, these results suggest that secukinumab 300mg subcutaneously represents a safe, well-tolerated treatment option that could be considered in the treatment of moderate-to-severe plaque psoriasis in skin of color patients.

No serious adverse events occurred during the course of this study. All reported AEs were mild in severity. This adds to the available safety data regarding the use of secukinumab for the treatment of plaque psoriasis in skin of color patients.

Notably, there are multiple limitations to this study. The sample size was small and underpowered to detect statistically significant changes in many endpoints. Furthermore, while all subjects completed the study, there was a total of sixteen mixed visits secondary to restrictions that occurred at the onset of the COVID-19 pandemic. This prevented the inclusion of numerous data points in an already limited subject number, further limiting statistical power.

In conclusion, secukinumab 300 mg administered subcutaneously is a safe, well-tolerated, and viable treatment option for the management of moderate-to-severe plaque psoriasis in skin of color patients. Given the paucity of data with regards to the use of biologic medications in skin of color patients, our study provides additional data where more is needed and provides important insight into treating SOC populations with the inclusion of psoriasis-associated dyspigmentation as a secondary endpoint.

As the US and global population becomes increasingly diverse, it is increasingly important to have clinical trials that include populations that have been historically under-represented in dermatologic research. We believe that such efforts are an important path toward promoting equity in dermatologic care.[23]

DISCLOSURES

Andrew Alexis MD has received grants (funds to his institution) from Leo, Amgen, Galderma, Arcutis, Dermavant, Abbvie, and Castle. He has served on advisory boards or as a consultant for Leo, Galderma, Pfizer, Sanofi-Regeneron, Dermavant, Beiersdorf, Ortho, L'Oreal, BMS, Bausch Health, UCB, Arcutis, Janssen, Allergan, Almirall, Abbvie, Amgen, VisualDx, Eli Lilly, Swiss American, Cutera, Cara, EPI, Incyte, Castle, Apogee, Canfield, Alphyn, Avita Medical, and Genentech. Additionally, he has been a speaker for Regeneron, Sanofi-Genzyme, BMS, L'Oreal, Janssen, and J&J. He has received royalties from Springer, Wiley-Blackwell, and Wolters Kluwer Health, and has received equipment from Aerolase.

ACKNOWLEDGMENT

Novartis provided the study drug and a grant for study-related tests and procedures.

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doi:10.36849/JDD.7993

August 2024 607 Volume 23 • Issue 8

ORIGINAL ARTICLE

Journal of Drugs in Dermatology

Preference for Cal/BDP Cream or Foam in Patients With Mild-to-Moderate Plaque Psoriasis

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ABSTRACT

Background: The combined use of topical calcipotriol/betamethasone dipropionate (Cal/BDP) is commonly used and demonstrated to be effective for the management of psoriasis and is shown to confer local anti-inflammatory and immunoregulatory effects. The use of the two agents in combination is synergistic. Despite the demonstrated efficacy of topically applied combination Cal/BDP, successful management of a chronic, relapsing inflammatory skin disease such as psoriasis in the real-world setting may be hindered if patients do not adhere to the dosing or frequency of application recommendations from their prescriber. Patient preference for and satisfaction with the topical treatment vehicle have been shown to influence adherence. A recent analysis has determined that patients perceived Cal/BDP cream vehicle with PAD technology as having favorable characteristics. This randomized, split-body study was undertaken to further assess patient satisfaction with Cal/BDP cream and Cal/BDP foam formulations.

Trial Design: This was a split-body, subject-blind study. Study cream was administered in a single application to one side of the scalp and/or body; study foam was applied to the contralateral side. Patient self-administered questionnaires were completed before and after product application after a single site visit.

Results: Mean overall Vehicle Preference Measure (VPM) scores were higher for Cal/BDP cream than Cal/BDP foam (P=0.0043). Cal/BDP cream also achieved higher individual scores for ease of application, feeling to the touch, smell, and feeling on the skin (P<0.03). With regards to scalp application, subject assessments show that the cream was significantly more preferred in terms of limiting daily disruption (P=0.0008)

Conclusion: Results of this study suggest that patients may prefer Cal/BDP cream over Cal/BDP foam for the management of psoriasis on the body and the scalp. Cal/BDP cream outperformed Cal/BDP foam on several specific measures of satisfaction and overall satisfaction measures.

J Drugs Dermatol. 2024;23(8):607-611. doi:10.36849/JDD.7993

INTRODUCTION

The combined use of topical calcipotriol/betamethasone dipropionate (Cal/BDP) is commonly used and demonstrated to be effective for the management of psoriasis. Used in combination, topical calcipotriol and betamethasone dipropionate confer local anti-inflammatory and immunoregulatory effects. The combination has also been shown to produce a reduction of keratinocyte hyperproliferation and to help normalize keratinocyte differentiation.[1] Of note, the use of the two agents in combination is synergistic; overall evidence suggests that the combination of the two agents is more effective than the use of either agent alone.[1]

Despite the demonstrated efficacy of topically applied combination Cal/BDP, successful management of a chronic, relapsing inflammatory skin disease such as psoriasis in the real-world setting may be hindered if patients do not adhere to the dosing or frequency of application recommendations from their prescriber.[2] Among the multiple factors that can either encourage or hinder adherence is patient preference for and satisfaction with the topical treatment vehicle.[3]

Through innovations in topical formulation science, calcipotriol and betamethasone dipropionate, two otherwise incompatible

ingredients, have been effectively combined into a variety of fixed-combination topical products featuring different vehicle bases.[4] In the United States, topical ointment, foam, suspension, and cream formulations of Cal/BDP are available.[5] Comparison of already-published data from various studies of individual formulations suggests that different previously available fixed-dose formulations of Cal/BDP have similar efficacy, but there may be differences in patient satisfaction with the other formulations.[5-7] Moreover, there does not appear to be a significant difference in safety profiles for the various formulations.[5]

Most recently, pooled data from two, phase 3 controlled trials for the novel, fixed-dose calcipotriol 0.005% and betamethasone dipropionate 0.064% combination cream based on Poly-Aphron Dispersion (PAD) Technology, a technology that encapsulates the active ingredients in oil droplets, protecting them from hydrolytic degradation and designed to allow efficient drug delivery, have demonstrated significantly greater efficacy for cream for all efficacy endpoints, including Physician Global Assessment (PGA) treatment success, modified Psoriasis Area and Severity Index (mPASI) score, and mPASI75 score, compared to Cal/BDP topical suspension.[8] The combination cream was highly rated and superior to topical suspension on the Psoriasis Treatment Convenience Scale. In an indirect comparison to Cal/BDP foam, Cal/BDP cream was reported to be statistically superior in four out of five treatment satisfaction domains.[9]

A recent analysis has determined that patients perceived Cal/BDP PAD-cream vehicle as having a low stickiness, low grease behavior, good wetness, and good spreadability with minimal residue.[10]

A randomized, split-body study was undertaken to further assess patient satisfaction with Cal/BDP cream and Cal/BDP foam formulations.

MATERIALS AND METHODS

This was a split-body, subject-blind study. Study treatment was dispensed in a measured amount of product into the subject's hand in a single-blind fashion. Study cream was administered in a single application to one side of the scalp and/or body; study foam was applied to the contralateral side. Patients assessing both body and scalp were given separate products for each application. Patient self-administered questionnaires were completed before and after product application after a single site visit.

Assessments included Vehicle Preference Measure (VPM), Psoriasis Treatment Convenience Scale (PTCS), Skin use questionnaire, SCALPDEX, Scalp use questionnaire, and Final Preference.

Subject Demographics

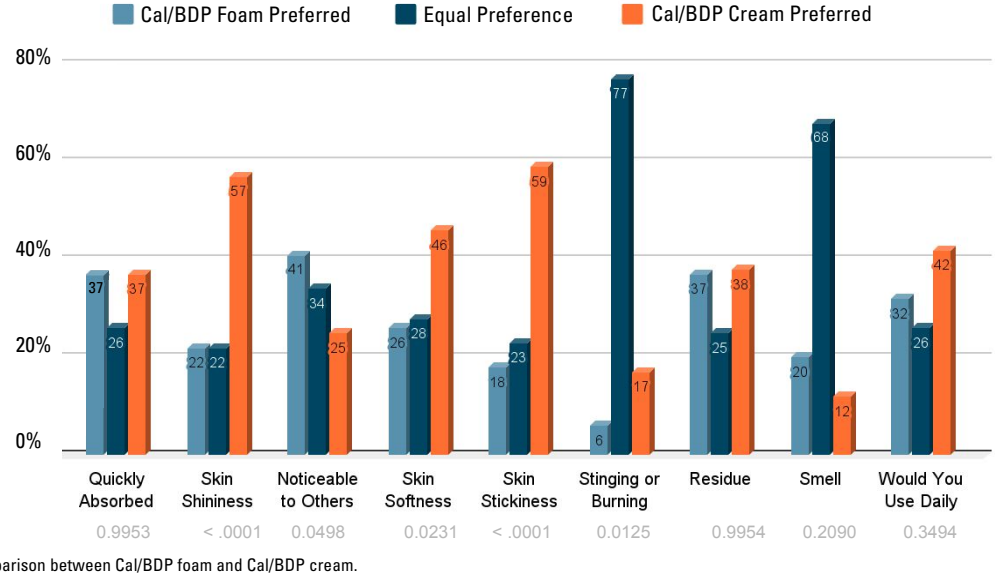
Of 150 subjects enrolled at 5 treatment sites, 146 subjects with mild to moderate psoriasis assessed the formulation for use on the body (102 body only) and 49 subjects assessed the formulation for use on the scalp (5 scalp only). The average age was 54 years, with ages ranging from 19 to 91.

A majority of subjects were female (62%); 37% were male, and 1 had unspecified sex. Eighty-five (85%) percent of subjects were White, 12% were Black, 2% were Asian, and 1% were Hispanic.

RESULTS

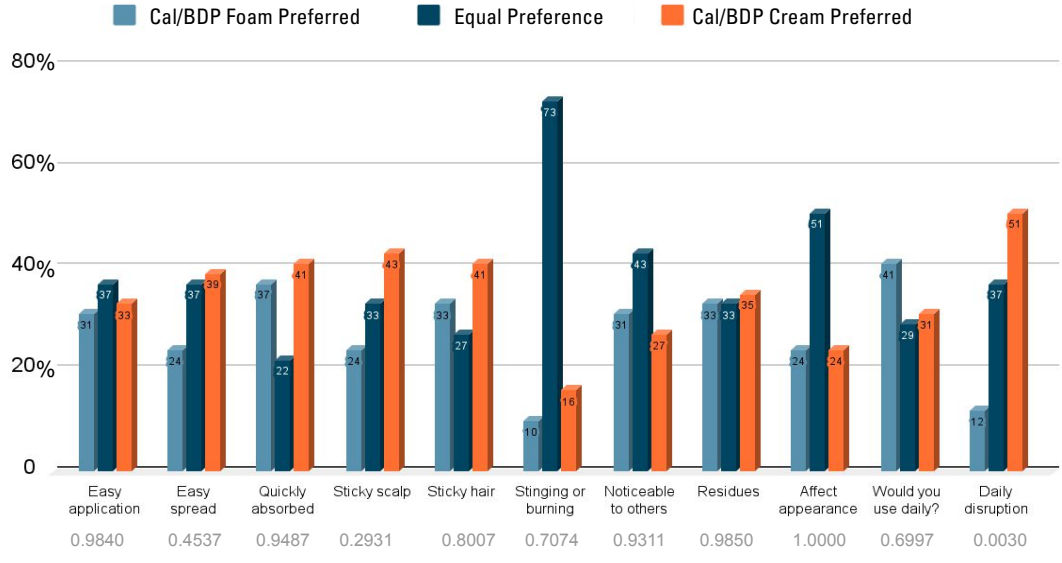
Mean overall Vehicle Preference Measure (VPM) scores were higher for Cal/BDP cream than Cal/BDP foam (P=0.0043). Cal/

FIGURE 1. Skin Use Questionnaire Items. Percent of subjects responding due to rounding, totals may not equal 100.



P-values represent comparison between Cal/BDP foam and Cal/BDP cream.

FIGURE 2. Scalp Use Questionnaire Items. Percent of subjects responding due to rounding, totals may not equal 100.

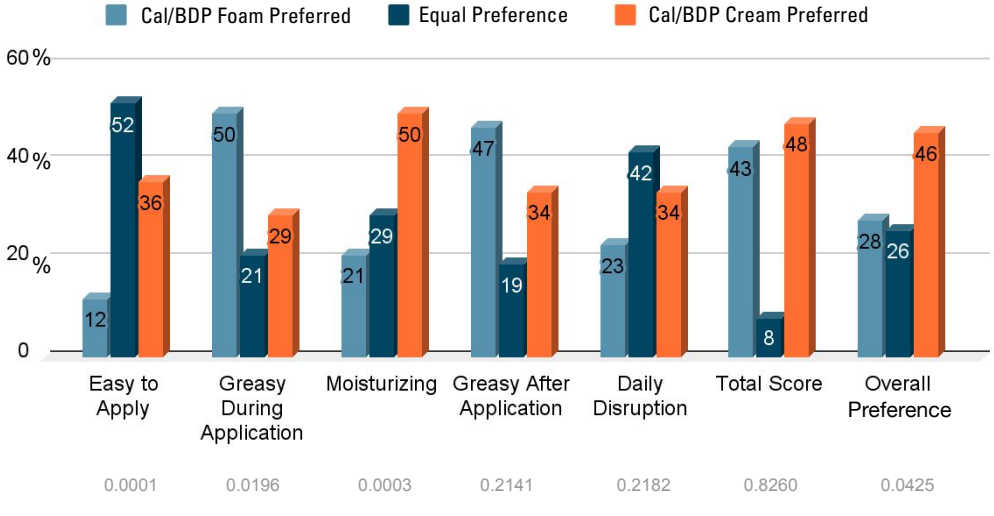


P-values represent comparison between Cal/BDP foam and Cal/BDP cream.

BDP cream also achieved higher individual scores for ease of application, feeling to the touch, smell, and feeling on the skin ($P<0.03$). Subject responses on the Skin Use Questionnaire indicate that Cal/BDP cream outperformed Cal/BDP foam on several variables that may be important for patient satisfaction. For example, Cal/BDP cream was associated with significant preference for measures of skin shininess ($P<0.0001$), skin softness ($P=0.0231$), skin stickiness ($P<0.0001$) and stinging or burning ($P=0.0125$) (Figure 1). Regarding scalp application, subject assessments show that the cream was significantly preferred in terms of limiting daily disruption ($P=0.0030$; Figure 2).

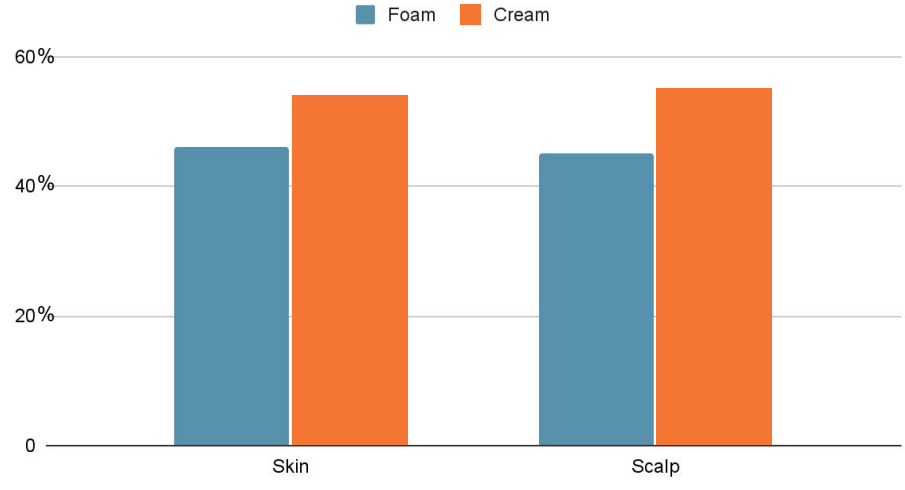
Cal/BDP cream outperformed Cal/BDP foam on multiple measures of the Psoriasis Treatment Convenience Scale (PTCS). Subjects preferred the cream in terms of ease of application, moisturization, and overall satisfaction ($P<0.05$, Wilcoxon signed-rank test). The foam was preferred in terms of greasiness during application ($P=0.01$). There were no significant differences

FIGURE 3. Psoriasis Treatment Convenience Scale (PTCS). Percent of subjects responding due to rounding, totals may not equal 100.



P-values represent comparison between Cal/BDP foam and Cal/BDP cream.

FIGURE 4. Final Preference (not statistically significant). Percent of subjects responding due to rounding, totals may not equal 100.



in terms of greasiness after application, daily disruption, and the total score (Figure 3).

A higher proportion of subjects noted a final preference for the cream for the body (54%) and scalp (55%) than for the foam, although this did not achieve statistical significance (Figure 4).

DISCUSSION

Traditionally, dermatologists have accepted general observations about patients' vehicle preferences, many of which are decades old and do not necessarily align with current innovations. A more appropriate modern approach to treatment includes assessment of patient preferences, anticipated drug efficacy, and shared decision-making.[11]

A National Psoriasis Foundation patient survey recently found that most participants (76%) reported using topical therapy at least once weekly. Of note, survey respondents preferred water-based creams (75.7%). Formulation attributes rated most important by respondents were application feel (55.2%), non-staining (49.9%), quick absorption (46.7%), non-sticky texture (39.7%), ease of application (28.5%), no unpleasant smell (22.4%), non-greasy (16.8%), works quickly (14.1%), absent sting or burn (10%), and lack of adverse skin reaction (9.7%).[2] Several of these attributes were assessed in the current study, and Cal/BDP cream outperformed foam on many of them. Specifically, Cal/BDP cream scored well for rapid absorption as well as for lack of hair or scalp stickiness. As noted, Cal/BDP cream was significantly preferred over foam for lack of skin stickiness.

Results of the current user preference study suggest that fixed-dose calcipotriol 0.005% and betamethasone dipropionate 0.064% combination cream with PAD technology may be a suitable option for topical treatment of psoriasis, including scalp psoriasis, and may be associated with high levels of patient satisfaction. High patient satisfaction may positively influence treatment adherence and therapeutic outcomes.

CONCLUSION

Results of this study suggest that patients may prefer Cal/BDP cream over Cal/BDP foam for the management of psoriasis on the body and the scalp. Cal/BDP cream outperformed Cal/BDP foam on several specific measures of satisfaction and overall satisfaction measures. It is a suitable treatment option to consider for patients requiring topical treatment, including treatment of hair-bearing skin.

DISCLOSURES

Dr Kircik has received funding either as an investigator, consultant, or speaker from the following pharmaceutical companies: Almirall, and LEO Pharma.

Cheryl Burgess MD FAAD has affiliations with AbbVie Allergan, Merz Aesthetics, Prollenium, and Janssen.

Brad Glick DO is an advisory board member, consultant, speaker and investigator for and received honoraria or grants from Amgen, AbbVie, AstraZeneca, Almirall, Acrutis, Bausch Health/Valeant, OrthoDermatologics, Boehringer Ingelheim, Bristol-Myers Squibb, Brickell Biotech, Cara Therapeutics, ChemoCentryx, Dermavant, Dermira, Eli Lilly, EPI/Novan Pharmaceuticals, Incyte, Janssen Pharmaceuticals, LEO Pharma, Galderma, Nimbus Lakshmi, Inc, Novartis Pharmaceutical Corporation, Sun Pharma, Pfizer, Sanofi, Regeneron, UCB and the CorEvitas AD, CorEvitas PSO and PROSE Registries. Dr. Glick is a shareholder of Top MD, LLC.

Lawrence Green MD has served as am investigator , advisor, and/or speaker for Amgen, Arcutis, BMS, Dermavant, Lilly, Janssen, Pfizer, UCB, Takeda, Highlittl, Apogee, Vyne, Incyte, and Galderma.

Zoe Diana Draelos MD has the following relevant financial relationships: Contracted researcher and consultant for: Aclaris Therapeutics, Inc.; Aesthetics Biomedical; Allergan, Almirall; Amderma; Amgen, Inc.; AOBiome; Arcutis Biotherapeutics, Inc.; Bausch Heath; Bayer AG; Biopelle; Boehringer Ingelheim Pharmaceuticals, Inc.; Boots; Botanix Pharmaceuticals; Brickell Biotech, Inc.; Burt's Bees; Carpe; Chattem Chemicals Inc.; The Chlorox Company; Clarke Pharmaceuticals, Inc.; Colgate-Palmolive Company; Coloplast Corp.; Combe; DelArrivo, Inc.; Dermavant Sciences, Inc.; Dermira, Inc.; Dial; Dr. Reddy's Laboratories Ltd.; Estée Lauder Inc.; E.T. Browne Drug Co., Inc.; Evolus, Inc.; Ferndale Laboratories, Inc.; Foamix Pharmaceuticals Ltd.; Galderma Laboratories, LP; Genentech, Inc.; General Mills, Inc.; GlaxoSmithKline; Helix Biomedix, Inc.; Henkel; International Specialty Products, Inc.; Johnson & Johnson Services, Inc.; Kamedis; Kao Corporation; La Roche-Posay; LEO Pharma Inc.; Lilly; L'Oréal; Maruho Co., Ltd.; Merck; Nice-Pak Products, Inc.; Novartis; Nu Skin; Perricone MD; Perrigo Company plc; Pfizer Inc.; PharmaNet, Inc.; Proctor & Gamble; Reckitt Benckiser Group plc; Revance Therapeutics, Inc.; Rodan & Fields, LLC; Roivant Sciences Ltd; Sanofi; SkinCeuticals; Symrise; Taro Pharmaceuticals Industries Ltd.; Teoxane; TEVA Pharmaceuticals USA, Inc.; Topix Pharmaceuticals, Inc.; Vanda Pharmaceuticals Inc.; Verrica Pharmaceuticals; Warner-Chilcott; WellSpring Pharmaceutical Corporation; YA-MAN Ltd; ZO Skin Health, Inc.

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doi:10.36849/JDD.8217

August 2024 612 Volume 23 • Issue 8

ORIGINAL ARTICLE

Journal of Drugs in Dermatology

Tildrakizumab Real-World Effectiveness and Safety Over 64 Weeks in Patients With Moderate-to-Severe Plaque Psoriasis

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ABSTRACT

Background: Tildrakizumab is a humanized anti–interleukin-23 p19 monoclonal antibody approved for the treatment of moderate-to-severe plaque psoriasis. This report describes real-world effectiveness and safety of tildrakizumab through 64 weeks of treatment.
Methods: In this Phase 4, multicenter, uncontrolled, open-label trial (NCT03718299), adults with moderate-to-severe plaque psoriasis received tildrakizumab 100 mg at weeks 0 and 4 and every 12 weeks thereafter through week 52. Effectiveness was assessed from body surface area (BSA) affected and static Physician Global Assessment (sPGA) through week 64 and Psoriasis Area and Severity Index (PASI) through week 52. Adverse events are reported.
Results: Of 55 patients enrolled, 45 completed the study and 36 received all doses of tildrakizumab. From baseline to week 64, mean ± standard deviation BSA decreased by 83.1% (from 14.5 ± 11.5 to 2.1 ± 3.6) and sPGA by 67.6% (from 3.2 ± 0.6 to 1.0 ± 1.0); sPGA x BSA decreased by 89.6% (from 47.0 ± 41.5 to 4.6 ± 9.4; all $P<0.001$). PASI scores decreased compared to baseline at weeks 4, 16, 28, and 52 ($P<0.001$). For PASI responses at week 52 compared with baseline, 87.0% achieved ≥75% improvement, 56.5% achieved ≥90% improvement, and 32.6% achieved 100% improvement. Of 85 treatment-emergent adverse events in 34/55 patients, none were considered related to tildrakizumab treatment.
Conclusions: Tildrakizumab treatment was effective in adult patients with moderate-to-severe plaque psoriasis in real-world settings, with no new safety signals.

J Drugs Dermatol. 2024;23(8):612-618. doi:10.36849/JDD.8217

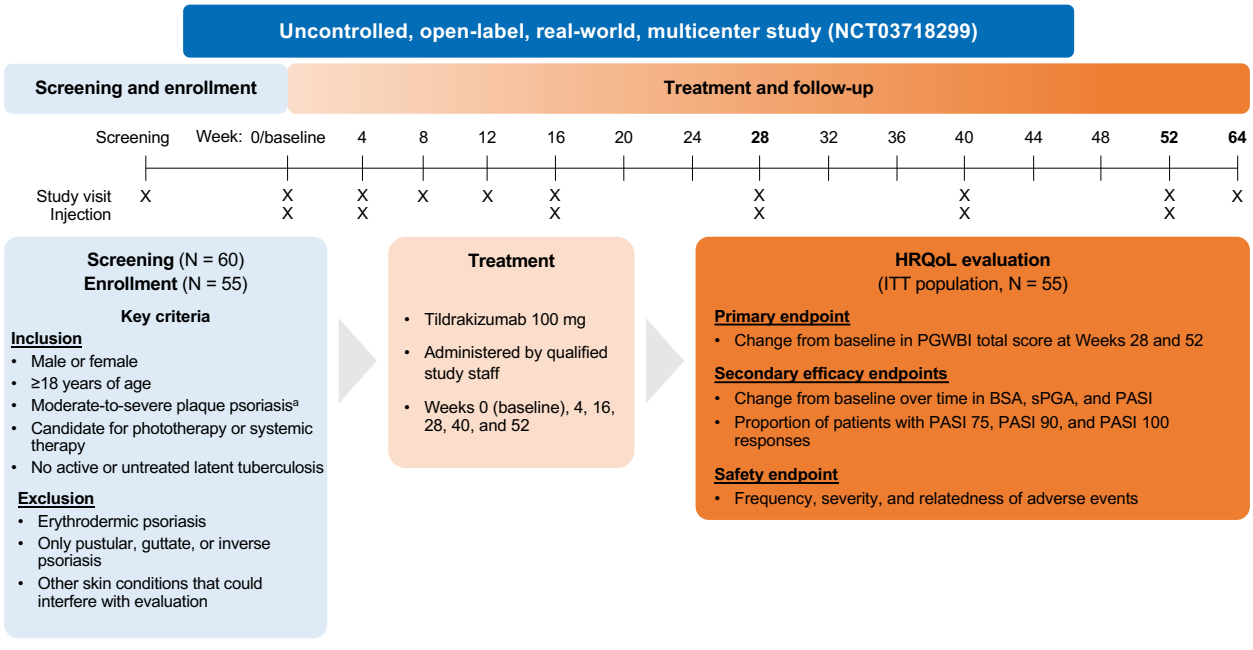
INTRODUCTION

Plaque psoriasis, the most common type of psoriasis, is a chronic, inflammatory skin disorder that requires life-long management.[1-3] This multisystem disease is associated with a range of medical and psychological comorbidities, including cardiovascular disease, obesity, type 2 diabetes, psoriatic arthritis, inflammatory bowel disease, and depression.[1,3] Moderate-to-severe plaque psoriasis typically requires systemic treatment, although topical treatments and phototherapy are also available.[3]

Tildrakizumab is a humanized anti–interleukin-23 p19 monoclonal antibody therapy approved for the treatment of adults with moderate-to-severe plaque psoriasis who are candidates for systemic or phototherapy.[4-6] The safety and efficacy of tildrakizumab in patients with moderate-to-severe plaque psoriasis were established in two Phase 3 randomized, double-blind clinical trials (reSURFACE 1 [NCT01722331] and reSURFACE 2 [NCT01729754]).[7-9] Patients receiving tildrakizumab who completed the 64-week reSURFACE 1 or 52-week reSURFACE 2 study with at least a ≥50% improvement from baseline Psoriasis Area and Severity Index (PASI) score could enroll in optional extension studies continuing the same dose for an additional 4 years.[10,11] Pooled analysis of data from reSURFACE 1 and reSURFACE 2 and corresponding extension studies demonstrated sustained disease control and a favorable safety profile for up to 5 years of treatment in patients who achieved a ≥75% improvement from baseline PASI score (PASI 75 response) at week 28.[11]

The long-term efficacy and safety of tildrakizumab are well established in randomized, blinded clinical trial settings, but real-world evidence is limited.[3] To address this gap, we performed a Phase 4 study to assess the effect of tildrakizumab treatment on health-related quality of life in patients with moderate-to-severe plaque psoriasis over 64 weeks of treatment under real-world conditions.[12,13] Effectiveness and safety were also assessed as secondary endpoints, and interim analysis results demonstrated sustained clinical improvement through week 28, with no new reported safety concerns.[14] Here, we report the effectiveness and safety results through week 64 of the Phase 4 study.

FIGURE 1. Study design.



[a]BSA ≥3%. BSA, body surface area; HRQoL, health-related quality of life; ITT, intention-to-treat; PASI, Psoriasis Area and Severity Index; PASI 75/90/100 responses, proportion of patients achieving ≥75%/≥90%/100% improvement from baseline in PASI score; PGWBI, Psychological General Well-Being Index; sPGA, static Physician Global Assessment.

MATERIALS AND METHODS

Study Design and Patients

This Phase 4, 64-week, multicenter, uncontrolled, open-label, real-world study was conducted at 2 study sites in the US (NCT03718299; Figure 1).[12] The study design has been described in detail elsewhere. Briefly, eligible patients were immunocompetent adults ≥18 years of age with moderate-to-severe plaque psoriasis affecting ≥3% of total body surface area (BSA) who were diagnosed ≥6 months before study entry and were candidates for phototherapy or systemic therapy. Exclusion criteria included a diagnosis of erythrodermic psoriasis; only pustular, guttate, or inverse psoriasis; evidence of skin conditions other than psoriasis that would interfere with study-related psoriasis evaluations; treatment with any biological drug other than tildrakizumab within 1 week prior to baseline; or use of any investigational agent or device within 12 weeks of baseline. Patients were administered subcutaneous injections of tildrakizumab 100 mg at week 0, week 4, and every 12 weeks thereafter through week 52. Postbaseline study visits occurred at weeks 4, 8, 12, 16, 28, 40, 52, and 64.

The study protocol and all amendments were approved by a central institutional review board in compliance with pertinent sections of the Code of Federal Regulations prior to study initiation. The study was conducted in accordance with the principles of the Declaration of Helsinki and current guidelines for Good Clinical Practice. All patients provided written informed consent before any study-related procedures were performed.

Assessments

Effectiveness

On all study visits, investigators assessed the percentage of BSA affected using the estimate that 1% BSA is equivalent to the area of the patient's closed hand (palm with fingers held together). For the static PGA (sPGA), the investigator first rated the severity of induration, erythema, and scaling of the psoriatic plaques on individual 6-point scales from 0 (no evidence) to 5 (severe).[15] The scores for each attribute were averaged over the entire body. The final sPGA score was obtained using a scale from 0 (clear, except for residual discoloration) to 5 (severe, lesions have individual scores for induration, erythema, and scaling of at least 5). The sPGA was assessed at all study visits. The PASI score, which captures the severity (erythema, induration, and desquamation) and extent of psoriasis plaques on the head, trunk, upper limbs, and lower limbs on a scale of 0 (no psoriasis) to 72 (most severe), was assessed at baseline and weeks 4, 16, 28, and 52.

Safety

Adverse events (AEs) were recorded throughout the study and classified according to severity and relationship to treatment.

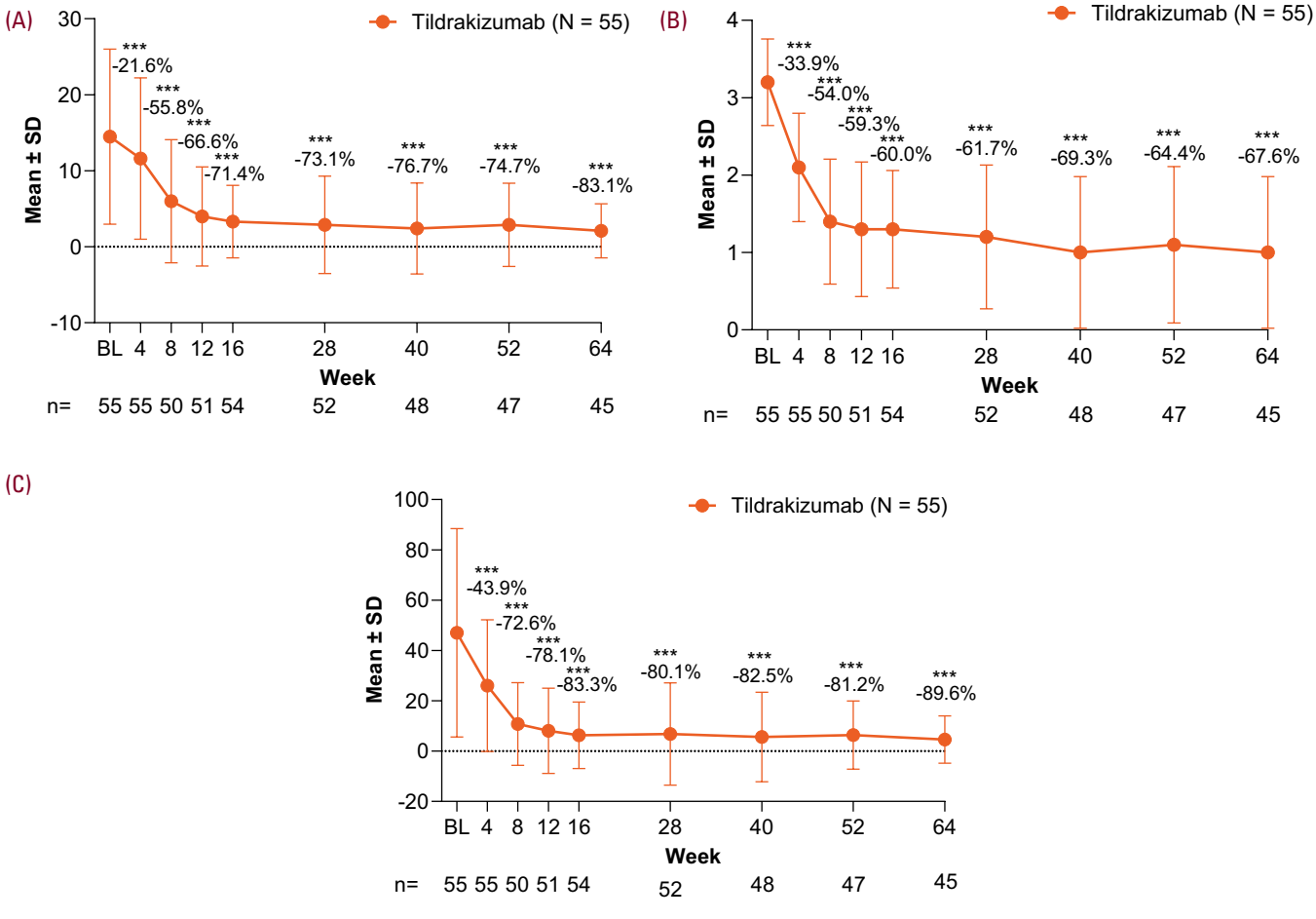
Endpoints

The primary endpoint was change in quality of life defined as the improvement from baseline in the total Psychological General Well-Being Index score at weeks 28 and 52; results are reported elsewhere.[12,13] Secondary effectiveness endpoints reported here include the change in disease activity, based on the percentage of BSA affected, sPGA, and the product of BSA and sPGA (BSA x sPGA) over time through week 64, and clinical improvement through week 52, based on change in PASI score from baseline and proportions of patients achieving PASI 75, PASI 90 (≥90% improvement from baseline in PASI score), and PASI 100 (100% improvement from baseline in PASI score) responses at weeks 4, 16, 28, and 52. Safety endpoints included the incidence, severity, and relationship to treatment of treatment-emergent AEs (TEAEs) and treatment-emergent serious AEs through week 64.

Statistical Analysis

No formal power analysis was performed. A sample size of 60 patients screened was expected to provide adequate estimates of probable events in the population. Effectiveness was analyzed in the intention-to-treat population, consisting of all patients who enrolled and were assigned to receive tildrakizumab. Hypothesis testing of the difference from baseline of the BSA, sPGA, BSA x sPGA, and PASI scores was performed using Student's t-tests. The PASI 75, PASI 90, and PASI 100 response rates are presented as the number and proportion of patients with each level of response. Missing data were not imputed for most time points; however, for all efficacy by visit analyses, an additional end-of-treatment (EOT) value is reported for the final assessment time point using last-observation-carried-forward imputation from each patient's final evaluation for each endpoint. Safety analysis was performed in all enrolled patients who received at least 1

FIGURE 2. Mean change from baseline in (A) BSA, (B) sPGA, and (C) the product of BSA and sPGA (BSA x sPGA) over time through week 64. Data are graphed as the absolute score with the percent change from baseline over each time point.



***P<0.001. BL, baseline; BSA, body surface area; SD, standard deviation; sPGA, static Physician Global Assessment.

dose of tildrakizumab. Reported TEAEs were classified by Medical Dictionary for Regulatory Activities System Organ Class and Preferred Term and summarized by frequency, severity, and relationship to treatment. Analyses were performed using SAS® Version 9.4 or higher. Results are presented as mean ± standard deviation (SD) unless otherwise noted.

RESULTS

Study Population

Of the 60 patients screened, 55 enrolled and 45 (81.8%) of these completed the study and were assessed at week 64; 36 (65.5%) received all doses of tildrakizumab through week 52. The 10 patients who discontinued the study did so due to withdrawal by patient (n = 6), physician decision (n = 2), loss to follow-up (n = 1), and an AE (n = 1). The majority of patients were male (28/55; 50.9%) and White (52/55; 94.5%), with a mean ± SD age of 48.6 ± 15.3 years (Table 1).

Effectiveness

Disease severity improved in tildrakizumab-treated patients through week 64. Affected BSA significantly decreased from a mean of 14.5 ± 11.5 at baseline to 2.1 ± 3.6 at week 64 (95% confidence interval [CI] of change, –16.3 to –9.1; *P*<0.001; mean percent change from baseline, –83.1%; Figure 2A); the week 64/EOT value was 3.1 ± 5.9 (95% CI of change, –14.4 to –8.3; *P*<0.001; mean percent change from baseline, –78.1%). Mean sPGA scores significantly decreased from 3.2 ± 0.6 at baseline to 1.0 ± 1.0 at week 64 (95% CI of change, –2.5 to –1.9; *P*<0.001; mean percent change from baseline, –67.6%; Figure 2B); the week 64/EOT value was 1.1 ± 1.1 (95% CI of change, –2.4 to –1.8; *P*<0.001; mean percent change from baseline, –64.8%). The product of BSA and sPGA, which captures both the severity and extent of plaques, decreased from 47.0 ± 41.5 at baseline to 4.6 ± 9.4 at week 64 (95% CI of change, –55.8 to –30.7; *P*<0.001;

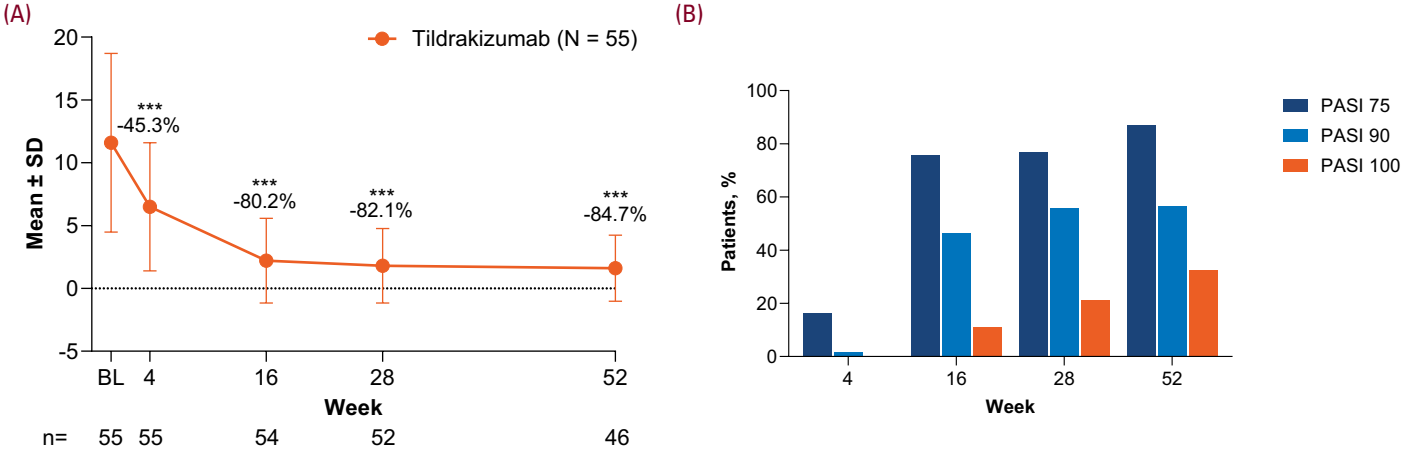
TABLE 1.

Demographics and Baseline Characteristics of the ITT Population

Characteristic	Tildrakizumab N = 55
Sex	
Female	27 (49.1)
Male	28 (50.9)
Age, years, mean ± SD	48.6 ± 15.3
Race	
White	52 (94.5)
Black or African American	2 (3.6)
Asian	1 (1.8)
Ethnicity	
Hispanic or Latino	5 (9.1)
Not Hispanic or Latino	50 (90.9)
BSA, %, mean ± SD	14.5 ± 11.5
sPGA	
0	0
1	0
2	4 (7.3)
3	36 (65.5)
4	15 (27.3)
5	0
PASI, mean ± SD	11.6 ± 7.1

Data presented as n (%) unless otherwise noted.
BSA, body surface area; ITT, intention-to-treat; PASI, Psoriasis Area and Severity Index; SD, standard deviation; sPGA, static Physician Global Assessment.

FIGURE 3. (A) Disease activity and (B) clinical improvement based on PASI score through week 52. Data are graphed as the absolute score with the percent change from baseline over each time point.



***P<0.001. BL, baseline; PASI, Psoriasis Area and Severity Index; PASI 75/90/100 response, ≥75%/≥90%/100% improvement from baseline in PASI score; SD, standard deviation.

TABLE 2.

TEAEs (Safety Population)	
Evaluation	**Tildrakizumab N = 55**
Number of TEAEs	85
Patients with ≥1 TEAE	34 (61.8)
Treatment-related TEAEs	0
Serious TEAEs	4 (7.3)
Ischemic stroke	1 (1.8)
Transitional cell carcinoma	1 (1.8)
IgA nephropathy	1 (1.8)
COVID-19 pneumonia	1 (1.8)
TEAEs leading to treatment discontinuation	2 (3.6)
Transitional cell carcinoma	1 (1.8)
COVID-19 pneumonia	1 (1.8)
Deaths	0
Most frequent TEAEs (>3% of patients)	
Psoriasis	7 (12.7)
Hypertension	5 (9.1)
Dermatitis	3 (5.5)
Arthralgia	2 (3.6)
Eczema	2 (3.6)
Hematuria	2 (3.6)
Large intestine polyp	2 (3.6)
Nasopharyngitis	2 (3.6)
Skin papilloma	2 (3.6)
Upper respiratory tract infection	2 (3.6)

Data presented as n (%) of patients with event in the safety population and reported using MedDRA preferred terms.
COVID-19, coronavirus disease 2019; IgA, immunoglobulin A; MedDRA, Medical Dictionary for Regulatory Activities; TEAE, treatment-emergent adverse event.

mean percent change from baseline, –89.6%; Figure 2C) and to 7.1 ± 15.1 (95% CI of change, –50.9 to –29.0; *P*<0.001; mean percent change from baseline, –84.6%) at week 64/EOT. Clinical improvement of psoriasis as indicated by statistically significant decrease in PASI scores from baseline (11.6 ± 7.1) was observed at weeks 4 (6.5 ± 5.1; 95% CI of change, –6.3 to –3.8), 16 (2.2 ± 3.4; 95% CI of change, –11.2 to –7.4), 28 (1.8 ± 3.0; 95% CI of change, –11.3 to –7.4), and 52 (1.6 ± 2.6; 95% CI of change, –12.2 to –7.8; *P*<0.001 for all; mean percent change from baseline of –45.3%, –80.2%, –82.1%, and –84.7%, respectively; Figure 3A). The week 52/EOT PASI score was 2.1 ± 3.6 (95% CI of change, –11.4 to –7.6; *P*<0.001; mean percent change from baseline, –82.5%). At week 52, 87.0%, 56.5%, and 32.6% of patients achieved PASI 75, PASI 90, and PASI 100 responses, respectively (Figure 3B); the corresponding values for week 52/EOT were 81.8%, 54.5%, and 30.9% of patients achieving PASI 75, PASI 90, and PASI 100 responses, respectively.

Safety

Among the 55 patients who enrolled and received at least 1 dose of tildrakizumab (safety population), 34 (61.8%) patients experienced a total of 85 TEAEs during the study (Table 2). No TEAEs were considered related to tildrakizumab treatment by the investigators. Psoriasis (n = 7 patients), hypertension (n = 5 patients), and dermatitis (n = 3 patients) were the most common TEAEs; all other TEAEs occurred in ≤2 patients each. The majority of TEAEs were reported as mild in severity (n = 63, 74.1%), 18 (21.2%) were reported as moderate, and 4 (4.7%) were reported as severe. A total of 4 serious TEAEs occurred in 4 (7.3%) of patients, including coronavirus disease 2019 (COVID-19)–related pneumonia, transitional cell carcinoma, ischemic stroke, and immunoglobulin A nephropathy reported in 1 patient each. Two (3.6%) patients experienced TEAEs, moderate transitional cell carcinoma and severe COVID-19–related pneumonia, that led to treatment discontinuation. There were no deaths during the study.

DISCUSSION

Tildrakizumab was effective at improving multiple measures of disease severity in patients with moderate-to-severe plaque psoriasis in the real-world setting of this open-label, Phase 4 clinical trial. Improvement was noted as early as week 4 (ie, after 1 dose) and maintained through week 64. Patients had significant decreases from baseline in BSA, sPGA, and BSA x sPGA through week 64 and significantly improved PASI scores from baseline through week 52. The real-world safety profile of tildrakizumab was consistent with observations in the clinical trials; >95% of TEAEs were mild or moderate in severity, and none were considered to be related to treatment.

The results of this study show that the efficacy and safety observed in the pivotal Phase 3 clinical trials of tildrakizumab in moderate-to-severe plaque psoriasis translate to real-world effectiveness. The PASI response rates observed here (PASI 75, 87.0%; PASI 90, 56.5%; PASI 100, 32.6%), for example, are consistent with the values observed at week 52 in patients in the reSURFACE 1 and reSURFACE 2 trials who were PASI 75 responders to tildrakizumab 100 mg at week 28 and continued receiving the same dose (observed cases analysis: PASI 75, 91.2%; PASI 90, 73.2%; PASI 100, 34.4%).[7,10]

The patients enrolled in this real-world study differed from the reSURFACE trial patients in several respects, suggesting that the effectiveness and safety of tildrakizumab are stable across differing subgroups of patients with moderate-to-severe plaque psoriasis in the US. The reSURFACE patients generally had more severe disease at baseline, with a mean percentage BSA affected of 29.7% to 34.2% compared with 14.5% in the Phase 4 study and a mean PASI score of 20.0 to 20.5 vs 11.6 in the current study.[7] The distribution of patients by sex and race also differed between this trial and the Phase 3 trials, likely due in part to this

study being conducted at 2 sites in the US compared with the large, multinational reSURFACE trials.

Other prospective real-world studies have demonstrated rapid and sustained improvement of disease severity with tildrakizumab treatment based on PASI, BSA, or PGA scores.[16-19] Results of an interim analysis of the TILOT study, an ongoing 3-year, prospective, multicenter study of tildrakizumab for the treatment of moderate-to-severe psoriasis in Germany, were similar to the current study, with 78.7% and 57.7% of patients achieving PASI 75 and 90 responses, respectively, at week 52.[19] Results of previously published prospective real-world studies were also comparable to the overall safety and tolerability profile of tildrakizumab observed in the reSURFACE 1 and reSURFACE 2 clinical trials.[16-19] The consistency of the Phase 4 effectiveness and safety results with other real-world studies and the Phase 3 trials support the use of tildrakizumab to treat patients with moderate-to-severe plaque psoriasis.

This study has several limitations that may affect the applicability and interpretation of the results. First, the small sample size (N=55) may restrict the identification of uncommon AEs. Additionally, given the open-label and single-arm design of this study, the interpretation of improvement in disease severity under treatment may have been confounded by the natural history of the underlying plaque psoriasis. The prolonged nature of improved disease severity measured by multiple assessments, however, argues against this scenario. Finally, as no data imputation took place in this study, and results were based only on observed data, our results may be biased toward either greater or lesser treatment effectiveness than would be seen with a more rigorous analysis.

CONCLUSION

Tildrakizumab treatment resulted in improvement across multiple measures of disease severity in adult patients with moderate-to-severe plaque psoriasis in the real-world setting. The reported AEs were consistent with the previously established safety profile of tildrakizumab.

DISCLOSURES

JH has been a speaker, adviser, and consultant for AbbVie, Amgen, Boehringer Ingelheim, Celgene, Eli Lilly, Janssen, and Novartis; an adviser for Galderma, Mayne Pharma, Regeneron Pharmaceuticals, and Sanofi; an adviser and consultant for Ortho Dermatologics; and a speaker and adviser for Sun Pharma, Incyte, LEO Pharma, and Beiersdorf. JGV reports nothing to disclose. TB has received research funding from AbbVie, Celgene, Galderma, Janssen, Eli Lilly, Pfizer, Regeneron Pharmaceuticals, and Sun Pharma. and has served as an adviser for AbbVie, Boehringer Ingelheim, Bristol Myers Squibb, Pfizer, LEO Pharma, and Novartis. JK has served as an adviser for AbbVie, Amgen, Celgene, EPI Health, Janssen, LEO Pharma, Eli Lilly, Novartis, Ortho Dermatologics, Pfizer, Regeneron Pharmaceuticals, Sanofi, Sun Pharma, and UCB. JM, RG, and TF are employees of Sun Pharmaceutical Industries, Inc. NB is an adviser, consultant, and investigator for AbbVie, Almirall, Arcutis Biotherapeutics, Advanced Derm Solutions, Amytrx, Beiersdorf, Biofrontera, Boehringer Ingelheim, Bristol Myers Squibb, Cara Therapeutics, Castle, Dermavant Sciences, Eli Lilly, Ferndale, Foamix, Galderma, Incyte, ISDIN, Johnson & Johnson, La Roche-Posay, LEO Pharma, Mindera, Novartis, Ortho Dermatologics, Pfizer, Procter & Gamble, Regeneron Pharmaceuticals, Sanofi, Sun Pharma, Skinfix, Soligenix, Verrica Pharmaceuticals, and Zerigo Health.

Funding: The study was funded by Sun Pharma. Medical writing and editorial support were provided by Nitish Chaudhari, PhD, of AlphaBioCom, a Red Nucleus company, and funded by Sun Pharma.

Data Availability Statement

Data and other documents will be made available after publication, with no end date, to anyone who submits a reasonable request to the study sponsor.

ACKNOWLEDGMENT

The authors express gratitude and appreciation to the trial patients and staff who participated in these trials. We thank Tonya Smoot, PhD, of Therapeutics, Inc., for statistical support. The authors acknowledge medical writing and editorial support provided by Nitish Chaudhari, PhD, of AlphaBioCom, a Red Nucleus company, and funded by Sun Pharma.

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doi:10.36849/JDD.8160

August 2024 619 Volume 23 • Issue 8

ORIGINAL ARTICLE

Journal of Drugs in Dermatology

Benefits Over Five Years of Ixekizumab Treatment in Patients With Psoriasis Involving Challenging Body Areas

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ABSTRACT

Background: Psoriasis involving challenging body areas, such as the scalp, face, palmoplantar surfaces, or nails, can be challenging to treat and negatively affects patient outcomes.

Objective: To assess clear responses and cumulative clinical benefits over 5 years of ixekizumab treatment of moderate-to-severe plaque psoriasis in patients with and without baseline involvement of challenging body areas.

Methods: This *post hoc* analysis included patients treated with ixekizumab in the UNCOVER-3 trial. We assessed PASI100 responses through the week (W) 264 and cumulative clinical benefits at W264 (calculated as least-squares mean of the percentage of maximum area under the curve for PASI100 and PASI% improvement and expressed as cumulative clearance days). Statistical differences were calculated via ANCOVA.

Results: A total of 385 patients were analyzed: 349 with scalp involvement, 152 with facial involvement, 96 with palmoplantar involvement, and 229 with nail involvement. Proportions of patients achieving PASI100 were numerically similar between patients with and without scalp and nail involvement. More patients without facial and palmoplantar involvement achieved PASI100 at W60 (only palmoplantar), W108, W156, W204, and W264 (only palmoplantar). At W264, cumulative clinical benefits for PASI100 and PASI% improvement were high and similar in both patient groups, with and without challenging body areas. A significant difference (P=0.006) was only observed for PASI% improvement between patients with and without nail involvement.

Conclusion: For most efficacy measures, patients treated with ixekizumab over 5 years achieved similar clear responses and cumulative clinical benefits regardless of baseline involvement of challenging body areas.

J Drugs Dermatol. 2024;23(8):619-625. doi:10.36849/JDD.8160

INTRODUCTION

Challenging body areas include the scalp, face, palmoplantar surfaces (ie, palms and soles), nails, intertriginous areas, and genitalia. Psoriasis involving challenging body areas is associated with a higher degree of disease severity,[1,2] and can be challenging to treat.[3,4] Additionally, psoriasis involving challenging body areas carries a significant burden on patients, disproportionately impacts their quality of life,[5-7] and has worse patient-reported outcomes.[6] Furthermore, patients with psoriasis involving the face have a higher risk of psoriasis in the scalp, genitalia, and nails; similarly, patients with psoriasis involving the soles have a higher risk of palms and nail involvement.[8]

Ixekizumab, a high-affinity monoclonal antibody that selectively targets interleukin (IL)-17A,[9] is an approved treatment for moderate-to-severe plaque psoriasis. In the phase III randomized UNCOVER-3 trial (NCT01646177), ixekizumab demonstrated sustained efficacy and consistent safety through 264 weeks in patients with moderate-to-severe plaque psoriasis.[10] Ixekizumab has also been shown to confer cumulative clinical benefits, calculated as area under the curve (AUC) and expressed as total days of benefit realized by patients.[11] In the phase IV randomized head-to-head IXORA-R trial (NCT03573323), patients with moderate-to-severe plaque psoriasis treated for 24 weeks with ixekizumab vs the IL-23 inhibitor guselkumab experienced greater cumulative clinical benefits, with more days at 90% and 100% improvement from baseline in the Psoriasis Area and Severity Index (PASI90 and PASI100, respectively), more days when psoriasis did not impact the quality of life, and more itch-free days.[12] In a meta-analysis of phase III data of approved treatments of moderate-to-severe psoriasis, ixekizumab showed the greatest cumulative benefits for complete clearance (ie, PASI 100) responses compared to all the other analyzed biologics.[13,14] However, long-term data on clear responses and cumulative clinical benefits are not well documented for patients with psoriasis involving challenging body areas.

To address this knowledge gap, clear responses, and cumulative clinical benefits were assessed over 5 years of ixekizumab treatment in patients with moderate-to-severe plaque psoriasis with and without involvement of challenging body areas at baseline.

MATERIALS AND METHODS

Study Design and Patient Population

This *post hoc* analysis included patients with moderate-to-severe plaque psoriasis who participated in the UNCOVER-3 trial (NCT01646177) and who were treated with the approved dose of ixekizumab through 264 weeks (ie, 5 years). The study design of this randomized, double-blinded, placebo-controlled, active-controlled, multicenter, phase III trial has been previously described.[10,15]

Briefly, patients (N=1,346) were randomly assigned in a 1:2:2:2 ratio to receive subcutaneous injections of placebo, 50 mg etanercept twice weekly, or 160 mg ixekizumab starting dose followed by 80 mg ixekizumab every 2 weeks (Q2W) or every 4 weeks (Q4W) for the induction dosing period (from week 0 to week 12). At week 12, all patients entered a long-term extension period during which they received ixekizumab Q4W through week 264; after week 60, patients could escalate dosing to ixekizumab Q2W at the patient's and investigator's discretion. An institutional review board reviewed and approved study protocols and informed consent forms at each participating site. The study was conducted according to the principles of the Declaration of Helsinki and the Council for International Organizations of Medical Sciences International Ethical Guidelines.

Outcome and Statistical Analysis

This *post hoc* analysis was conducted on the ixekizumab intent-to-treat population of the UNCOVER-3 trial, including patients treated with ixekizumab Q2W or Q4W during the induction dosing period and the long-term extension period, excluding data from visits with titrated Q2W long-term dosing. Response rates for complete skin clearance were assessed from week 2 to 264 and presented as the proportions of patients achieving 100% improvement from baseline in their PASI score (PASI100). The PASI is a tool that assesses the extent of body-surface involvement in 4 anatomical regions (head, trunk, arms, and legs) and the severity of desquamation (scaling), erythema, and plaque induration/infiltration (thickness) in each region, yielding an overall score of 0 for no psoriasis to 72 for the most severe disease.[16] Data presented are observed. Cumulative clinical benefits of ixekizumab treatment were determined at week 264 as the least-squares mean of the percentage of maximum AUC for PASI100 and PASI% improvement and expressed as cumulative clearance days. Missing data in categorical variables were imputed with non-responder imputation (NRI); missing data in continuous variables were imputed with modified baseline observation carried forward (mBOCF). Statistical differences for cumulative clearance days between patients with and without involvement of each challenging special body area at baseline were calculated via analysis of covariance (ANCOVA), adjusted for baseline PASI and pooled sites.

RESULTS

A total of 385 patients were analyzed from the UNCOVER-3 population treated with ixekizumab: 349 with scalp involvement vs 36 without, 152 with facial involvement (1 patient was not assessed for facial PsO) vs 232 without, 96 with palmoplantar involvement vs 289 without, 229 with nail involvement vs 156 without (Table 1). Specifically, the proportions of patients with challenging body areas at baseline were 90.6% with scalp involvement, 39.6% with facial involvement, 24.9% with palmoplantar involvement, and 59.5% with nail involvement.

Baseline Characteristics

Demographics and baseline characteristics were rather balanced across the subgroups of patients with baseline involvement of challenging body areas and were consistent with the overall patient population (Table 1). At baseline, the overall patient population had a mean (standard deviation [SD]) age of 45.6 (13.1) years, included mainly males (n=254, 66.0%), was slightly obese with a body mass index of 30.2 kg/m^2 (7.1), had psoriasis symptoms for 17.8 (12.2) years, had a psoriasis involvement of 28.0% of the body surface area, and some patients had concurrent psoriatic arthritis (n=77, 20.0%). Most patients were

TABLE 1.

Demographics and Baseline Characteristics of the Overall Population and of the Patients With Baseline Involvement of Challenging Body Areas

	Overall N=385[a]	Scalp N=349	Facial N=152	Palmoplantar N=96	Nail N=229
Age, years	45.6 (13.1)	45.0 (13.1)	42.4 (13.3)	47.9 (13.7)	45.5 (12.5)
Male, n (%)	254 (66.0)	232 (66.5)	103 (67.8)	67 (69.8)	163 (71.2)
BMI, kg/m^2	30.2 (7.1)	30.2 (7.3)	30.4 (7.5)	29.7 (6.0)	30.3 (7.4)
BMI category, n (%)					
Underweight (<18.5 kg/m^2)	0	0	0	0	0
Normal (≥18.5-<25 kg/m^2)	87 (22.7)	79 (22.6)	32 (21.1)	25 (26.0)	54 (23.6)
Overweight (≥25-<30 kg/m^2)	137 (35.7)	126 (36.1)	61 (40.1)	30 (31.3)	79 (34.5)
Obese (≥30-<40 kg/m^2)	123 (32.0)	110 (31.5)	43 (28.3)	35 (36.5)	71 (31.0)
Extreme obese (≥40 kg/m^2)	37 (9.6)	34 (9.7)	16 (10.5)	6 (6.3)	25 (10.9)
Scalp PsO, n (%)	349 (90.6)	349 (100)	148 (97.4)	86 (89.6)	208 (90.8)
Facial PsO[b], n (%)	152 (39.6)	148 (42.4)	152 (100)	43 (44.8)	99 (43.2)
Palmoplantar PsO, n (%)	96 (24.9)	86 (24.6)	43 (28.3)	96 (100)	26 (16.7)
Nail PsO, n (%)	229 (59.5)	208 (59.6)	99 (65.1)	70 (72.9)	229 (100)
Duration of PsO symptoms, years	17.8 (12.2)	17.6 (12.0)	16.1 (10.7)	17.3 (12.5)	18.8 (11.9)
Psoriatic arthritis, n (%)	77 (20.0)	66 (18.9)	32 (21.1)	26 (27.1)	26 (16.7)
Previous biologic therapy, n (%)	58 (15.1)	53 (15.2)	22 (14.5)	14 (14.6)	32 (14.0)
PASI	20.7 (8.2)	20.9 (8.3)	22.1 (9.2)	23.4 (10.1)	21.7 (8.8)
DLQI	12.4 (6.9)	12.4 (6.9)	12.2 (7.0)	13.4 (7.1)	12.1 (6.9)
sPGA score	3.5 (0.6)	3.5 (0.6)	3.6 (0.7)	3.7 (0.7)	3.6 (0.6)
% BSA involvement	28.0 (17.3)	28.2 (17.3)	28.1 (16.8)	30.1 (20.2)	29.7 (19.4)

Data are presented as mean (standard deviation) unless stated otherwise.
[a]Patients with involvement in multiple challenging body areas were included in each of the body areas for which they had involvement.
[b]N=384 (1 patient was not assessed for facial PsO involvement).
BMI, body mass index. BSA, body surface area. DLQI, Dermatology Life Quality Index. N, number of patients in the analysis population. n, number of patients in the specified category. PASI, Psoriasis Area, and Severity Index. PsO, psoriasis. sPGA, static Physician Global Assessment.

biologic-naïve (n=327, 84.9%), with a few patients (n=58, 15.1%) having previously used biologic therapies. Mean (SD) scores for PASI, static Physician Global Assessment (sPGA), and Dermatology Life Quality Index (DLQI) were 20.7 (8.2), 3.5 (0.6), and 12.4 (6.9), respectively.

Response Rates

Proportions of patients achieving PASI100 were numerically similar between patients with and without scalp and nail involvement at baseline (Figure 1). Conversely, more patients without vs with facial involvement achieved PASI100 at week 108 (65.1% vs 47.1%), at week 156 (69.2% vs 56.5%), and at week 204 (69.4% vs 62.7%), and more patients without vs with palmoplantar involvement achieved PASI100 at week 60 (68.8% vs 47.6%), at week 108 (63.8% vs 39.7%), at week 156 (71.1% vs 43.1%), at week 204 (71.3% vs 52.1%), and at week 264 (70.6% vs 51.2%).

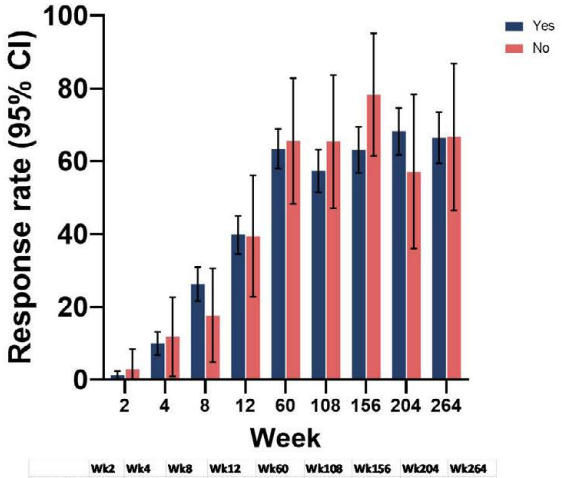
Cumulative Clinical Benefits

At week 264 (ie, 1848 days), cumulative clinical benefits for PASI100 and PASI% improvement were high in both patient groups, with no statistically significant differences (P>0.05) in most instances between patients with and without baseline involvement of challenging body areas (Figure 2).

Specifically, the cumulative days of clinical benefits for PASI100 in patients with vs without baseline involvement of challenging body areas were, respectively: scalp involvement 821.8 days vs 724.6 days (difference 12%, P=0.442), facial involvement 844.8 days vs 793.2 days (difference 6%, P=0.515), palmoplantar involvement 693.5 days vs 853.6 days (difference -23%, P=0.098), and nail involvement 845.0 days vs 765.5 days (difference 9%, P=0.382).

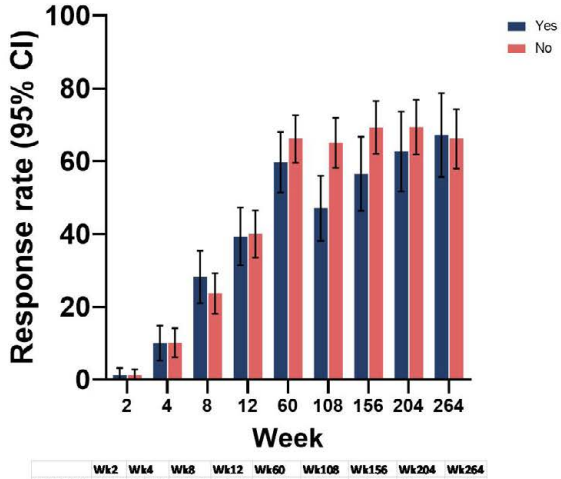
FIGURE 1. Response rates for PASI100 from week 2 to 264 in patients with and without baseline involvement of challenging body areas. (A) Scalp involvement, (B) Facial involvement, (C) Palmoplantar involvement, and (D) Nail involvement.

(A)



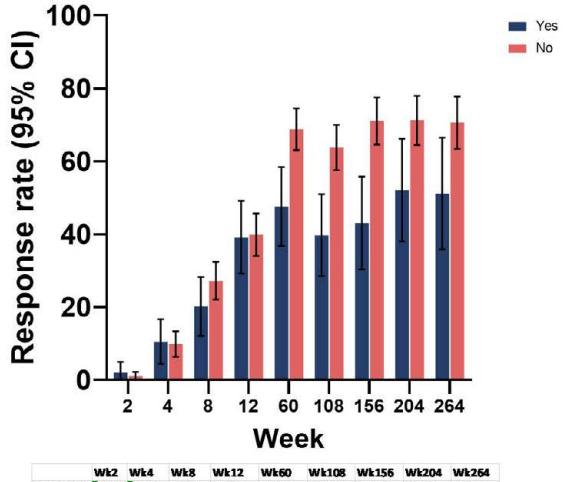
	Wk2	Wk4	Wk8	Wk12	Wk60	Wk108	Wk156	Wk204	Wk264
YES (n/Nx)	4/345	34/343	89/339	132/332	194/306	160/279	142/225	137/201	115/173
NO (n/Nx)	1/35	4/34	6/34	13/33	19/29	17/26	18/23	12/21	14/21

(B)



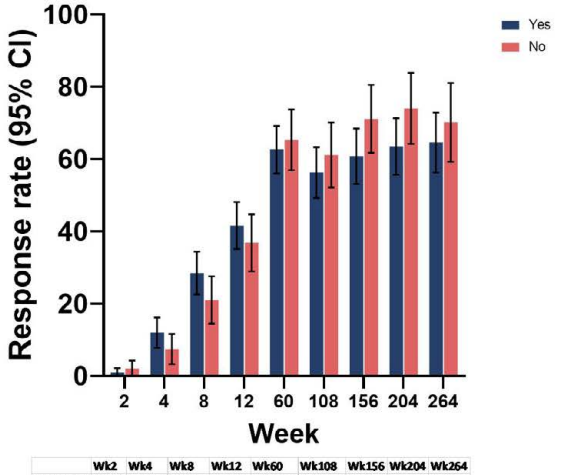
	Wk2	Wk4	Wk8	Wk12	Wk60	Wk108	Wk156	Wk204	Wk264
YES (n/Nx)	2/150	15/150	42/149	57/145	80/134	56/119	52/92	47/75	43/64
NO (n/Nx)	3/230	23/227	53/224	88/220	133/201	121/186	108/156	102/147	86/130

(C)



	Wk2	Wk4	Wk8	Wk12	Wk60	Wk108	Wk156	Wk204	Wk264
YES (n/Nx)	2/95	10/95	19/94	36/92	39/82	29/73	25/58	25/48	21/41
NO (n/Nx)	3/285	28/282	76/279	109/273	174/253	148/232	135/190	124/174	108/153

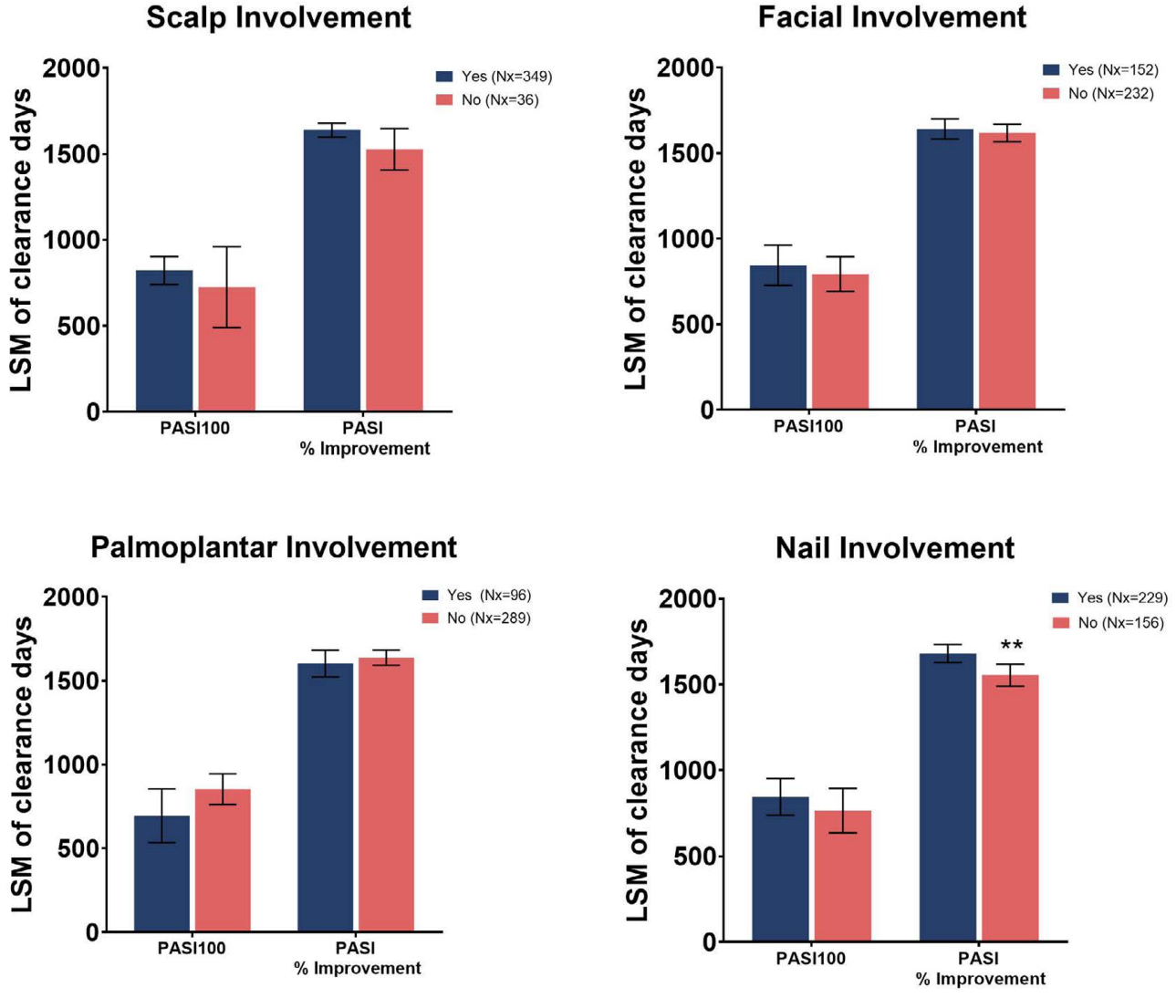
(D)



	Wk2	Wk4	Wk8	Wk12	Wk60	Wk108	Wk156	Wk204	Wk264
YES (n/Nx)	2/228	27/227	64/225	92/221	132/211	108/192	96/158	92/145	82/127
NO (n/Nx)	3/152	11/150	31/148	53/144	81/124	69/113	64/90	57/77	47/67

Data are observed with 95% CI.
CI, confidence interval. n, number of patients in the specified category. Nx, number of patients with non-missing data in each category. PASI100, 100% improvement from baseline in Psoriasis Area and Severity Index. Wk, week.

FIGURE 2. Cumulative clinical benefits for PASI100 and PASI% improvement at week 264 in patients with and without baseline involvement of challenging body areas. (A) Scalp involvement, (B) Facial involvement, (C) Palmoplantar involvement, and (D) Nail involvement.



Data are LSM with 95% CI; ANCOVA P<0.01 (**); NRI was used for PASI100; mBOCF was used for PASI% improvement.
ANCOVA, analysis of covariance. CI, confidence interval. LSM, least-squares mean. mBOCF, modified baseline observation carried forward. Nx, number of patients with non-missing values. NRI, non-responder imputation. PASI100, 100% improvement from baseline in the Psoriasis Area and Severity Index.

Similarly, the cumulative days of clinical benefits for PASI% improvement in patients with vs without baseline involvement of challenging body areas were, respectively: scalp involvement 1,639.0 days vs 1,526.6 days (difference 7%, *P*=0.079), facial involvement 1,641.7 days vs 1,618.1 days (difference 1%, *P*=0.553), palmoplantar involvement 1,601.7 days vs 1,637.3 days (difference -2%, *P*=0.463), and nail involvement 1,679.8 days vs 1,554.1 days (difference 7%, significant *P*=0.006).

DISCUSSION

Psoriasis involving challenging body areas is associated with higher degrees of disease severity and often influences treatment decisions.[1,2] According to recent guidelines derived from the International Psoriasis Council, patients with psoriasis involving challenging body areas are categorized as candidates for systemic therapy even when the total involved body surface area is less than 10%.[1] Additionally, psoriasis involving

challenging body areas can be challenging to treat[3,4] and carries a higher burden and impact on patients' quality of life.[5-7]

When evaluating treatment efficacy, assessing the cumulative clinical benefits is an intuitive and instructive method that captures the magnitude and speed of onset, as well as the maintenance of clinical response over time.[14] Here, we found out that, in most cases, clearance responses and cumulative clinical benefits over 5 years of ixekizumab treatment were similar in patients with and without involvement of challenging body areas at baseline. Clear responses and cumulative clinical benefits were high in patients with and without individual challenging body areas, as well as among different challenging body areas. These findings imply that, regardless of baseline involvement of challenging body areas, patients treated with ixekizumab can achieve similar clear responses and cumulative clinical benefits over long periods of time. In the analyzed population, baseline involvement of challenging body areas was 1.7 to 2.6 times higher than observed in a large prospective United States cohort, including 3,825 patients with psoriasis, where Merola et al identified the following prevalence for psoriasis phenotypes: scalp 52%, palmoplantar 14%, and nail 23%.[17]

One limitation of this analysis is that data were evaluated post hoc. We also focused only on patients with involvement of the scalp, face, palms, soles, and nails, excluding other challenging body areas (eg, intertriginous areas and genitalia), which were not specifically evaluated in the UNCOVER-3 trial. Another limitation included the small sample size of patients without scalp involvement at baseline (N=36); thus, these results should be interpreted with caution.

In conclusion, in most instances, patients with moderate-to-severe plaque psoriasis treated with ixekizumab over 5 years achieved similar clearance responses and cumulative clinical benefits regardless of baseline involvement of the analyzed challenging body areas: scalp, face, palms, soles, and nails.

DISCLOSURES

AB Gottlieb has received honoraria as an advisory board member; and serves as a consultant for Amgen, AnaptysBio, Avotres Therapeutics, Boehringer Ingelheim, Bristol-Myers Squibb, Dice Therapeutics, Eli Lilly and Company, Janssen, Highlights Therapeutic, Novartis, Sanofi, UCB, and Xbiotech; and has received research/educational grants from AnaptysBio, Bristol-Myers Squibb, Immunotherapeutics AG, Janssen, MoonLake. Novartis, and UCB Pharma (all paid to Mount Sinai School of Medicine). A. Armstrong has served as a consultant, speaker, and/or investigator for AbbVie, Almirall, Arcutis, ASLAN Pharmaceuticals, Boehringer Ingelheim, Bristol Myers Squibb, Dermavant, Dermira, Eli Lilly and Company, EPI Health, Incyte Corporation, Janssen, LEO Pharma, Modernizing Medicine, Nimbus Therapeutics, Novartis, Ortho Dermatologics, PAREXEL, Pfizer, Regeneron, Sanofi, Sun Pharma, and UCB Pharma. A. Blauvelt has served as a speaker (received honoraria) for AbbVie, Eli Lilly and Company, Pfizer, and UCB, served as a scientific adviser (received honoraria) for AbbVie, Abcentra, Aclaris, Affibody, Aligos, Almirall, Alumis, Amgen, AnaptysBio, Apogee, Arcutis, Arena, Aslan, Athenex, Bluefin Biomedicine, Boehringer Ingelheim, Bristol Myers Squibb, Cara Therapeutics, CTI BioPharma, Dermavant, EcoR1, Eli Lilly and Company, Escient, Evelo, Evommune, Forte, Galderma, HighlightII Pharma, Incyte, InnoventBio, Janssen, Landos, Leo, Lipidio, Microbion, Merck, Monte Rosa Therapeutics, Nektar, Novartis, Overtone Therapeutics, Paragon, Pfizer, Q32 Bio, Rani, Rapt, Regeneron, Sanofi Genzyme, Spherix Global Insights, Sun Pharma, Takeda, TLL Pharmaceutical, TrialSpark, UCB Pharma, Union, Ventyx, Vibliome, and Xencor, and has acted as a clinical study investigator (institution has received clinical study funds) for AbbVie, Acelyrin, Allakos, Almirall, Alumis, Amgen, Arcutis, Athenex, Boehringer Ingelheim, Bristol-Myers Squibb, Concert, Dermavant, Eli Lilly and Company, Evelo, Evommune, Galderma, Incyte, Janssen, Leo, Merck, Novartis, Pfizer, Regeneron, Sanofi, Sun Pharma, UCB Pharma, and Ventyx. C. E. M. Griffiths has received honoraria and/or research funds from: AbbVie, Almirall, Anaptysbio, Boehringer Ingelheim, Bristol Meyers Squibb, Celgene, Eli Lilly and Company, Evelo Biosciences, Inmagene, Kyowa Kirin, Janssen, Novartis, ONO Pharmaceuticals, Pfizer, Sun Pharma, and UCB Pharma. A. Pinter has served as an investigator and/or speaker and/or advisor for AbbVie, Almirall Hermal, Amgen, Biogen, BioNTech, BMS, Boehringer Ingelheim, Celgene, Eli Lilly and Company, Galderma, GlaxoSmithKline, Hexal, Janssen, LEO Pharma, MC2 Therapeutics, Medac, Merck Serono, Merck Sharp & Dohme, Mitsubishi Tanabe Pharma, Novartis, Pascoe Natural Healthcare, Pfizer, Regeneron, Roche, Sandoz, Sanofi, Schering-Plough, Tigercat Pharma, UCB Pharma, and Zuellig Pharma. M. Gooderham has been an investigator, speaker, and/or advisor for AbbVie, Akros Pharma, Amgen, Arcutis, Aristea Therapeutics, Bausch Health, Bristol Myers Squibb, Boehringer Ingelheim, Celgene, Dermavant, Dermira, Eli Lilly and Company, Galderma, GlaxoSmithKline, Incyte Corporation, Janssen, Kyowa Kirin, LEO Pharma, MedImmune, Merck, MoonLake, Nimbus Therapeutics, Novartis, Pfizer, Regeneron, Reistone Biopharma, Roche, Sanofi, Sun Pharma, and UCB Pharma. M. Lomaga has been an advisory board member and/or investigator for AbbVie, Amgen, Dermavant, Dermira, Devonian Health Group, Eli Lilly and Company, Janssen, LEO Pharma, Merck, Novartis, Pfizer, Sun Pharma, UCB Pharma, and Valeant Pharmaceuticals. R. T. Burge is a shareholder of Eli Lilly and Company and is an employee of Eli Lilly and Company and the University of Cincinnati, Cincinnati, OH, USA. BW Konicek and K. See are employees and shareholders of Eli Lilly and Company. M. Feely McDonald is associate staff at Mount Sinai Hospital, Mount Sinai West, and Mount Sinai Morningside; is a current employee and shareholder of Eli Lilly and Company; has received consulting,

travel, or speaker fees from American Academy of Dermatology, Aerolase, Castle Biosciences, CeraVe-L'Oréal, DREAM USA, Galderma Aesthetics, Glow Recipe, La Roche-Posay - L'Oréal, Revian, Sonoma Pharmaceuticals, Sun Pharma, and Suneva Medical. M. McKean-Matthews is an employee of Syneos Health. T. Mabuchi has received lecture fees from Maruho Co., Ltd., Janssen Pharmaceutical K.K., Celgene Corporation, Kyowa Kirin Co., Ltd., Eli Lilly Japan K.K., Taiho Pharmaceutical Co., Ltd., and UCB Japan Co., Ltd. and has received manuscript fees from Kyowa Kirin Co., Ltd., Torii Pharmaceutical Co., Ltd., and Eli Lilly Japan K.K. and has received clinical research funding from Janssen Pharmaceutical K.K., Eli Lilly Japan K.K., AbbVie GK., Bristol-Myers Squibb Company, and Parexel and has received research/educational grants from Maruho Co., Ltd., Kyowa Kirin Co., Ltd., Torii Pharmaceutical Co., Ltd., Eli Lilly Japan K.K., Taiho Pharmaceutical Co., Ltd., LEO Pharma K.K., and Sun Pharma Japan Ltd.

Funding sources: This study was funded by Eli Lilly and Company, which contributed to study design, data collection, data analysis, data interpretation, manuscript preparation, and publication decisions.

Data availability statement: Eli Lilly and Company provides access to all individual participant data collected during the trial, after anonymization, except for pharmacokinetic or genetic data. Data are available for request 6 months after the indication studied has been approved in the United States and European Union and after primary publication acceptance, whichever is later. No expiration date for data requests is currently set once data are made available. Access is provided after a proposal has been approved by an independent review committee identified for this purpose and after receipt of a signed data-sharing agreement. Data and documents, including the study protocol, statistical analysis plan, clinical study report, and blank, or annotated case report forms, will be provided in a secure data-sharing environment. For details on submitting a request, see the instructions provided at www.vivli.org.
Clinical trial number: NCT01646177

ACKNOWLEDGMENT

Eli Lilly and Company would like to thank the clinical trial participants and their caregivers, without whom this work would not be possible. The authors would like to acknowledge Elsa Inman PhD and Marcus Ngantcha MS employees of Eli Lilly and Company, for medical and statistical review, respectively. Medical writing assistance was provided by Elisa Di Carlo PhD, an employee of Eli Lilly and Company.

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doi:10.36849/JDD.7612R1

August 2024 626 Volume 23 • Issue 8

ORIGINAL ARTICLE

Journal of Drugs in Dermatology

Palmoplantar Pustulosis: Therapy Update

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ABSTRACT

Palmoplantar pustulosis is a variant of psoriasis and a chronic skin disorder in which pruritic pustular eruptions appear on the palms and soles. It is thought to arise from a variety of genetic and environmental factors, is limited in prevalence, and has proven quite difficult to treat. The symptoms it inflicts on those affected are quite debilitating and the treatment landscape is constantly evolving, thus emphasizing the need for updates of the literature as time passes. Current treatments include topical agents, oral therapies, and phototherapy, amongst other treatments. In this systemic review, we explore newer literature from 2015 to 2022 on various treatment regimens for palmoplantar pustulosis.

J Drugs Dermatol. 2024;23(8):626-631. doi:10.36849/JDD.doi:10.36849/JDD.7612R1

INTRODUCTION

Palmoplantar pustulosis (PPP), also known as palmoplantar pustular psoriasis, is a chronic skin disorder in which pruritic pustular eruptions appear on the palms and soles. It is thought to be a variant of psoriasis.[1] Despite its localized involvement, PPP is chronic and has been shown to reduce quality of life. The disorder affects all ages, with females more likely to be affected than males.[2]

Although its exact cause is unknown, PPP is thought to be multifactorial and caused by a combination of genetic and environmental factors. Although the PSORS1 locus that is associated with psoriasis vulgaris is not associated with PPP, variations of IL-19, IL-20, and IL-24 genes may be associated with both psoriasis and PPP. Human leukocyte antigen (HLA) Cw6, CARD14, and ATG16L1 genes have also been associated with the conditions. Additionally, environmental triggers, such as smoking, stress, drugs, infection, sweating, repetitive trauma, and irritants play a role in the pathophysiology.[3] The underlying immunologic mechanism is hypothesized to involve inflammation that destroys the acrosyringium, the primary site of sterile pustule formation. Mast cells, lymphocytes, neutrophils, and eosinophils contribute to this process. Furthermore, chemotactic factors such as IL-8 and IL-17 related cytokines, tumor necrosis factor alpha, interferon-gamma, and complement pathway activation are also thought to be involved. Genetic factors and environmental triggers spur an immune cascade, leading to immune cell proliferation and the formation of lesions on the skin.[4]

PPP lesions often induce itching, pain, and breakdown of the skin barrier that can be exacerbated in flares of disease. On examination, the skin contains thick, hyperkeratotic plaques and/or sterile pustules that can be symmetric, erythematous, and scaly. Although most patients only exhibit lesions on the palms and soles, nail changes, including pitting and ridging, can be observed in approximately 60% of cases. More extensive nail changes are found in Acrodermatitis continua of Hallopeau, a relatively rare subset of pustular psoriasis that classically affects the nail apparatus, giving rise to its clinical description as "nails floating away on a lake of pus." This condition can coexist with PPP and is important to recognize because it can lead to anonychia or osteolysis of the distal phalanges if left untreated. A subset of patients with PPP may also have arthritic symptoms. Associated disorders include pustulotic arthro-osteitis (PAO) and Synovitis, Acne, Pustulosis, Hyperostosis, and Osteitis syndrome (SAPHO).[5] The presentation of PPP may mimic numerous other conditions such as dyshidrotic eczema, contact dermatitis, pityriasis rubra pilaris, and tinea pedis and manuum. As a result, a thorough history and physical examination are warranted, though additional workup is also

necessary. A potassium hydroxide preparation and bacterial culture are often performed to rule out fungal and bacterial infections. While biopsies on acral surfaces are challenging, they can help diagnose PPP where biopsies will show histologic findings consistent with epidermal changes, spongiosis, and accumulations of various cell types, such as lymphocytes, eosinophils, mast cells, and neutrophils.[6]

PPP is limited in prevalence and has proven to be quite difficult to treat. The condition is chronic and stems from an interplay of genetic and environmental factors. Furthermore, high-quality data on the treatment of PPP is sparse. Nonetheless, the research landscape is constantly evolving, thus emphasizing the need for an updated review of the literature.

Aim

In this comprehensive review, we discuss the evaluation of PPP and the mechanism of action, efficacy, and safety profiles of existing, alternative, and upcoming therapeutics for this debilitating condition.

MATERIALS AND METHODS

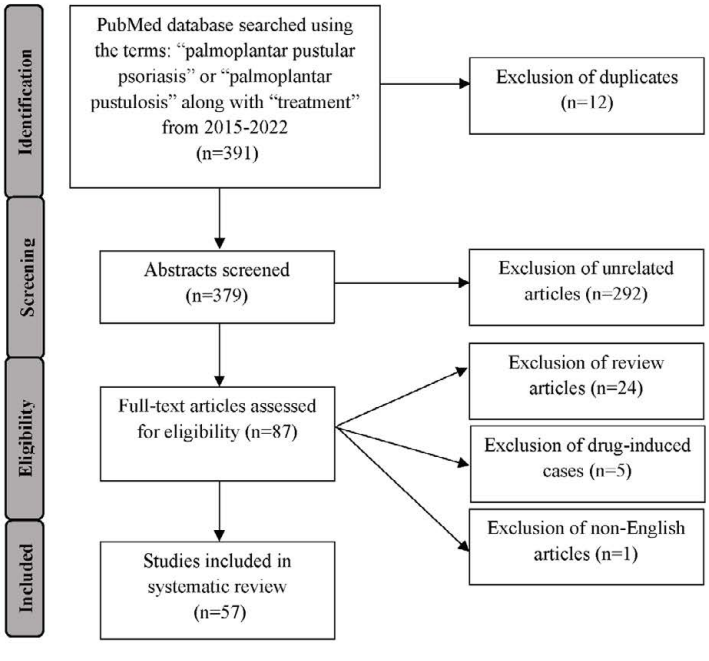
Published articles assessing the efficacy and safety of therapeutic agents for the treatment of PPP were identified through the healthcare journal database, Pubmed. The keywords "palmoplantar pustular psoriasis" or "palmoplantar pustulosis" and "treatment" were queried from 2015 to 2022. Initially, articles were screened by their titles and abstracts. Those that appeared to meet the inclusion criteria were assessed further, by full text, and were included in the analysis if subjects were diagnosed with PPP based on the assessment by the authors of each publication and if subjects were being treated for their condition with medication or alternative therapy. Incorporation of efficacy and safety of the attempted treatment were required for the inclusion criteria. Articles that were duplicates of others, review articles, or drug-induced cases of PPP were excluded.

Efficacy outcomes were analyzed by a reduction in the PPP Area and Severity Index (PPPASI), the PPP Physician Global Assessment (PPPGA), the Dermatology Life Quality Index score (DLQI), or another standardized criterion of characterizing symptom reduction.

RESULTS

An initial search on Pubmed for the keywords PPPASI, PPPGA, and DLQI, identified 391 published articles. After excluding duplicates, 379 articles were screened by title and abstract, leaving 87 articles for full-text review. Following a full-text review, 57 articles were ultimately included in our analysis (Figure 1). Ten articles evaluated apremilast, a phosphodiesterase 4 inhibitor (PDE-4i), eighteen articles studied biologics, four examined Janus kinase inhibitors (JAKi), five studied retinoids, four evaluated disease-modifying antirheumatic drugs (DMARDs), 1 examined topical agents, 3 studied alternative treatments, and 5 assessed phototherapies.

FIGURE 1. Flow chart illustrating the literature search using Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRIMA) guidelines.



Topical Agents

Topical corticosteroids have historically been considered first-line therapeutic options for PPP with limited cutaneous involvement. Their minimal side effect profile and easy application make them a viable option. A 2016 randomized left-right comparison study evaluated the efficacy of combination therapy, maxacalcitol ointment (vitamin D derivate), and betamethasone butyrate propionate (BBP) ointment, versus monotherapy with BBP in 27 PPP patients for 8 weeks. Patients treated with combination therapy had a significantly greater improvement (P<0.05) in symptoms than those treated with monotherapy, demonstrating the efficacy of combination corticosteroids and vitamin D treatment in PPP.[7]

Biologics

Multiple biologics have been used to treat PPP with varying degrees of success. However, it is important to note that notwithstanding various publications citing treatment success, the development of PPP in patients being treated with biologics (with the majority of TNF-alpha inhibitors) for other indications has regularly been reported.[8] This, combined with the fact that various case reports show differing efficacy of various biologics, makes the data sometimes difficult to interpret. There are several larger studies, including randomized controlled trials, that have studied the use of biologics for PPP and have somewhat helped to elucidate the confusion.

IL-36 Receptor Blockers

Spesolimab functions by blocking interleukin-36 (IL-36), which is thought to play a role in the pathogenesis of PPP in some patients. A 2022 cohort study comparing blood and skin samples from patients with PPP showed that spesolimab was able to modulate dysregulated molecular pathways common to PPP.[9] In a 2021 multicenter randomized control trial, 31.6% of patients treated with 300 mg or 900 mg of spesolimab achieved PPPASI50 vs 23.8% treated with placebo. Although these results were below the primary endpoint, individuals treated with spesolimab improved at a faster rate.[10] Given current evidence, further studies on subsets of PPP patients who may respond better to spesolimab may be warranted given the clear pathophysiologic link between IL-36 and forms of PPP.

IL-17 Inhibitors

IL-17 inhibitors have become a mainstay of treatment of psoriasis over the past several years, as IL-17 is the effector cytokine that leads to hyperproliferation of keratinocytes seen in psoriasis. These medications have shown efficacy in both skin and joint disease in psoriasis and have proven to be important therapies for patients with psoriasis and PPP, specifically.

Dramatic improvement of psoriatic lesions was noted within 2 weeks of administering brodalumab after failure of adalimumab and secukinumab in a case report in 2019.[11] Another case series showed no improvement or moderate improvement in four patients with severe PPP.[12]

Ixekizumab has also shown some efficacy in patients with PPP. A case report in 2022 showed successful treatment of PPP with ixekizumab after the patient had failed numerous other therapies, suggesting that ixzekizumab can be a potential treatment option for recalcitrant PPP.[13]

The only prespecified trial on PPP among the IL-17 inhibitors is one that was performed with secukinumab. A 2019 phase 3b multicenter, randomized, double-blind, placebo-controlled, parallel-group study compared treatment with 300 mg secukinumab to 150 mg secukinumab and placebo in subjects with moderate-to-severe PPP over 1 year. The primary endpoint of achieving a 75% reduction in PPPASI at week 16 was not met, the significance level was set at 2.5%, but patients treated with secukinumab 300 mg still showed benefit in PPPASI 75 responses (numerically higher than placebo; 26.6% for secukinumab vs 14.1% for placebo, P=0.0411) as well as improved quality of life.[14]

Interestingly, a prospective cohort study of both palmoplantar psoriasis and PPP showed reasonable efficacy for secukinumab, with over half of the patients in the PPP cohort achieving a PPPGA of clear or almost clear.[15] These results were similar across the palmoplantar psoriasis and PPP groups, though it should be noted that there was a relatively small number of patients with PPP (n=17) and a relatively high attrition rate. Notwithstanding, this study highlighted some interesting findings, such as the need to treat for longer periods of time to achieve treatment success, which may help guide our understanding of further trial data in PPP. Multiple case reports showed improvement of PPP symptoms with minimal side effects in patients with refractory disease treated with 300 mg secukinumab.[16-17]

IL-23 Inhibitors

Various studies have identified the IL-23/IL-17 axis as the primary signaling pathway leading to the abnormal growth of keratinocytes and the production of psoriatic skin.[18] As a result, interleukin-23 (IL-23) inhibitors are efficacious in the treatment of psoriasis and its subtypes. They generally require less frequent dosing than IL-17 inhibitors and have demonstrated a favorable side effect profile without carrying a risk of exacerbating inflammatory bowel disease (IBD). Guselkumab, tildrakizumab, and risankizumab all operate by similar mechanisms.

Tildrakizumab is a humanized IgG1 kappa monoclonal antibody that targets the p19 subunit of IL-23. It is approved for plaque psoriasis, but little evidence exists for its use in difficult-to-treat areas such as palmoplantar surfaces. A 2021 case report showed efficacy with tildrakizumab in a patient with PPP refractory to other therapies.[19]

Another IL-23 inhibitor targeting the p19 subunit of IL-23 is risankizumab. A case report in 2021 showed significant improvement in recalcitrant PPP and concomitant ichthyosis vulgaris in a 60-year-old female patient after 16 weeks of therapy.[20]

Guselkumab also binds the p19 subunit of IL-23 and is effective in treating psoriasis and its subtypes. There is more data available for guselkumab in treating PPP as compared to other IL-23 inhibitors. A 24-week randomized clinical trial in 2018, including 49 patients with PPP treated with either 200 mg subcutaneous guselkumab or placebo, found significant improvements in the experimental group at both week 16 and week 24. No safety concerns were identified and improvements in skin-related outcomes were visible as early as after the second dose, or four weeks into treatment.[21] Another randomized phase 3 study echoed these results, with roughly 79% sustained improvement in PPPASI scores from baseline to week 84 in those treated with guselkumab vs placebo.[22] A 2020 case report describing a patient with PPP refractory to both cyclosporine and apremilast demonstrated complete clearance of symptoms with guselkumab.[23]

IL-12/23 Inhibitor

Ustekinumab binds to the p40 subunit of IL-12 and IL-23 to prevent its interaction with its receptor. A 2016 case series of nine patients with PPP treated with ustekinumab demonstrated an average of 71.6% improvement in the PPPASI in 24 weeks. No adverse effects were observed aside from local injection site reactions and mild infections.[24] A similar response was cited in another article in 2018.[25] Additionally, 1 case described a patient with PPP who initially failed treatment with a standard dose of ustekinumab, but achieved a response with the use of higher doses following a new diagnosis of inflammatory bowel disease.2[6]

Apremilast

Apremilast is a low-molecular-weight oral phosphodiesterase 4 (PDE-4) inhibitor that has been used to treat psoriasis and various psoriasis subtypes. By blocking PDE-4, apremilast upregulates intracellular cyclic adenosine monophosphate (cAMP) and subsequently suppresses interleukin-8 (IL-8), which is thought to be involved in the pathogenesis of PPP. As a result, pustule formation is decreased, reducing symptoms and disease burden.[27] Several case reports and cohort studies of up to 300 patients support the role of apremilast in treating PPP with limited adverse effects.[28-33] A number of these studies demonstrated PPPASI reductions of greater than 50%. Two case reports even showed the efficacy of using apremilast in cases of PPP refractory to topical steroids, UVA, and multiple systemic therapies.[34-35] One larger open-label trial (APLANTUS) of 21 patients, reported that palmoplantar pustulosis PASI decreased by a median of 57.1% and pustule lesion counts decreased significantly as well, with over three-quarters of patients exceeding 50% decrease in pustule counts by week 20. DLQI scores decreased substantially, from a median of 8.5 at baseline to 2.0 at week 20.[36] Notable side effects of apremilast include GI side effects, namely diarrhea, headache, and photosensitivity.

JAK Inhibitors

Janus kinase (JAK) inhibitors have been approved for a variety of immune-mediated chronic conditions. By blocking a wider array of proinflammatory cytokines, the mixed inflammatory picture of PPP can be more effectively treated. Tofacitinib inhibits JAK1, JAK2, and JAK3, thus blocking a cascade of cytokines (eg, IL-23, IL-22, and IFN-gamma) involved in the pathogenesis of the disease. A case report in 2019 demonstrated the efficacy of tofacitinib in treating PPP and recalcitrant PPP within a 6-month period.[37] Many of the patients studied also had a history of psoriatic arthritis.[38] Another study found that tofacitinib was beneficial in spurring T-cell differentiation in a patient with PPP and concomitant rheumatoid arthritis.[39] A single-arm, prospective pilot study in 2021 studied the efficacy of tofacitinib in the treatment of PPP in 13 female Asian patients with SAPHO. Significant improvements in both PPASI (P<0.001) and DLQI scores (P<0.001) were observed at week 12 and no serious adverse events were reported.[40]

DMARDs

Disease-modifying antirheumatic drugs (DMARDs) are a group of medications commonly used to treat types of inflammatory arthritis via the suppression of the body's overactive immune response. There are a variety of DMARDs with various mechanisms. Anakinra is a biologic medication originally derived from *E. coli* and acts as an interleukin-1 (IL-1) receptor antagonist that binds to and blocks the effects of IL-1. A randomized, double-blind, multicenter, two-staged, adaptive placebo-controlled trial was performed in 2020. Despite postulations that anakinra would deliver therapeutic benefit in PPP, no evidence of the superiority of anakinra over placebo was found. The mean difference in PPASI was greater in the anakinra subgroup, but this difference was not significant.[41-43]

Methotrexate is a folate antagonist that interferes with DNA synthesis and repair, thus inhibiting the formation of major cell lineages involved in the inflammatory cascade of immune disease. One case report of beta-blocker-induced PPP was treated successfully with low-dose methotrexate (2.5 mg weekly) after failure of acitretin. It should be noted that despite beta-blocker discontinuation, the patient's PPP improved minimally, therefore treatment with other systemics was attempted and the natural history of PPP in this case could not be ascertained.[44]

Retinoids

Alitretinoin is an orally administered systemic retinoid often used for acne and occasionally for recalcitrant eczema. It is

a retinoid X receptor and retinoid A receptor agonist that is thought to inhibit sebaceous gland function and keratinization. A double-blind, placebo-controlled trial was performed to evaluate alitretinoin 30 mg daily vs placebo for treatment-resistant PPP using PPPASI after 24 weeks. No significant differences were found between both groups, which differed from other case studies and series conducted in the past that found significant efficacy of isotretinoin for PPP. The authors attribute these differences to differences in study design.[45-46] Another retinoid, acitretin, was not tolerated well in a case series of 2 patients with PPP refractory to topical treatments. However, isotretinoin monotherapy worked remarkably in 1 of the 2 patients.[47] It should be noted that, while out of the scope of the present systematic review, previous studies have proven the efficacy of acitretin in treating PPP.[48-49]

Phototherapy

Phototherapy has emerged as a safe and effective therapeutic agent for various dermatologic conditions. Targeted modalities, such as topical psoralen-ultraviolet phototherapy (tPUVA), paint psoralen-ultraviolet phototherapy (pPUVA), ultraviolet A1 (UVA1), and narrowband ultraviolet B (UVB), have proven to be efficacious forms of phototherapy. Various case studies, cohort studies, and randomized prospective studies have demonstrated the efficacy of narrowband UVB for PPP with minimal side effects. These studies largely demonstrated the delivery of UVB at a 308 nm wavelength using an XeCl excimer laser.[50-52] UVA1 was also successful in reducing PPPASI scores in a pilot prospective study in 2016 with minimal adverse effects including burning, pruritus, and hyperpigmentation.[53] When compared with one another, UVA1 was found to be more effective than narrowband UVB, with a greater reduction in the PPPASI score (P<0.05).[54]

Alternative Treatment

Given the difficult treatment landscape of PPP, alternative treatments have been devised over the years to help patients with recalcitrant disease and shorten the course to remission. A few case studies have described the use of radiation therapy for PPP. A 2019 study with 2 patients demonstrated significant improvement in PPP within 3 to 4 treatments of radiation, with 1 patient experiencing recurrence after cessation of radiation.[55] Brachytherapy, or radiation therapy in which radiation is placed inside or next to the area requiring treatment, was also shown to be efficacious in a case of treatment-resistant PPP.[56]

Six patients with PPP treated with an oral rinse containing ozone nanobubble water were found to achieve complete remission within 3 to 4 months of continuous use. The rinse's mechanism of action involves the destruction of oral bacteria that are thought to be involved in the formation of PPP lesions.[57]

CONCLUSION

While no medications are FDA-approved for PPP, a variety of therapeutic options have shown promise. Topical medications are often useful for patients with limited disease involvement, but they may not sustain their response long-term. Systemic treatments, including biologics, JAK inhibitors, DMARDs, and retinoids can be effective in achieving PPP clearance, but not without side effects. Phototherapy, while efficacious, may pose other challenges of accessibility and cost.

The multifactorial origin and often chronic nature of PPP makes it challenging to treat. Despite hundreds of studies and trials, a treatment schematic for PPP has yet to be established. While the efficacy of these treatments has been studied in clinical trials, some studies are limited by small sample sizes, varying methodologies and endpoints, and short follow-up periods. Direct comparisons between different treatment options are often not found, further complicating the ability of clinicians to choose the appropriate treatment for their patients. Additional large, double-blinded, placebo-controlled randomized trials and studies with direct comparisons between treatments will be helpful for healthcare providers and patients in making informed decisions about PPP treatments.

DISCLOSURES

Dr Wu is or has been an investigator, consultant, or speaker for AbbVie, Almirall, Amgen, Arcutis, Aristea Therapeutics, Bausch Health, Boehringer Ingelheim, Bristol-Myers Squibb, Dermavant, DermTech, Dr. Reddy's Laboratories, Eli Lilly, EPI Health, Galderma, Janssen, LEO Pharma, Mindera, Novartis, Pfizer, Regeneron, Samsung Bioepis, Sanofi Genzyme, Solius, Sun Pharmaceutical, UCB, and Zerigo Health. Dr Han is or has been an investigator, consultant/advisor, or speaker for AbbVie, Athenex, Boehringer Ingelheim, Bond Avillion, Bristol-Myers Squibb, Celgene Corporation, Dermavant, Eli Lilly, Janssen, LEO Pharma, MC2, Novartis, Ortho Dermatologics, PellePharm, Pfizer, Regeneron, Sanofi/Genzyme, SUN Pharmaceutical, and UCB. Authors Devjani, Smith, and Collier have no conflicts of interest to declare.

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doi:10.36849/JDD.7486R1

August 2024 632 Volume 23 • Issue 8

ORIGINAL ARTICLE

Journal of Drugs in Dermatology

Real-Life Effectiveness and Safety of Guselkumab in Moderate-to-Severe Plaque Psoriasis: A 104-Week Retrospective Single-Center Study

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ABSTRACT

Background: Guselkumab is a monoclonal antibody approved for treating moderate-to-severe plaque psoriasis. Long-term data on the effectiveness and safety of guselkumab in a real-world setting are still limited.

Materials and Methods: We conducted a 104-week monocentric retrospective study on 102 psoriasis patients, all treated with guselkumab for at least 16 weeks. At each visit, we used the Psoriasis Area and Severity Index (PASI): effectiveness endpoints were the percentages of patients achieving 75%/90%/100% (PASI 75/90/100) improvement in PASI compared with baseline. The Kaplan-Meier curve was used to assess the drug survival.

Results: At week 16, PASI 90 and PASI 100 were achieved by 49.02% and 32.35% of patients. At week 52, PASI 90 and PASI 100 were achieved by 71.58% and 55.79% of patients. After 2 years, PASI 90 and PASI 100 were achieved by 79.63% and 61.11% of patients. Obese and overweight patients had comparable PASI 90 and PASI 100 responses throughout the study. At week 104, no significant differences were observed between bio-naïve and bio-experienced patients regarding all effectiveness endpoints. No significant safety signals were reported in our study. After 24 months, 91.57% of our cohort was still on treatment with guselkumab.

Conclusion: Our findings, although limited by the study's retrospective nature, confirm that guselkumab is a safe and effective therapeutic option for a "real-life" cohort of patients with psoriasis.

J Drugs Dermatol. 2024;23(8):632-639. doi:10.36849/JDD.7486R1

INTRODUCTION

Psoriasis is a chronic inflammatory disorder affecting up to 2% to 4% of the general population worldwide.[1] The treatment of moderate-to-severe psoriasis includes systemic disease-modifying antirheumatic drugs (DMARDs), such as cyclosporin, methotrexate, and acitretin. Biological drugs are the treatment of choice when there is a contraindication or an incomplete/inadequate response to conventional DMARDs.[2,3] Biologics are engineered monoclonal antibodies that block specific cytokines or receptors critical to psoriatic inflammation.[4]

Guselkumab is the first human IgG1λ monoclonal antibody that inhibits IL-23 selectively,[5] and it has been evaluated in 3 phase 3 clinical trials (VOYAGE1, VOYAGE2, and NAVIGATE), showing superior efficacy compared with placebo, adalimumab, and ustekinumab.[6-8] Some real-life experiences have also been published, with results in line with those observed in clinical trials.

The study reported here is a monocentric retrospective real-world experience including 102 patients, all followed for at least 16 weeks. Out of this cohort, 95 completed 52 weeks of treatment, while 54 of them reached at least 2 years of follow-up.

MATERIALS AND METHODS

We conducted a non-interventional retrospective single-center study by analyzing our psoriasis database records between 2019 and 2022. One hundred and two patients were included, and all received at least 16 weeks of treatment. Patient eligibility for guselkumab treatment was assessed following the Italian adaptation of EuroGuiDerm guidelines.[3] Before starting guselkumab, all patients underwent screening for tuberculosis, HIV, and viral hepatitis.[3] Each patient received guselkumab 100 mg at week 0 and week 4, and then every 8 weeks, according to the summary of product characteristics.[9]

Patient demographics and other characteristics, including comorbidities, previous biological treatments, and the Psoriasis Area and Severity Index (PASI) score at each visit, were retrieved from the electronic medical records. At week 16, week 52, and week 104, the percentages of patients achieving an improvement of 75%, 90%, and 100% in PASI (PASI 75/90/100), compared with baseline PASI, were registered. An additional endpoint was the percentage of patients achieving an absolute PASI≤2, following the Italian adaptation of EuroGuiDerm guidelines.[3]

The potential occurrence of any adverse events (AEs) was recorded at each visit, including serious AEs and AEs leading to discontinuation.

Because of the study's retrospective nature, it was not possible to retrieve missing data. Clinical scores of the last observation carried forward (LOCF) were analyzed for patients who skipped the scheduled dermatological visits.

Institutional Review Board (IRB) approval was not required for this study because none of the procedures deviated from routine practice. In addition, all patients provided written informed consent for retrospective analyses of data collected during clinical practice.

Statistical analysis was conducted following the intention-to-treat (ITT) principle. We used Stata/SE 17.0 software and Microsoft Excel for the analyses and tables.

Discrete parameters were described as count and percentage, while continuous data were presented using mean and standard deviation (SD). The proportions of patients achieving PASI 75/PASI 90/PASI 100 responses and an absolute PASI≤2 were examined in relation to body mass index (BMI) class, involvement of difficult areas, previous exposure to biologics, presence of psoriatic arthritis (PsA), and cardio-metabolic comorbidities (CMD). The categorical variables were analyzed using the Chi-square test and Exact Fisher's Test where needed. Regarding the continuous variables, the differences between the 2 groups were analyzed by the Student's t-test and the Mann-Whitney U test if the parametric test assumption was not met. The differences between more than 2 groups were tested with ANOVA or Kruskal-Wallis test if the distributions were not normal.

Drug survival analysis was performed using Kaplan-Meier estimates. Data were censored for patients still receiving treatment at the time of this study and for patients lost to follow-up. The event date was defined as the date when treatment was stopped by any cause.

Results were considered statistically significant when the probability value (*P*-value) was less than *P*=0.05.

RESULTS

One hundred and two patients were included in our study. Seventy were male (68.63%), and the mean age was 52.36 years (SD 13.79). The mean disease duration was 16.77 years (12.70). The mean BMI was 25.50 (4.67), and 21.57% of patients were obese. Nineteen patients (18.63%) had a diagnosis of PsA, and 48 (47.06%) had at least 1 CMD (arterial hypertension, obesity, hypercholesterolemia, cardiovascular diseases, type II diabetes mellitus). Four patients had serological evidence of viral hepatitis B, and 2 had a positive TB Quantiferon test. Fifty patients (49.02%) were previously treated with at least 1 other biological drug before receiving guselkumab. At least 1 difficult-to-treat area was involved in 77 patients (75.49%). Additional characteristics of our population are summarized in Table 1.

During the study period, mean PASI (mPASI) decreased from 11.17 (SD 7.39) at baseline to 1.72 (2.39) at week 16, 0.65 (1.31) after 1 year, and 0.59 (1.02) after 2 years (Figure 1). At week 16, PASI 75 was achieved by 69.61% of our patients, PASI 90 by 49.02%, and PASI 100 by 32.35%. An absolute PASI≤2 was observed in 74.51% of our population at week 16. Data on the effectiveness of guselkumab at week 52 were higher, as PASI 75 was reached by 95.79% of our patients, PASI 90 by 71.58%, and PASI 100 by 55.79%. At week 104, data were available for 54 patients: the percentages of PASI 75, PASI 90, and PASI 100 were 94.44%, 79.63%, and 61.11%, respectively. An absolute PASI≤2 was observed in 94.44% of patients at week 104 (Figure 1).

TABLE 1.

Characteristics of the 102 Patients Receiving Guselkumab	
Number of patients	102
Male	70/102 (68,63%)
Age (years)	52,36 SD 13,79
BMI	25,50 SD 4,67
Obese	22/102 (21,57%)
Disease duration (years)	16,77 SD 12,70
PsA	19/102 (18,63%)
Difficult-site involvement	77/102 (75,49%)
Cardiometabolic comorbidities	48/102 (47,06%)
Infectious diseases	6/102 (5,88%)
Bio-Experienced	50/102 (49,02%)
Previous biologic treatments	
Adalimumab	8/102 (7,84%)
Brodalumab	1/102 (0,98%)
Etanercept	3/102 (2,94%)
Infliximab	1/102 (0,98%)
Ixekizumab	4/102 (3.92%)
Secukinumab	11/102 (10,78%)
Ustekinumab	36/102 (35,29%)

BMI, body mass index; PsA, psoriatic arthritis; SD, standard deviation.

FIGURE 1. Effectiveness endpoints throughout the study period.

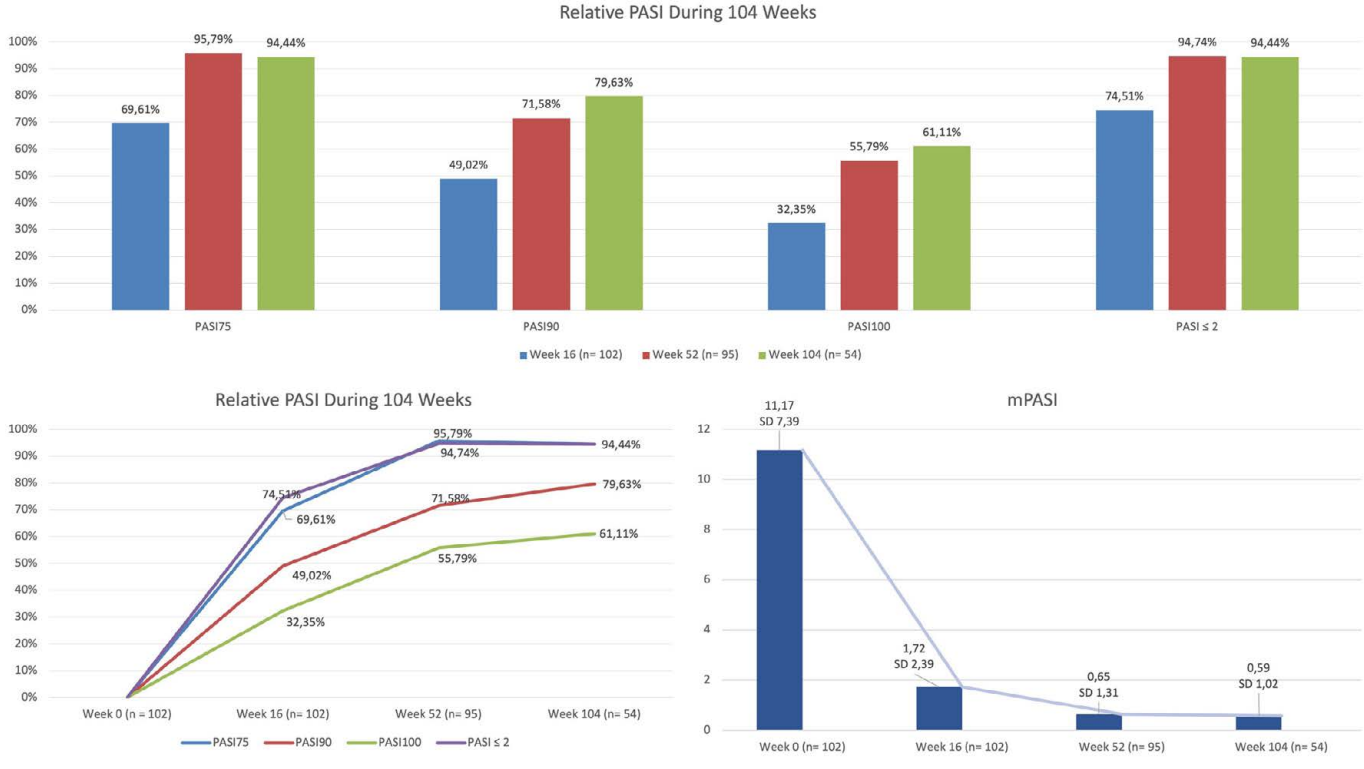


TABLE 2.

Percentages of Patients Achieving PASI 75/90/100 and ≤2 and Reduction in Mean PASI Score (mPASI) at Weeks 16/52/104 in Relation to BMI and Presence of Cardio-Metabolic Comorbidities).

	BMI ≥ 30	25 ≤ BMI <30	BMI < 25	*P*-value	CMD	Non-CMD	*P*-value
mPASI w0	12,79	12,09	9,87	0,444	12,15	10,3	0,208
mPASI w16	2,03	1,55	1,7	0,704	1,81	1,64	0,683
PASI 75 w16	15/22 (68,18%)	24/31 (77,42%)	32/49 (65,31%)	0,511	35/48 (72,92%)	36/54 (66,67%)	0,493
PASI 90 w16	12/22 (54,55%)	14/31 (45,16%)	24/49 (48,98%)	0,797	26/48 (54,17%)	24/54 (44,44%)	0,327
PASI 100 w16	8/22 (36,36%)	11/31 (35,48%)	14/49 (28,57%)	0,733	16/48 (33,33%)	17/54 (31,48%)	0,842
PASI ≤ 2 w16	12/22 (54,55%)	25/31 (80,65%)	39/49 (79,59%)	0,052	32/48 (66,67%)	44/54 (81,48%)	0,087
mPASI w52	1,33	0,36	0,51	0,585	0,80	0,51	0,278
PASI 75 w52	19/21 (90,48%)	30/30 (100%)	42/44 (95,45%)	0,246	43/45 (95,56%)	48/50 (96%)	0,914
PASI 90 w52	12/21 (57,14%)	25/30 (83,33%)	31/44 (70,45%)	0,121	33/45 (73,33%)	35/50 (70%)	0,719
PASI 100 w52	12/21 (57,14%)	18/30 (60%)	23/44 (52,27%)	0,798	27/45 (60%)	26/50 (52%)	0,433
PASI ≤ 2 w52	17/21 (80,95%)	30/30 (100%)	43/44 (97,73%)	0,005	41/45 (91,11%)	49/50 (98%)	0,133
mPASI w104	0,35	0,86	0,44	0,329	0,50	0,82	0,240
PASI 75 w104	10/10 (100%)	19/21 (90,48%)	22/23 (95,65%)	0,210	25/26 (96,15%)	26/28 (92,86%)	0,597
PASI 90 w104	9/10 (90%)	16/21 (76,19%)	18/23 (78,26%)	0,543	23/26 (88,46%)	20/28 (71,43%)	0,120
PASI 100 w104	8/10 (80%)	12/21 (57,14%)	13/23 (56,52%)	0,402	18/26 (69,23%)	15/28 (53,57%)	0,238
PASI ≤ 2 w104	10/10 (100%)	18/21 (85,71%)	23/23 (100%)	0,091	25/26 (96,15%)	26/28 (92,86%)	0,597

P-value *P*<0.05 indicated in bold.
BMI, body mass index; CMD, cardio-metabolic diseases; PASI, Psoriasis Area and Severity Index.

TABLE 3.

Percentages of Patients Achieving PASI 75/90/100 and ≤2 and Reduction in Mean PASI Score (mPASI) at Weeks 16/52/104 According to Previous Exposure to Biologics, Presence of PsA, and Involvement of Difficult-to-Treat Areas

	Bio-naïve	Bio-experienced	*P*-value	PsA	Non-PsA	*P*-value	≥ 1 Difficult Areas	No Difficult Areas	*P*-value
mPASI w0	13,34	8,92	0,002	8,38	11,81	0,032	10,68	12,7	0,113
mPASI w16	1,58	1,88	0,492	2,86	1,47	0,07	1,67	1,89	0,29
PASI 75 w16	40/52 (76,92%)	31/50 (62%)	0,101	9/19 (47,37%)	62/83 (74,7%)	0,019	51/77 (66,23%)	20/25 (80%)	0,194
PASI 90 w16	29/52 (55,77%)	21/50 (42%)	0,164	6/19 (31,58%)	44/83 (53,01%)	0,092	32/77 (41,56%)	18/25 (72%)	0,008
PASI 100 w16	18/52 (34,62%)	15/50 (30%)	0,618	4/19 (21,05%)	29/83 (34,94%)	0,243	23/77 (29,87%)	10/25 (40%)	0,347
PASI ≤ 2 w16	41/52 (78,85%)	35/50 (70%)	0,305	11/19 (57,89%)	65/83 (78,31%)	0,065	56/77 (72,23%)	20/25 (80%)	0,468
mPASI w52	0,38	0,93	0,038	0,89	0,59	0,097	0,74	0,35	0,029
PASI 75 w52	49/49 (100%)	42/46 (91,3%)	0,035	15/17 (88,24%)	76/78 (97,44%)	0,087	69/72 (95,83%)	22/23 (95,65%)	0,970
PASI 90 w52	42/49 (85,71%)	26/46 (56,52%)	0,002	9/17 (52,94%)	59/78 (75,64%)	0,060	49/72 (68,06%)	19/23 (82,61%)	0,178
PASI 100 w52	33/49 (67,35%)	20/46 (43,48%)	0,019	7/17 (41,18%)	46/78 (58,97%)	0,181	35/72 (48,61%)	18/23 (78,27%)	0,013
PASI ≤ 2 w52	48/49 (97,96%)	42/46 (91,3%)	0,147	16/17 (94,12%)	74/78 (94,87%)	0,900	68/72 (94,44%)	22/23 (95,65%)	0,821
mPASI w104	0,47	0,70	0,636	1,14	0,50	0,033	0,68	0,32	0,306
PASI 75 w104	27/27 (100%)	24/27 (88,89%)	0,075	6/7 (85,71%)	46/47 (95,74%)	0,280	37/40 (92,5%)	14/14 (100%)	0,292
PASI 90 w104	24/27 (88,89%)	19/27 (70,37%)	0,091	3/7 (42,86%)	40/47 (85,11%)	0,010	30/40 (75%)	13/14 (92,86%)	0,153
PASI 100 w104	17/27 (62,96%)	16/27 (59,26%)	0,780	2/7 (28,57%)	31/47 (65,96%)	0,058	23/40 (57,5%)	10/14 (71,43%)	0,358
PASI ≤ 2 w104	26/27 (96,3%)	25/27 (92,59%)	0,552	7/7 (100%)	44/47 (93,62%)	0,492	37/40 (92,5%)	14/14 (100%)	0,292

P-value *P*<0.05 indicated in bold.
PASI, Psoriasis Area and Severity Index; PsA, psoriatic arthritis.

FIGURE 2. Mean PASI (mPASI), relative PASI reduction (PASI 75/90/100), and percentages of patients reaching PASI≤2 at weeks 16, 52 and 104, according to previous exposure to biologics.

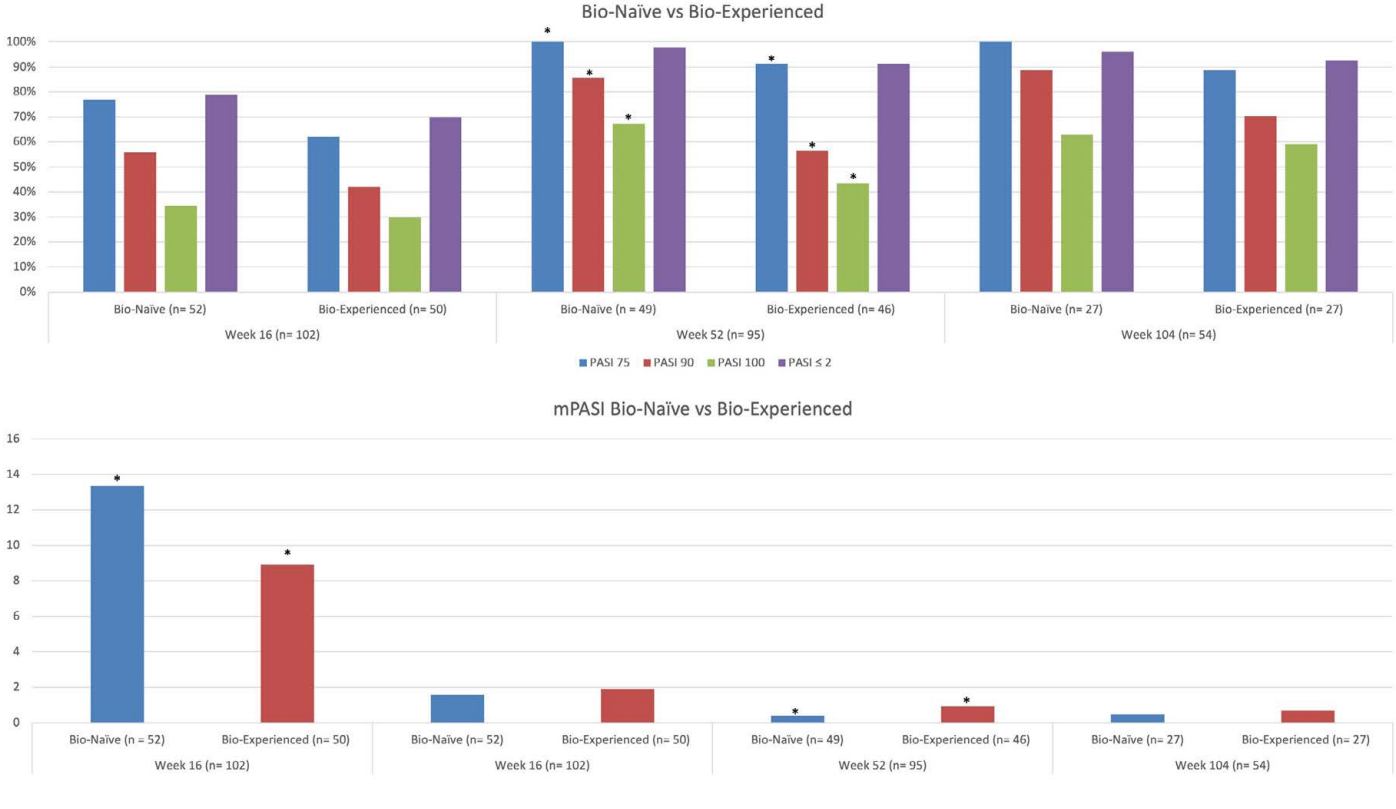


FIGURE 3. Mean PASI (mPASI), relative PASI reduction (PASI 75/90/100), and percentages of patients reaching PASI≤2 at weeks 16, 52, and 104, according to the concomitant presence of psoriatic arthritis (PsA).

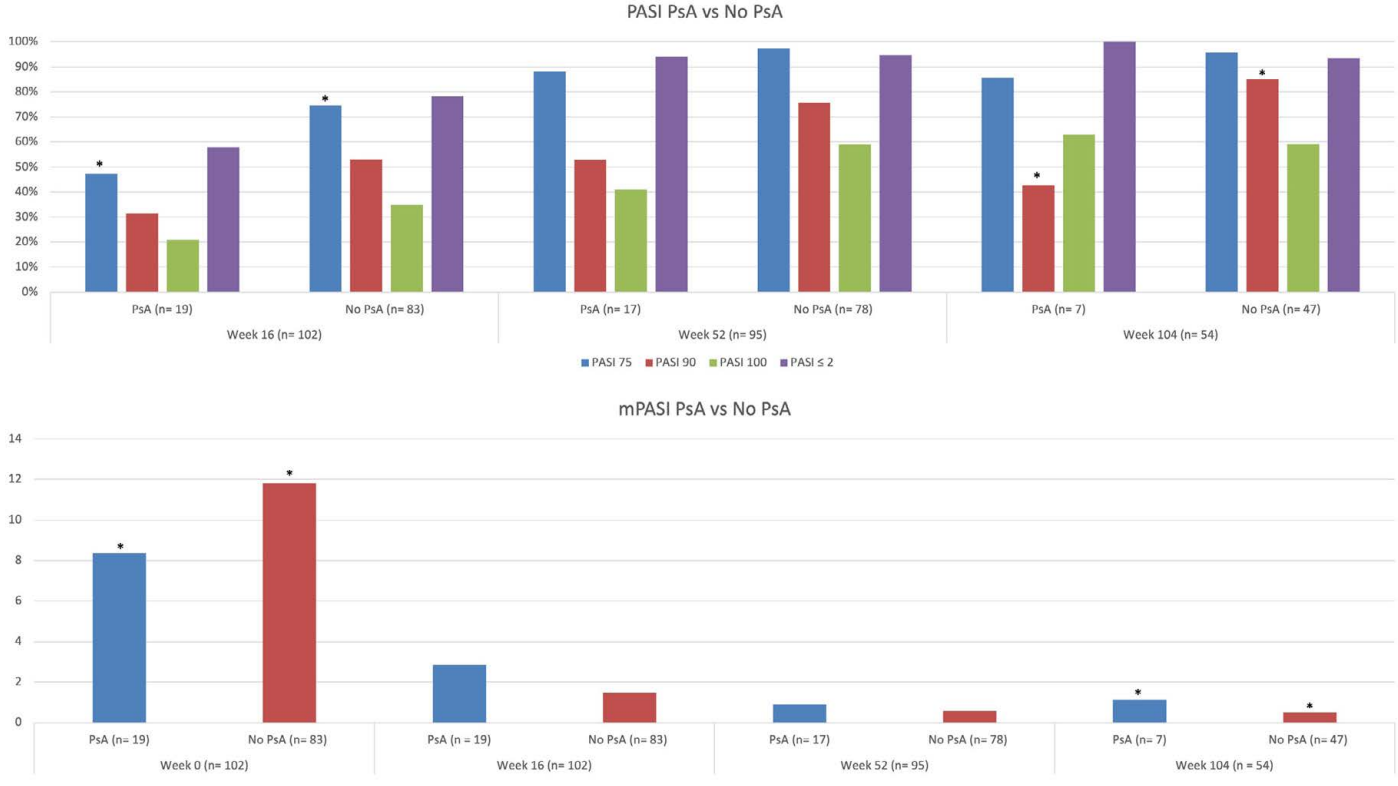
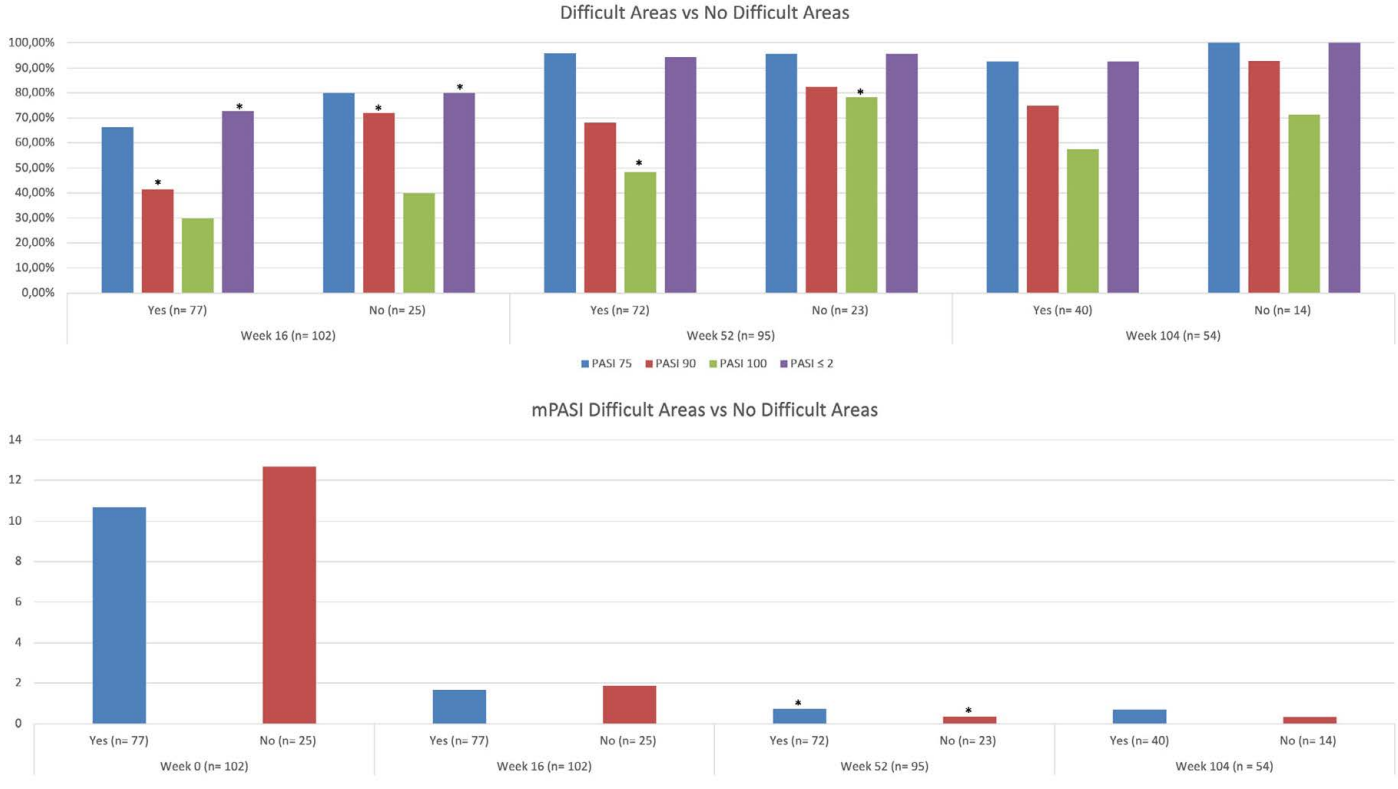


FIGURE 4. Mean PASI (mPASI), relative PASI reduction (PASI 75/90/100), and percentages of patients reaching PASI≤2 at weeks 16, 52 and 104, according to the involvement of difficult-to-treat areas.



The therapeutic response to guselkumab was analyzed based on different parameters (Tables 2 and 3). Regarding BMI (Table 2), patients were classified as obese if their BMI was ≥30, overweight if their BMI was <30 and ≥25, and normal-weight if their BMI was <25. PASI 75, PASI 90, and PASI 100 responses throughout the study period were comparable among the groups. However, at week 52 we observed significantly higher percentages of patients with an absolute PASI of 2 or less among the overweight and normal-weight patients, compared with obese (100% and 97.63% vs 80.95%, *P*=0.005).

We analyzed all effectiveness endpoints, also comparing patients with and without at least 1 CMD (Table 2). No statistically significant differences were observed throughout the study period regarding mean PASI, PASI 75/PASI 90/PASI 100 responses, and PASI≤2.

Regarding previous exposure to biologics (Table 3, Figure 2), as expected, mPASI at baseline was higher among bio-naïve patients (13.34 compared with 8.92, *P*=0.002). At week 16, we observed comparable responses regarding all effectiveness endpoints. However, at week 52, bio-naïve patients experienced better PASI 75/90/100 responses (100% vs 91.30%, *P*=0.035; 85.71% vs 56.52%, *P*=0.002; 67.35% vs 43.48%, *P*=0.019, respectively). No differences were observed in terms of absolute PASI≤2.

We also divided our patients into groups with concomitant diagnosis of PsA and without joint involvement (Table 3, Figure 3). At baseline, mPASI was lower in those with concomitant PsA (8.38 vs 11.81, *P*=0.032). At week 16, a significantly higher percentage of patients without PsA achieved PASI 75 (74.40% vs 47.37%, *P*=0.019), while at week 52 the 2 groups achieved comparable responses regarding all effectiveness endpoints. However, at week 104, a higher proportion of patients without PsA achieved PASI 90 (85.11% vs 42.86%, *P*=0.010).

In our cohort, despite comparable mPASI scores at baseline, more patients without involvement in difficult-to-treat areas achieved PASI 90 at week 16 (72% vs 41.56%, *P*=0.008) and PASI 100 at week 52 (78.27% vs 48.61%, *P*=0.013). However, at week 104, comparable responses were observed between the groups (Table 3, Figure 4).

We assessed the Kaplan-Meier curve to evaluate the maintenance of guselkumab after 2 years of treatment (Figure 5). At 24 months, 91.57% of our population [95% CI 83.81%-95.70%] was still on treatment. Nine patients discontinued guselkumab during the study period, and the most common reason for drug discontinuation was the loss of efficacy (6 patients).

Regarding the safety of guselkumab (Table 4), 2 patients discontinued the treatment because of a concomitant cancer diagnosis. They were diagnosed with lung and prostate cancer 4 months after starting guselkumab. The most commonly reported AE was nasopharyngitis (4 patients). Five patients were lost to follow-up after more than 52 weeks. No COVID-19-related hospitalizations or deaths were observed. Regarding the patients with positive tuberculosis (TB) Quantiferon test, there were no signs of reactivation at the pneumologic visits and annual thorax radiography. Although 4 patients had serological evidence of chronic hepatitis B, despite not receiving anti-viral therapy in accordance with the hepatologist, periodic hepatological visits and follow-up laboratory tests showed no signs of viral reactivation.

FIGURE 5. Kaplan-Meier survival curve.

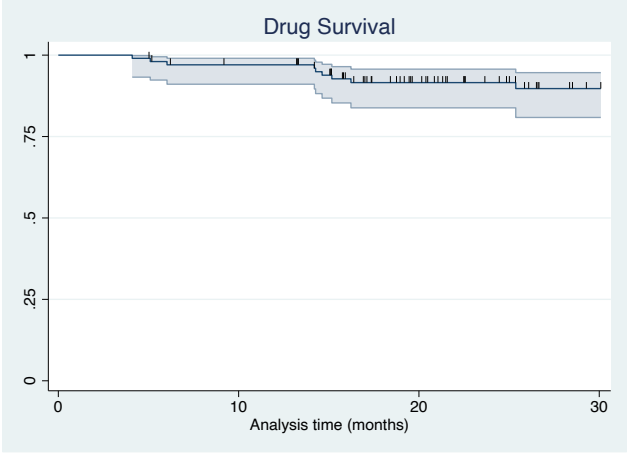


TABLE 4.

Adverse Events Experienced During the Treatment With Guselkumab	
Nasopharyngitis	4 (3,92%)
Upper respiratory tract infections	2 (1,96%)
Neoplasia	2 (1,96%)
Headache	1 (0,98%)
Reaction at injection site	1 (0,98%)
Total	10 (9,80%)
Severe AEs	0 (0%)
AEs leading to discontinuation	0 (0%)

DISCUSSION

Our data confirm the effectiveness of guselkumab in a real-life cohort with moderate-to-severe plaque psoriasis, with 54 patients completing at least 104 weeks of treatment.

Our patients, compared with those enrolled in the VOYAGE1 trial, were slightly older (mean age of 52.36 ± 13.79, compared with 43.9 ± 12.74), and had a comparable disease duration (16.77 ± 12.70 vs 17.9 ± 12.27).[6] In addition, the proportion of

bio-experienced patients was far more significant in our study compared with VOYAGE1 (49.02% compared with 21.6%). At baseline, mPASI was lower in our cohort because of the strict inclusion criteria of Phase 3 trials.[6]

Our data after 1 year of treatment are comparable to or slightly better than those observed in VOYAGE1, which reported a PASI 90 response in 76.3% of patients and PASI 100 in 47.4% (observed at week 48).[6] Data from a pooled analysis of VOYAGE1 and VOYAGE2 trials showed that 82.1% and 79.1% of the patients achieved a PASI 90 response at week 100 in the 2 studies, respectively.[10] Complete skin clearance was observed in 51.1% and 48.4% of the patients in the 2 trials at week 100. Our findings are consistent with those data, with a higher rate of PASI 100 responses (61.11% at week 104).[6-8]

Regarding BMI, we did not observe any significant difference in clinical responses, with comparable PASI 75/90/100 percentages throughout the study among the 3 groups. Our findings are consistent with those observed in other real-life studies on IL-23 inhibitors.[11,12] A post-hoc analysis of VOYAGE 1 and VOYAGE 2 identified a lower BMI among the predictors of a PASI 100 response at weeks 20 and 28. However, our data did not show significant differences at weeks 52 and 104 among the groups, supporting the effectiveness of guselkumab in obese and overweight patients.

In our study, CMDs had no impact on the therapeutic response to guselkumab. Our data showed no significant difference regarding all the effectiveness endpoints at weeks 16, 52, and 104. These findings support the role of anti-IL-23 drugs in patients with concomitant CMD, which is consistent with the results of pooled analyses from the open-label studies on tildrakizumab, where metabolic syndrome did not represent a predictor of lower response.[13]

As expected, mPASI was significantly lower at baseline in bio-experienced patients. At week 52, bio-naïve patients showed higher effectiveness regarding almost all effectiveness endpoints. However, after 104 weeks of treatment, no significant differences were observed between bio-naïve and bio-experienced patients, supporting the effectiveness of guselkumab in patients with previous exposure to biologics. Our data are consistent with recent real-life experiences, which have compared the effectiveness of guselkumab in bio-naïve and bio-experienced cohorts.[14,15]

Similarly, we did not observe substantial differences regarding the effectiveness of guselkumab between patients with and without concomitant PsA. The only exception was the higher rate of PASI 75 response at week 16 in patients with PsA, which could be explained by a lower mean PASI at baseline in this subgroup.

Despite a lower percentage of patients with psoriasis of difficult-to-treat areas achieving complete skin clearance at week 52 and week 104, no significant differences were observed. A secondary analysis of VOYAGE 1 and VOYAGE 2 showed that, compared with adalimumab, guselkumab was associated with a significant improvement in psoriasis on the scalp and palms/soles.[16]

Regarding drug survival, our study showed that 91.57% of our cohort was still on treatment after 24 months. Villaverde et al obtained similar results, with 94% of their patients continuing to receive guselkumab after 93.4 weeks.[17]

In our study, guselkumab showed no significant safety findings up to week 104 (Table 4) compared with clinical trials and other real-life studies.[6,7,15,18] The 2 patients who experienced a malignancy received the diagnosis after 16 weeks of treatment with guselkumab. Given the short period, no causal effect could be assessed between the drug and cancer. Moreover, a few reports on the safety profile of anti-IL-23 in patients with concomitant malignancies have been recently published.[19,20] It is worth noticing that none of the patients experienced severe forms of COVID-19 despite our study being conducted during the apex of the SARS-CoV-2 pandemic in Western Europe. Furthermore, none of the 4 patients with serological evidence of viral hepatitis B experienced viral reactivation during guselkumab, confirming other published data regarding the safety of anti-IL-23 drugs in this population.[21]

Our study has some limitations, the major being the retrospective nature, which does not allow retrieval of missing data. Other relevant limitations are the lack of a randomized controlled setting and the single-center nature of the study.

CONCLUSION

Our study confirmed the effectiveness of guselkumab throughout 104 weeks, with a high percentage of patients maintaining the treatment after 24 months. Our data demonstrate the high effectiveness of guselkumab in routine clinical practice in an extensive cohort of patients with moderate-to-severe plaque psoriasis, with a higher proportion of bio-experienced patients compared with clinical trials.

Compared with clinical trials, our study observed comparable PASI 90/100 responses at weeks 52 and 104, supporting the role of guselkumab as an effective therapeutic option in real-world conditions. No differences in PASI 90 and PASI 100 responses throughout the study were observed among BMI classes. Percentual PASI reduction and absolute mPASI were comparable in bio-naïve and bio-experienced patients at week 104. The long-term effectiveness of guselkumab was not influenced by concomitant CMD, presence of PsA, and involvement of difficult-to-treat areas, with comparable responses after 2 years of treatment.

Guselkumab showed no significant safety findings throughout the 104 weeks. Longer and larger prospective studies are needed to evaluate the safety and effectiveness of guselkumab further in a real-life setting.

DISCLOSURES

L. Gargiulo has been a consultant for Almirall. M. Valenti has been a consultant and/or speaker for Sanofi, Leo Pharma, Eli Lilly, and Boehringer. A. Costanzo has served as an advisory board member, and consultant and has received fees and speaker's honoraria or has participated in clinical trials for Abbvie, Almirall, Biogen, LEO Pharma, Lilly, Janssen, Novartis, Pfizer, Sanofi Genzyme, and UCB-Pharma. A. Narcisi has served on advisory boards, received honoraria for lectures, and received research grants from Almirall, Abbvie, Leo Pharma, Celgene, Eli Lilly, Janssen, Novartis, Sanofi-Genzyme, Amgen, and Boehringer Ingelheim. The other authors have nothing to disclose.

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doi:10.36849/JDD.7550

August 2024 640 Volume 23 • Issue 8

ORIGINAL ARTICLE

Journal of Drugs in Dermatology

The Hidden Costs of Psoriasis: A Population-Based Study Evaluating How Psoriasis Severity Impacts Work Absenteeism

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ABSTRACT

Background: Psoriasis patients experience physical and emotional burdens, which may lead to work-related productivity loss. This loss carries professional and financial repercussions. It is unknown whether the extent of psoriasis affects work absenteeism.
Objective: This study aims to compare work absenteeism between employed adults with mild vs moderate-to-severe psoriasis.
Methods: A national, cross-sectional study using the 2009 to 2019 Medical Expenditure Panel Survey evaluated 5,209,956 (weighted) adults aged ≥ 22 years. Work absenteeism was compared between adults with mild (4,521,687 weighted) and moderate-to-severe psoriasis (688,269 weighted).
Results: Work absenteeism, as measured by the average number of episodes per year that someone was absent from work for at least a half day, was significantly higher in patients with moderate-to-severe psoriasis than in patients with mild disease (4.4 episodes vs 2.8 episodes, P=0.002). Multivariable logistic regression models showed moderate-to-severe patients were 2.68 times more likely (95% CI:1.72-4.21; P<0.001) to take a half-day or more off from work than those with mild disease after adjusting for age, sex, race, ethnicity, poverty, cognitive limitations, insurance, education, and comorbidities.
Conclusion: Disease severity directly impacts work absenteeism in psoriasis patients. Early diagnosis and treatment with appropriate therapies are needed to reduce disease severity and limit economic loss and professional ramifications associated with psoriasis.

J Drugs Dermatol. 2024;23(8):640-644. doi:10.36849/JDD.7550

INTRODUCTION

Psoriasis is a chronic inflammatory skin disease that affects nearly 8 million adults in the United States (US).[1] The disease is characterized by sharply demarcated, scaly, erythematous plaques that can involve a large percentage of one's body surface area.[2-3] In addition to disease symptoms like pruritus, pain, and bleeding, associated medical comorbidities, such as cardiometabolic diseases and psoriatic arthritis, contribute to the high burden of disease among patients.[2,4] Psoriasis can also have a profound impact on patients' mental health. Psoriasis patients are at increased risk of low self-esteem, depression, anxiety, self-harm, stress, and suicidality.[5-7]

The physical and emotional disease burden contributes to a reduced quality of life (QoL) and impaired function in psoriasis patients.[8] This loss in productivity carries professional and financial repercussions. The estimated total annual economic burden of psoriasis in the US is 112 billion dollars.[9] Up to 40% of the total costs of psoriasis are thought to be the result of decreased productivity and work loss.[10] One component of work loss is work absenteeism, which is defined as missing work due to illness or disability.[11] It has been found that adult psoriasis patients in the US miss approximately 1.26% more days of work than patients without psoriasis.[12-13]

While few studies examined work absenteeism between patients with and without psoriasis, little is known regarding how work absenteeism may differ between psoriasis patients with mild versus moderate-to-severe disease in the US This study aims to compare work absenteeism between employed adults with mild and moderate-to-severe psoriasis in the US.

MATERIALS AND METHODS

Data Source and Population Selection

A cross-sectional, population-based study was performed using the Medical Expenditure Panel Survey (MEPS) from 2009 to 2019. MEPS is a nationally representative survey of the civilian non-institutionalized US population that collects data at the individual and household levels.[14] The survey is conducted by the Agency for Health Care Policy and Research (AHCPR) and employs a stratified, multi-staged area probability design to facilitate the inclusion of minority populations. It specifically collects information on healthcare use, healthcare expenditures, access to care, prescribed medications, and sociodemographic characteristics of the American civilian, noninstitutionalized population.[15]

The study population included employed adults ≥ 22 years old who reported a diagnosis of psoriasis. A diagnosis of psoriasis was identified using the *International Classification of Diseases, Ninth Revision* (ICD-9) 696 code in the Medical Conditions File from 2009-2015 and the *International Classification of Diseases*, Tenth Revision (ICD-10) L40 code in the Medical Conditions File from 2016-2019. The reported treatment prescribed for psoriasis was obtained from the 2009-2019 Prescribed Medicines File and used as a proxy for disease severity. This method has been used by a number of immunologic studies in the past.[16-18] Mild disease was defined as no treatment or topical therapies only. Moderate-to-severe disease was defined as the use of oral or biologic therapies. Socioeconomic and sociodemographic information was also obtained from the Full-Year Consolidated File.

Variables

The independent variable was psoriasis disease severity as determined by prescribed treatment. The dependent variable was work absenteeism. Work absenteeism was defined using the MEPS DDNWRK variable obtained from the Full-Year Consolidated File. The DDNWRK is a count variable indicating the number of episodes per year that someone was absent from work for at least a half day because of illness, injury, or mental or emotional problems.

Analysis

We performed descriptive analyses of age, sex, race, ethnicity, poverty category, education, cognitive limitations, and calculated the Charlson Comorbidity Index (CCI) among mild and moderate-to-severe psoriasis patients. The CCI accounts for a number of medical comorbidities, including rheumatic diseases such as inflammatory arthritides. Individuals were considered to have cognitive limitations if they reported experiencing confusion or memory loss, having problems making decisions, or requiring supervision for safety. Chi-squared analyses for categorical variables and two-tailed t-tests for continuous data were performed to test the null hypothesis that there were no differences in the sociodemographic and clinical factors between the mild and moderate-to-severe psoriasis populations.

A two-tailed t-test was performed to test the null hypothesis that there were no differences in work absenteeism between mild and moderate-to-severe patients. Additionally, a multivariable regression analysis was performed to examine the relationship between psoriasis disease severity and work absenteeism. Age, sex, race, ethnicity, poverty category, insurance, education, cognitive limitations, and Charlson comorbidities were adjusted for in the multivariate regression model. All statistical analyses were performed using STATA 17.0 (StataCorp LP, College Station, TX). *P*-values ≤0.05 were considered statistically significant.

RESULTS

Sample Characteristics

A total of 5,209,956 psoriasis patients were identified from the pooled 2009-2019 MEPS data files. The weighted mild population size was 4,521,687 patients, and the weighted moderate-to-severe population was 688,269 patients. Across the overall psoriasis cohort, 54.3% (n= 2,830,549) were on no treatment, 32.5% (n= 1,691,138) were on topical-only treatment, 6.0% (n=311,085) were receiving oral systemic therapies, and 7.2% (n=377,184) were being treated with biologic agents. The study population's reported psoriasis treatments are presented in Table 2.

The mean ± SEM age for the mild population was 47.5 ± 0.56 years old while the mean ± SEM age for the moderate-to-severe population was 45.9 ± 1.55 years old. Females comprised 49.0% of the mild population and 41.5% of the moderate-to-severe population. There was a significant difference between the mild and moderate-to-severe psoriasis populations in the poverty

TABLE 2.

Treatment Characteristics for Psoriasis Patients Between 2009 and 2019 From MEPS

Treatment for Psoriasis	Weighted Psoriasis Population (n=5,209,956)	Percent (%)
No treatment	2,830,549	54.3
Topicals	1,691,138	32.5
Biologics	377,184	7.2
Adalimumab	196,798	52.2
Etanercept	180,386	47.8
Oral Systemics	311,085	6.0
Methotrexate	159,583	51.3
Oral Steroids	91,735	29.5
Sulfasalazine	42,321	13.6
Azathioprine	17,446	5.6

TABLE 1.

Weighted Sample Demographic and Clinical Characteristics of Mild vs Moderate-Severe Psoriasis Patients Between 2009 and 2019 From MEPS

Variables	Mild Psoriasis Cohort (Weighted n = 4,521,687)	Moderate-to-Severe Cohort (Weighted n = 688,269)	*P*-value
Mean Number of Episodes Per Year an Individual Took Off a Half-day or More From Work (SEM)	2.8 (0.17)	4.4 (0.47)	0.002*
Mean Age, years (SEM)	47.5 (0.56)	45.9 (1.55)	0.33*
Sex, n (%)			0.25†
Female	2,217,658 (49.0)	285,600 (41.5)	
Race, n (%)			0.48†
White	3,917,466 (86.6)	627,581 (91.2)	
Black	253,362 (5.6)	14,878 (2.1)	
Native American Indian/Alaskan	31,386 (0.7)	0 (0)	
Asian/Hawaiian/Pacific Islander	191,212 (4.2)	33,012 (4.8)	
Multiple	128,261 (2.9)	12,798 (1.9)	
Ethnicity, n (%)			0.20†
Hispanic	485,659 (10.7)	34,937 (5.1)	
Education, n (%)			
No Degree	104,222 (2.3)	14,028 (2.1)	0.79†
High School/GED	1,640,821 (36.3)	242,242 (35.2)	
Bachelors	1,133,847 (25.1)	220,357 (32.0)	
Advanced	864,781 (19.1)	121,230 (17.6)	
Other	778,016 (17.2)	90,412 (13.1)	
Annual Household Income, n (%)			<0.001†
Very low income	199,549 (4.4)	39,422 (5.7)	
Low income	180,209 (4.0)	140,894 (20.5)	
Middle income	1,003,064 (22.2)	128,498 (18.7)	
High income	3,138,865 (69.4)	379,455 (54.2)	
Insurance Status, n (%)			0.29†
Private	4,143,628 (91.6)	649,771 (94.4)	
Public	194,774 (4.3)	9,411 (1.4)	
Uninsured	183,285 (4.1)	29,087 (4.2)	
Cognitive Limitations, n (%)	90,689 (2.0)	3,233 (0.5)	0.12†
CCI, mean (SEM)	0.15 (0.02)	0.14 (0.02)	0.77*

Abbreviations: *GED*, General Education Development; *CCI, Charlson* Comorbidity Index; MEPS, Medical Expenditure Panel Survey; *SEM*, standard error of the mean
*Two-tailed t-tests of the differences between US employed adult residents with mild and moderate-to-severe psoriasis
†X^2 Test of the differences between US employed adult residents with mild and moderate-to-severe psoriasis

category (*P*<0.001). Additional sociodemographic and clinical characteristics of the mild and moderate-to-severe psoriasis study populations are further detailed in Table 1.

The mean number of episodes per year that someone was absent from work for at least a half day was 2.8 in the mild psoriasis population, while the moderate-to-severe psoriasis population reported a mean of 4.4 episodes of absence per patient per year (*P*=0.002).

Association Between Disease Severity and Work Absenteeism

On multivariable logistic regression, moderate-to-severe patients were 2.68 times more likely (95% CI: 1.72-4.21; *P*<0.001) to take a half-day or more off from work than those with mild disease, after adjusting for age, sex, race, ethnicity, poverty category, insurance, education, cognitive limitations, and Charlson Comorbidity Index.

TABLE 3.

Multivariable Logistic Regression Analysis of Work Absenteeism for Mild vs Moderate-to-Severe Psoriasis Patients

Independent Variables	Dependent Variable: Work Absenteeism	
	aOR (95% CI)	*P*-value[a]
Disease Severity		
Mild	1(Reference)	--
Moderate-to-Severe	2.68 (1.72-4.21)	<0.001
CCI	1.52 (0.95-2.42)	0.08
Age	0.99 (0.97-1.00)	0.18
Sex		
Male	1(Reference)	--
Female	1.35 (0.94-1.94)	0.10
Hispanic		
Hispanic	1(Reference)	--
Non-Hispanic	1.06 (0.63-1.77)	0.83
Race		
White	1(Reference)	--
Black	1.87 (0.93-3.79)	0.08
Native American Indian/Alaskan	1.18 (0.15-9.16)	0.87
Asian/Native Hawaiian/Pacific Islander	1.33 (0.62-2.87)	0.47
Multiple Races	1.21 (0.44-3.33)	0.71
Annual Household Income		
High Income	1(Reference)	--
Middle Income	0.64 (0.41-0.99)	0.05
Low Income	0.55 (0.26-1.18)	0.13
Very Low Income	0.41 (0.16-1.06)	0.07
Insurance Status		
Private	1(Reference)	--
Public	1.97 (0.89-4.35)	0.09
Uninsured	0.96 (0.39-2.35)	0.93
Education		
Advanced Degree	1(Reference)	--
Bachelor's Degree	1.14 (0.66-1.97)	0.64
High School Diploma/ GED	1.45 (0.85-2.48)	0.17
No Degree	2.54 (0.99-6.49)	0.05
Other Degree	2.14 (1.14-4.04)	0.02
Cognitive Limitations		
No Limitations	1(Reference)	--
Reported Limitations	1.00 (0.34-2.94)	0.99

Estimates are adjusted for survey sampling weights
aOR, adjusted Odds Ratio; *CI*, Confidence Interval; *CCI*, Charlson Comorbidity Index
[a]*P*-values are statistically significant at a threshold of 5%

DISCUSSION

In this nationally representative population of 5,209,956 employed adults with psoriasis, patients with moderate-to-severe disease were found to miss work more often than those with mild disease. This study specifically presents novel findings that directly compare work absenteeism rates and likelihood between mild and moderate-to-severe psoriasis patients. The average episodes of work absence lasting at least a half day per patient per year was significantly higher in patients with moderate-to-severe psoriasis than in patients with mild disease. Additionally, adult psoriasis patients with moderate-to-severe disease were over 2.5 times more likely to take off work than those with mild psoriasis. These findings support previous studies noting the impact of psoriasis on workplace productivity. Work productivity data gathered by the National Psoriasis Foundation demonstrated that 49% of psoriasis patients reported that they missed work regularly due to their condition.[19] Our findings also reinforce the role that disease severity plays in work absenteeism among psoriasis patients. A multinational study found that work-productivity loss progressively increases with disease severity and reported the average proportion of work hours lost by patients with severe psoriasis lost to be around 30%.[20]

Several factors may contribute to our study findings. For example, increased emotional burden may contribute to the higher reports of work absenteeism in moderate-to-severe psoriasis patients compared to patients with mild disease. Disease severity has been found to be associated with psoriasis patients' quality of life, as patient-reported quality of life has been found to decrease with increasing disease severity.[21,22] Additionally, past studies have noted a correlation between disease severity and the risk of depression.[5,23] A national Danish cohort study specifically found that the incidence of depression was nearly 1.5 greater in patients with severe psoriasis compared to patients with mild psoriasis.[23]

In addition to emotional burden, psoriasis results in symptoms that can profoundly impact patients' quality of life and work productivity. Itching, pain, and scaling of the skin are the most commonly reported symptoms of psoriasis.[24-26] Studies have shown patients with more severe psoriasis can experience more pronounced symptoms of pruritus, pain, and scaling and a greater reduction in quality of life and work productivity.[25-26] The severity of psoriatic pain and itch, in addition to the social stigma associated with scaling, may contribute to the increased rates of work absenteeism reported in moderate-to-severe psoriasis patients compared to those with milder disease.

Moderate-to-severe psoriasis patients are also likely to have a larger percentage of body surface involvement than mild psoriasis patients. Embarrassment about appearance may play a role in the increased rates of work absenteeism observed in

adults with moderate-to-severe psoriasis. Additionally, patients with moderate-to-severe psoriasis may need more complex care and require more frequent clinic visits than those with mild disease. This may account for the increased frequency of work absenteeism reported in adults with moderate-to-severe psoriasis when compared to those with mild psoriasis.

The findings of our study need to be interpreted in the context of our study design. The MEPS Prescribed Medicine data file does not include all oral and biologic psoriasis treatments or records related to phototherapy. This consequently precludes the identification of US residents receiving phototherapy.

CONCLUSION

The increased frequency of work absenteeism reported by psoriasis patients has deleterious effects on affected individuals' careers and livelihoods. Our study found that adults with moderate-to-severe disease were more than 2.5 times more likely to report work absenteeism than those with mild psoriasis, demonstrating how disease severity directly impacts work absenteeism in psoriasis patients. Our findings highlight the need for early diagnosis and treatment with appropriate therapies to reduce disease severity and limit economic loss and professional ramifications associated with psoriasis.

DISCLOSURES

AWA has served as a research investigator, scientific advisor, or speaker to AbbVie, Amgen, Almirall, Arcutis, ASLAN, Beiersdorf, BI, BMS, EPI, Incyte, Leo, UCB, Janssen, Lilly, Mindera, Nimbus, Novartis, Ortho, Sun, Dermavant, Dermira, Sanofi, Takeda, Organon, Regeneron, Pfizer and Ventyx.

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doi:10.36849/JDD.8293

August 2024 645 Volume 23 • Issue 8

ORIGINAL ARTICLE

Journal of Drugs in Dermatology

Selective Tyrosine Kinase 2 (TYK2) Inhibition in Plaque Psoriasis

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ABSTRACT

Members of the Janus kinase (JAK) superfamily, comprising tyrosine kinase 2 (TYK2) and JAK1, JAK2, and JAK3, mediate signaling by cytokines (eg, interleukin [IL]-23) involved in psoriasis pathogenesis. Binding of IL-23 to its receptor activates TYK2 and JAK2, which trigger signal transducer and activator of transcription (STAT) translocation to the nucleus to regulate target gene transcription, including genes of proinflammatory mediators such as IL-17. Physiologically, TYK2 solely mediates immune function, whereas JAK1,2,3 mediate broad systemic and immune functions. Inhibition of individual JAK family members is being evaluated in many dermatologic indications, including psoriasis. Selective TYK2 inhibition is therefore expected to be associated with few adverse effects in patients with psoriasis. People with genetic mutations leading to loss of function of TYK2 are protected from the development of psoriasis without an increased risk of infections or malignancies. In contrast, treatments with JAK1,2,3 inhibitors are associated with various systemic effects. We review the unique allosteric mechanism of action of the selective TYK2 inhibitor, deucravacitinib, which binds to the TYK2 regulatory (pseudokinase) domain, and the mechanisms of action of JAK1,2,3 inhibitors, which bind to the adenosine 5'-triphosphate-binding active (catalytic) site in the kinase domains of JAK1,2,3. Deucravacitinib, which is approved for the treatment of moderate to severe plaque psoriasis in adults in the United States and several other countries, represents a novel, targeted systemic treatment approach with a favorable safety profile.

J Drugs Dermatol. 2024;23(8):645-652. doi:10.36849/JDD.8293

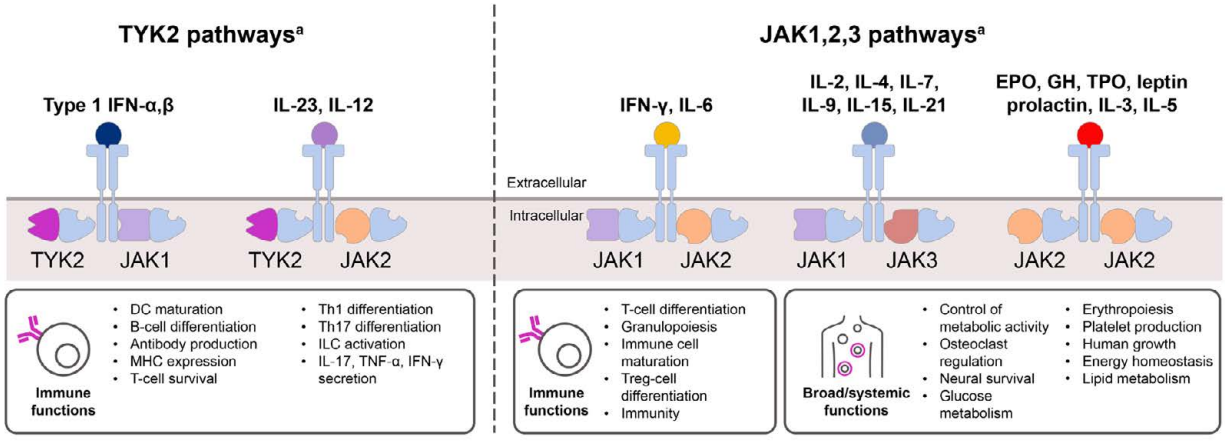
INTRODUCTION

The Janus kinase (JAK) family members, tyrosine kinase 2 (TYK2), JAK1, JAK2, and JAK3, are related nonreceptor tyrosine kinases that are associated with the cytoplasmic domains of cytokine receptors.[1,2] TYK2 solely mediates select immune functions; in contrast, JAK1,2,3 mediate broad systemic and immune functions (Figure 1).[1] JAK family members function predominantly as heterodimers and rarely as heterotrimers (JAK2 also functions as a homodimer), with specific pairings dictating their downstream effects.[1,2] The complex protein TYK2 has multiple domains, including a kinase or catalytic domain (also known as the Janus homology 1, or JH1, domain) and a pseudokinase or regulatory domain (also known as the JH2 domain), which lacks catalytic activity but plays an important role in regulating receptor-mediated activation of the catalytic domain via autoinhibitory interactions.[3,4]

TYK2 is involved in a key axis of inflammation in psoriasis (Figure 2),[5] mediating signaling by interleukin (IL)-12, IL-23, and Type I interferons (IFNs).[6-15] IL-23 stimulates T-helper 17 cells to produce IL-17, which then stimulates keratinocyte proliferation and epidermal hyperplasia. As other immune cells are attracted to the area, the inflammatory process is potentiated.[5] Support for TYK2 playing a central role in the inflammatory process comes from TYK2 loss-of-function genetic mutations shown to be associated with a reduced risk of developing immune-mediated inflammatory diseases (IMIDs) such as psoriasis.[16]

The pathogenesis of psoriasis involves complex interactions among 1) proinflammatory cytokines, including IL-17, IL-23, IL-12, IL-19, tumor necrosis factor (TNF), and Type I IFNs (eg, IFN-α)[1,3]; 2) immune cells, including T cells and dendritic cells[3]; and 3) keratinocytes.[17] Some of these proinflammatory cytokines are regulated by JAK family members such as TYK2.[2,18] Extracellular binding of a cytokine to its receptor activates the associated intracellular JAK family members to activate signal transducers and activators of transcription (STATs). Activated STATs

FIGURE 1. TYK2 pathways and JAK1,2,3 pathways involve specific pairings of JAK family members that mediate specific sets of cytokine signals to control different downstream functions.[1]

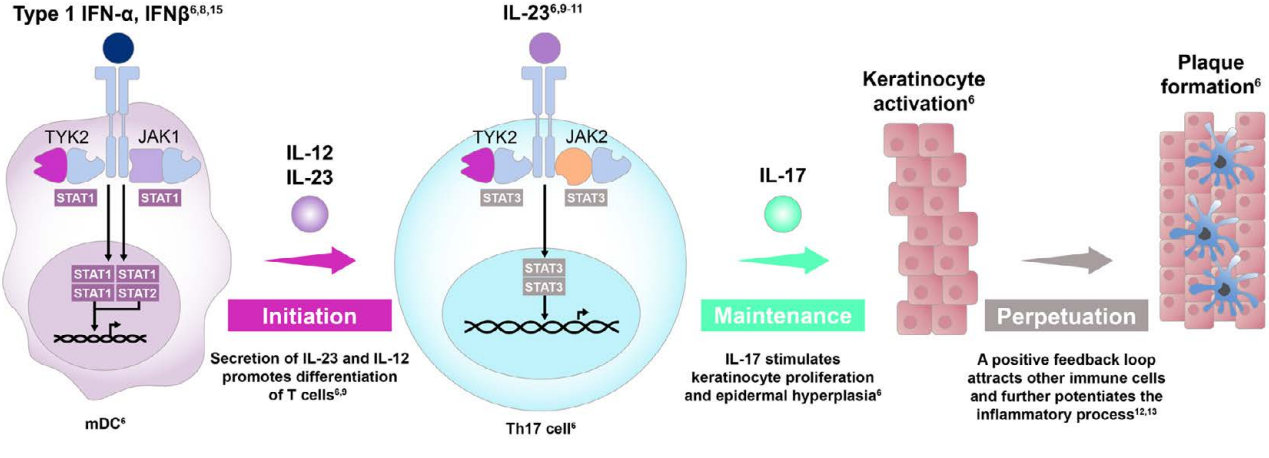


DC, dendritic cell; EPO, erythropoietin; GH, growth hormone; IFN, interferon; IL, interleukin; ILC, innate lymphoid cell; JAK, Janus kinase; MHC, major histocompatibility complex; Th, T helper; TNF, tumor necrosis factor; TPO, thrombopoietin; Treg cell, regulatory T cell; TYK2, tyrosine kinase 2. [a]List of cytokines and effects modulated by different JAK/JAK and TYK2/JAK pairs is not exhaustive. Adapted by permission from BMJ Publishing Group Limited. *Ann Rheum Dis*, Baker KF and Isaacs JD, 77, 175-187, 2023 with permission from BMJ Publishing Group Ltd.

dimerize and translocate from the cytoplasm to the nucleus to regulate the transcription of numerous target genes, resulting in increased expression of proinflammatory mediators such as IL-17.[1,2]

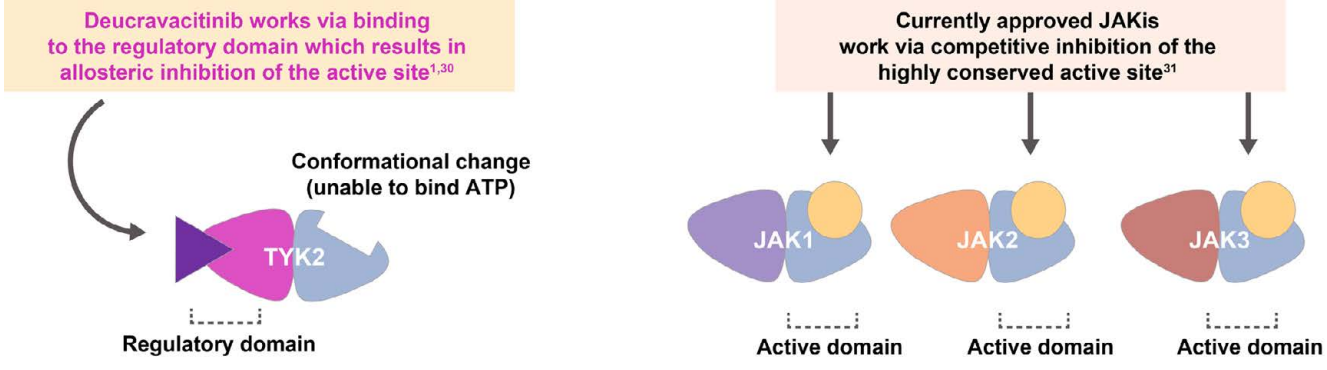
Systemic treatment of moderate to severe plaque psoriasis with targeted therapies has focused primarily on direct inhibition of IL-17, IL-23, and TNF with biologic agents[1,17] and inhibition of phosphodiesterase-4.[19] The monoclonal antibodies brodalumab, ixekizumab, bimekizumab, and secukinumab target IL-17; guselkumab, tildrakizumab, and risankizumab target IL-23; ustekinumab targets IL-12/23; and adalimumab, etanercept, infliximab, and certolizumab pegol target TNF-α, while the small molecule apremilast targets phosphodiesterase-4.[19,20] Targeting the JAK-STAT pathway is a current focus of research in dermatologic conditions. JAK1,2,3 inhibitors nonselectively bind to the adenosine 5'-triphosphate (ATP)-binding site on the catalytic domain of JAK1,2,3 and are not highly selective for any of the superfamily members, including TYK2.[21,22] JAK1,2,3 inhibitors are approved by the US Food and Drug Administration for use in dermatologic indications such as psoriatic arthritis, alopecia areata, atopic dermatitis, and vitiligo, as well as in additional disease states such as rheumatoid arthritis, ulcerative colitis, Crohn's disease, myelofibrosis, polycythemia vera, and graft versus host disease.[23]

FIGURE 2. TYK2 mediates a key axis of inflammation in psoriasis.[5]



IFN, interferon; IL, interleukin; JAK, Janus kinase; mDC, myeloid dendritic cell; STAT, signal transducer and activator of transcription; Th17, T-helper 17; TYK2, tyrosine kinase 2. Adapted with permission from Gonciarz et al. *Immunotherapy.* 2021;13:1135-1150.

FIGURE 3. Mechanism of action and binding location of deucravacitinib compared with JAK1,2,3 inhibitors.[22]

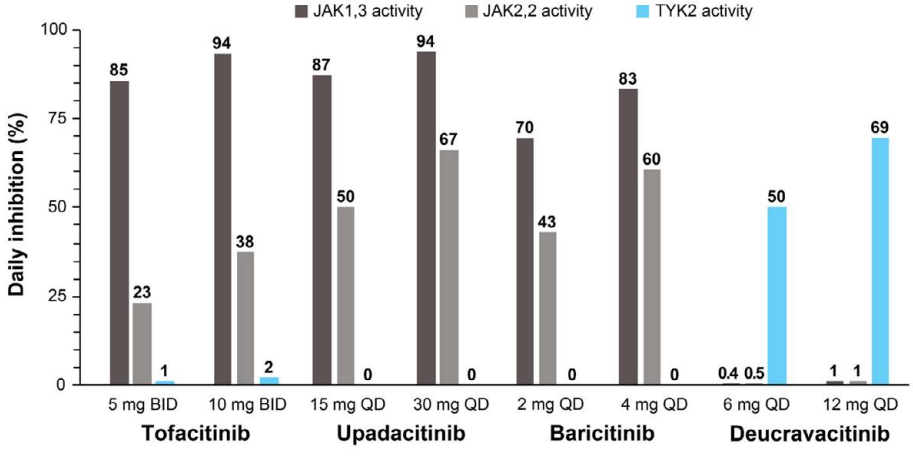


ATP, adenosine 5'-triphosphate; JAK, Janus kinase; JAKi, Janus kinase inhibitor; TYK2, tyrosine kinase 2. Reprinted from *J Am Acad Dermatol*, Krueger JG, McInnes IB, Blauvelt A, Tyrosine kinase 2 and Janus kinase-signal transducer and activator of transcription signaling and inhibition in plaque psoriasis, 86, 148-157, Copyright 2022, with permission from Elsevier.

Unlike JAK1,2,3 inhibitors (which are not approved for use in psoriasis), deucravacitinib, an oral, selective, allosteric TYK2 inhibitor, is approved in the United States, European Union, Japan, and other countries for the treatment of adults with moderate to severe plaque psoriasis who are candidates for systemic therapy.[24-29] Deucravacitinib selectively binds to the regulatory (pseudokinase) domain of TYK2 and locks the kinase in its native inactive state,[3,4,30,31] preventing receptor-mediated TYK2 activation and downstream signal transduction (Figure 3).[22] Deucravacitinib is highly selective for TYK2 at clinically relevant doses.[21] This mechanism of action differs from that of nonselective, orthosteric, oral TYK2 inhibitors such as ropsacitinib (PF-06826647), which binds to the active site of TYK2 and JAK2 and was shown to be more efficacious than placebo and was well tolerated in a phase 2b study of moderate to severe plaque psoriasis.[32] Similarly, a second nonselective, orthosteric, oral TYK2 inhibitor brepocitinib (PF-06700841), which binds to the active site of TYK2, JAK1, and JAK2, was also more efficacious than placebo and was well tolerated in a phase 2a study of patients with moderate to severe plaque psoriasis.[33] Given the differences in signaling across TYK2 and JAK1,2,3, coupled with the different mechanisms of action and downstream effects of TYK2 and JAK1,2,3, selective, allosteric inhibition of TYK2 is expected to have a different safety profile compared with nonselective inhibition of JAK1,2,3.[2,30,34]

The objectives of this review are to introduce a new pharmacologic class of oral, selective, allosteric inhibitors targeting the regulatory domain of TYK2; to describe how the mechanism of action, efficacy, safety, and tolerability profiles

FIGURE 4. Deucravacitinib, an allosteric TYK2 inhibitor, is highly selective for TYK2 versus JAK1,2,3 inhibitors (tofacitinib, upadacitinib, and baricitinib) at their clinically relevant doses.[21]



BID, twice daily; JAK, Janus kinase; QD, once daily; TYK2, tyrosine kinase 2. From Chimalakonda A, et al. Selectivity profile of the tyrosine kinase 2 inhibitor deucravacitinib compared with Janus kinase 1/2/3 inhibitors. *Dermatol Ther (Heidelb)*. 2021;11:1763-1776. https://doi.org/10/1007/s13555-021-00596-8. This work is licensed under a Creative Commons Attribution License (CC BY-NC-ND 2.0). https://creativecommons.org/licenses/by-nc/2.0.

of the only approved TYK2 inhibitor deucravacitinib differ from those of JAK1,2,3 inhibitors; and to summarize clinical data from phase 3 trials of deucravacitinib for the treatment of adults with moderate to severe plaque psoriasis.

Mechanism of Action and Profile of Deucravacitinib

Deucravacitinib is highly selective for the regulatory pseudokinase (JH2) domain of TYK2 and shows negligible activity against JAK1,2,3.[3,4,21] The TYK2 pseudokinase domain is structurally unique to TYK2, making deucravacitinib highly selective for TYK2.[3,4] Binding of deucravacitinib to the pseudokinase domain results in a conformational change to the TYK2 active site and allosterically inhibits its ability to bind ATP and phosphorylate its target (Figure 3).[4,22]

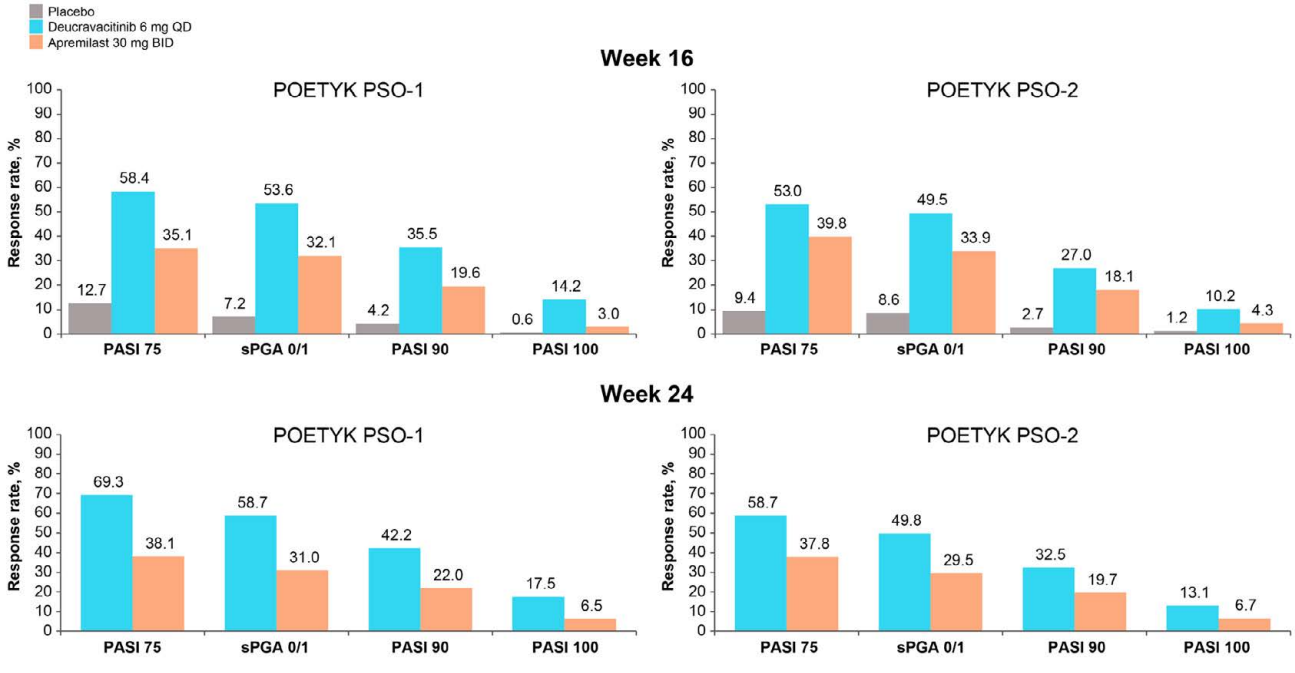
At physiologically relevant concentrations, deucravacitinib demonstrated ≥100-fold greater selectivity for TYK2 pathways versus JAK1,3 pathways and ≥2000-fold greater selectivity for TYK2 pathways versus JAK2 pathways in cellular assays.[3] In a simulation analysis, at clinically relevant doses of 6 mg and 12 mg once daily, the daily average percent inhibition of TYK2 by deucravacitinib was ≥50%, while TYK2 inhibition by clinically relevant doses of JAK1,2,3 inhibitors was ≤2% (Figure 4).[21] Conversely, the simulated daily average percent inhibition of JAK1,2,3 by deucravacitinib was ≤1%; the average percent inhibition of JAK1,3 by JAK1,3 inhibitors was ≥70% and of JAK2,2 by JAK2,2 inhibitors was 23% to 67%.[21]

The TYK2 signaling pathway influences a select group of immune-signaling molecules and is not implicated in broad systemic effects, unlike the pathways that mediate JAK1,2,3 signaling.[3,35] Selective inhibition of TYK2 by deucravacitinib inhibits IL-23 and Type I IFN signaling,[36] the key pathways involved in psoriasis pathogenesis (Figure 2).[5] Selective TYK2 inhibition by deucravacitinib also inhibits IL-12 signaling[36]; while IL-12 was initially thought to be a key driver in psoriasis pathogenesis, its role remains undetermined. Furthermore, in genome-wide association studies, patients with partial or near loss-of-function polymorphism of TYK2 exhibited a decreased risk of IMIDs such as psoriasis, rheumatoid arthritis, systemic lupus erythematosus, ankylosing spondylitis, Crohn's disease, and ulcerative colitis, as mentioned above.[16]

Clinical Efficacy of Deucravacitinib

In the 52-week, global, pivotal phase 3 POETYK PSO-1 and POETYK PSO-2 trials (NCT03624127 and NCT03611751, respectively) conducted in patients with moderate to severe plaque psoriasis, deucravacitinib was compared with placebo and an active control, the phosphodiesterase-4 inhibitor apremilast.[34,37] As shown in (Figure 5), patients in POETYK PSO-1

FIGURE 5. Summary of efficacy up to 24 weeks in the POETYK PSO trials.[34,37]



PASI 75/90/100, ≥75%/≥90%/100% reduction from baseline in Psoriasis Area and Severity Index; sPGA 0/1, static Physician Global Assessment score of 0 (clear) or 1 (almost clear) with a ≥2-point improvement from baseline. POETYK PSO-1: From Armstrong AW, et al. Deucravacitinib versus placebo and apremilast in moderate to severe plaque psoriasis: efficacy and safety results from the 52-week, randomized, double-blinded, placebo-controlled phase 3 POETYK PSO-1 trial. *J Am Acad Dermatol.* 2023;88:29-39. https://www.jaad.org/action/showPdf?pii=S0190-9622%2822%2902256-3. This work is licensed under a Creative Commons Attribution License (CC BY-NC-ND 4.0). https://creativecommons.org/licenses/by-nc-nd/4.0/. POETYK PSO-2: Adapted from Strober B, et al. Deucravacitinib versus placebo and apremilast in moderate to severe plaque psoriasis: efficacy and safety results from the 52-week, randomized, double-blinded, phase 3 POETYK PSO-2 trial. *J Am Acad Dermatol.* 2023;88:40-51. https://www.jaad.org/action/showPdf?pii=S0190-9622%2822%2902643-3. This work is licensed under a Creative Commons Attribution License (CC BY-NC-ND 4.0). https://creativecommons.org/licenses/by-nc-nd/4.0/.

TABLE 1.

Summary of Pooled Adverse Events Over 1 Year in the POETYK PSO Trials[a]

	Placebo, n=666 Total PY=240.9		Deucravacitinib, n=1364 Total PY=969.0		Apremilast, n=422 Total PY=221.1	
	n (%)	EAIR/100 PY (95% CI)	n (%)	EAIR/100 PY (95% CI)	n (%)	EAIR/100 PY (95% CI)
AE category						
Any AEs	347 (52.1)	217.4 (195.7, 241.5)	995 (72.9)	229.2 (215.4, 243.9)	299 (70.9)	281.1 (250.9, 314.8)
Serious AEs	14 (2.1)	5.7 (3.4, 9.6)	55 (4.0)	5.7 (4.4, 7.4)	9 (2.1)	4.0 (2.1, 7.7)
AEs leading to discontinuation	23 (3.5)	9.3 (6.2, 14.0)	43 (3.2)	4.4 (3.3, 5.9)	26 (6.2)	11.6 (7.9, 17.1)
Deaths	1 (0.2)	0.4	2 (0.1)[b]	0.2	1 (0.2)	0.4
Most common AEs (≥2%) in any treatment group						
Nasopharyngitis	54 (8.1)	22.7 (17.4, 29.7)	229 (16.8)	26.1 (23.0, 29.8)	54 (12.8)	25.9 (19.9, 33.9)
Upper respiratory tract infection	33 (5.0)	13.5 (9.6, 19.1)	124 (9.1)	13.4 (11.3, 16.0)	27 (6.4)	12.4 (8.5, 18.0)
Headache	21 (3.2)	8.6 (5.6, 13.1)	80 (5.9)	8.5 (6.8, 10.5)	53 (12.6)	26.0 (19.9, 34.0)
Diarrhoea	28 (4.2)	11.5 (7.9, 16.7)	69 (5.1)	7.3 (5.7, 9.2)	54 (12.8)	26.5 (20.3, 34.6)
Arthralgia	21 (3.2)	8.5 (5.6, 13.1)	55 (4.0)	5.7 (4.4, 7.4)	17 (4.0)	7.7 (4.8, 12.3)
Blood CPK increased	11 (1.7)	4.5 (2.5, 8.1)	45 (3.3)	4.7 (3.5, 6.3)	8 (1.9)	3.6 (1.8, 7.1)
Pharyngitis	4 (0.6)	1.6 (0.6, 4.3)	41 (3.0)	4.2 (3.1, 5.8)	5 (1.2)	2.2 (0.9, 5.4)
Hypertension	5 (0.8)	2.0 (0.8, 4.8)	39 (2.9)	4.0 (3.0, 5.5)	16 (3.8)	7.2 (4.4, 11.8)
Viral upper respiratory tract infection	6 (0.9)	2.4 (1.1, 5.4)	30 (2.2)	3.1 (2.2, 4.4)	3 (0.7)	1.3 (0.4, 4.1)
Acne	1 (0.2)	0.4 (0.1, 2.8)	28 (2.1)	2.9 (2.0, 4.2)	0	0
Oral herpes	2 (0.3)	0.8 (0.2, 3.2)	28 (2.1)	2.9 (2.0, 4.2)	2 (0.5)	0.9 (0.2, 3.5)
Psoriasis	31 (4.7)	12.8 (9.0, 18.2)	29 (2.1)	3.0 (2.1, 4.3)	10 (2.4)	4.5 (2.4, 8.3)
Urinary tract infection	8 (1.2)	3.2 (1.6, 6.5)	29 (2.1)	3.0 (2.1, 4.3)	4 (0.9)	1.8 (0.7, 4.7)
Back pain	8 (1.2)	3.2 (1.6, 6.4)	27 (2.0)	2.8 (1.9, 4.0)	17 (4.0)	7.7 (4.8, 12.3)
Bronchitis	4 (0.6)	1.6 (0.6, 4.3)	27 (2.0)	2.8 (1.9, 4.0)	5 (1.2)	2.2 (0.9, 5.3)
Folliculitis	0	0	27 (2.0)	2.8 (1.9, 4.0)	2 (0.5)	0.9 (0.2, 3.5)
Rhinitis	5 (0.8)	2.0 (0.8, 4.8)	26 (1.9)	2.7 (1.8, 3.9)	11 (2.6)	5.0 (2.7, 8.9)
Nausea	10 (1.5)	4.0 (2.2, 7.5)	20 (1.5)	2.1 (1.3, 3.2)	47 (11.1)	22.9 (17.2, 30.5)
Vomiting	7 (1.1)	2.8 (1.3, 5.9)	18 (1.3)	1.8 (1.2, 2.9)	9 (2.1)	4.0 (2.1, 7.7)
Myalgia	3 (0.5)	1.2 (0.4, 3.7)	13 (1.0)	1.3 (0.8, 2.3)	11 (2.6)	4.9 (2.7, 8.9)

[a]Includes patients who received the agent after treatment switches. [b]One additional death was reported at day 298 due to hepatocellular carcinoma in a patient with a history of hepatitis C virus infection and liver cirrhosis. This death was not considered to be drug-related by the investigator. AE, adverse event; CI, confidence interval; CPK, creatine phosphokinase; EAIR, exposure-adjusted incidence rate; PY, person-years.

TABLE 2.

Summary of Pooled Adverse Events of Interest Over 1 Year in the POETYK PSO Trials

Adverse event	Placebo, n=666 Total PY=240.9		Deucravacitinib, n=1364 Total PY=969.0		Apremilast, n=422 Total PY=221.1	
	n (%)	EAIR/100 PY (95% CI)	n (%)	EAIR/100 PY (95% CI)	n (%)	EAIR/100 PY (95% CI)
Infections						
Serious infections	2 (0.3)	0.8 (0.2, 3.2)	17 (1.2)	1.7 (1.1, 2.8)	4 (0.9)	1.8 (0.7, 4.7)
Herpes zoster	1 (0.2)	0.4 (0.1, 2.8)	9 (0.7)	0.9 (0.5, 1.8)	0	0
Adjudicated MACE	3 (0.5)	1.2 (0.4, 3.7)	3 (0.2)	0.3 (0.1, 0.9)	2 (0.5)	0.9 (0.2, 3.5)
Venous thromboembolic and peripheral arterial thromboembolic events						
Venous thromboembolic events[a]	0	0	2 (0.1)	0.2 (0.1, 0.8)	0	0
Peripheral arterial thromboembolic events	1 (0.2)	0.4 (0.1, 2.8)	2 (0.1)	0.2 (0.1, 0.8)	1 (0.2)	0.4 (0.1, 3.1)
Malignancies						
NMSC[b]	0	0	7 (0.5)	0.7 (0.3, 1.5)	1 (0.2)	0.4 (0.1, 3.1)
Malignancies excluding NMSC	0	0	3 (0.2)	0.3 (0.1, 0.9)	1 (0.2)	0.4 (0.1, 3.1)
Breast cancer[c]	0	0	1 (0.1)	0.1 (0.0, 0.7)	0	0
Hepatocellular carcinoma[d]	0	0	1 (0.1)	0.1 (0.0, 0.7)	0	0
Lung adenocarcinoma	0	0	0	0	1 (0.2)	0.4 (0.1, 3.1)
Hodgkin's disease[e]	0	0	1 (0.1)	0.1 (0.0, 0.7)	0	0
Skin events						
Acne	1 (0.2)	0.4 (0.1, 2.8)	28 (2.1)	2.9 (2.0, 4.2)	0	0
Folliculitis	0	0	27 (2.0)	2.8 (1.9, 4.0)	2 (0.5)	0.9 (0.2, 3.5)
Adjudicated suicidal ideation	1 (0.2)	0.4 (0.1, 2.8)	1 (0.1)	0.1 (0.0, 0.7)	1 (0.2)	0.4 (0.1, 3.1)

Total exposure: deucravacitinib, 969.0 PY; placebo, 240.9 PY; apremilast, 221.1 PY. Most placebo-related data were obtained over weeks 0-16. [a]A 19-year-old female patient discontinued deucravacitinib after 4 days of treatment due to a rash, and 12 days later developed thrombosis in the radial vein after peripheral cannulation for intravenous antibiotic therapy for a streptococcal infection. The thrombosis resolved with anticoagulant therapy. A 48-year-old male patient with multiple cardiovascular risk factors developed acute dissecting ascending aortic aneurysm on day 338 of deucravacitinib treatment, with coincident pulmonary artery thrombus/embolism but without confirmed evidence of deep vein thrombosis. Deucravacitinib treatment was briefly interrupted during surgery, and the patient subsequently enrolled in the long-term deucravacitinib extension trial, without recurrence of a venous thromboembolic event. Neither of these events was considered related to treatment by the investigator. [b]Four patients in the deucravacitinib group had basal cell carcinoma, and 1 patient each had squamous cell carcinoma, squamous cell carcinoma of the skin, and malignant sweat gland neoplasm. One patient had squamous cell carcinoma in the apremilast group. [c]A 64-year-old female with a family history of malignancy (mother had breast cancer) received apremilast over weeks 0-24 and deucravacitinib over weeks 24-52. This patient was diagnosed with breast cancer on day 341 and discontinued from the study due to breast cancer on day 360, with the last dose of deucravacitinib received on day 342. This event was considered not related to study treatment. [d]A 54-year-old male, who was a former smoker (16 packs/years; none in the past 6 years) with type 2 diabetes mellitus, a history of latent tuberculosis (2017; treated), and hepatitis C, was randomized to deucravacitinib treatment. This patient was diagnosed with hepatocellular carcinoma and a pancreatic mass on day 224, and the patient died on day 298. This event was considered unrelated to deucravacitinib treatment by the investigator. [e]A 48-year-old male with a history of type 2 diabetes mellitus, dyslipidemia, and hypertension was randomized to deucravacitinib treatment. At week 8, this patient was diagnosed with anemia and thrombocytopenia and, at week 20, had worsening cough, fatigue, anemia, and an unintended 29 lb weight loss. This patient was diagnosed with classical Hodgkin's lymphoma at week 25 based on lymph node biopsy for enlarged lymph nodes. The latent period of diagnosis was considered too short to attribute causality to deucravacitinib treatment, especially given complete blood count abnormalities detected at week 8. CI, confidence interval; MACE, major adverse cardiovascular event; NMSC, nonmelanoma skin cancer; PY, person-years.

and PSO-2 who received deucravacitinib had significantly higher rates of achieving ≥75%, ≥90%, and 100% reductions from baseline in Psoriasis Area and Severity Index (PASI) as well as a static Physician Global Assessment score of 0 (clear) or 1 (almost clear) with a ≥2-point improvement from baseline at weeks 16 and 24 compared with placebo and apremilast.[34]

Clinical Safety of Deucravacitinib

Patients with long-term exposure to deucravacitinib did not exhibit increased rates of adverse events reported with JAK1,2,3 inhibition, such as malignancies and cardiovascular events.[34,37] Total adjusted drug exposure across the POETYK PSO-1 and PSO-2 trials was 969.0 person-years for deucravacitinib, 240.9 person-years for placebo, and 221.1 person-years for apremilast. Adverse events reported for up to 1 year in the pooled POETYK PSO trials are summarized in (Table 1).[34,37] Adverse events of interest were infrequent with deucravacitinib and generally comparable to placebo and apremilast (Table 2). Serious infections and herpes zoster events were more common with deucravacitinib than with placebo; however, the incidence rates of these events were low in each treatment group. No clinically meaningful changes in mean levels of laboratory parameters were observed with deucravacitinib treatment for up to 1 year.

Long-term Safety and Efficacy of Deucravacitinib

POETYK long-term extension (LTE) (NCT04036435) is an ongoing, open-label trial designed to evaluate the long-term safety and efficacy of deucravacitinib in adults with moderate to severe plaque psoriasis.[38] Patients were eligible to enter the POETYK LTE trial and receive deucravacitinib 6 mg once daily after completing week 52 of POETYK PSO-1 or PSO-2.[38] The 2-year safety profile of deucravacitinib in POETYK LTE was consistent with the 1-year profile in POETYK PSO-1 or PSO-2, with no new or emerging safety signals identified.[38] Clinical efficacy was maintained over 2 years.[38] POETYK LTE will continue to evaluate the long-term safety and efficacy of deucravacitinib for an additional 5 years beyond the parent trials.

Mechanism of Action and Profile of JAK1,2,3 Inhibitors

Currently approved JAK1,2,3 inhibitors block the JAK1,2,3 ATP-binding active (catalytic) sites, as mentioned above.[2,3,22] JAK-STAT pathways mediate downstream signaling of multiple Type I and Type II cytokines.[39] Generally, JAK1 mediates lymphocyte development and IL-6 signaling, JAK2 mediates hematopoiesis and metabolic regulation, and JAK3 mediates lymphopoiesis and immune function.[2,23] JAK1,2,3 inhibition/deficiency is implicated in dysfunctional hematopoiesis, lipid metabolism abnormalities, and immunodeficiency due to dysregulation of T cells, B lymphocytes, and natural killer cells.[23] Systemic effects of JAK1,2,3 inhibition in clinical trials include dyslipidemia, serious and opportunistic infections, anemia, neutropenia, thrombocytopenia, major adverse cardiovascular events (MACE), venous thromboembolic events, and malignancies.[2,39-41]

JAK1,2,3 inhibitors are not approved for plaque psoriasis, despite showing efficacy in clinical trials.[22,42] Two phase 3 trials demonstrated that oral tofacitinib 5 mg and 10 mg twice daily was superior to placebo,[43] and an additional phase 3 trial demonstrated that oral tofacitinib 10 mg twice daily was noninferior to subcutaneous etanercept 50 mg twice weekly and superior to placebo.[44] However, increased infections (especially herpes zoster), MACE, malignancy, and lipid abnormalities were reported with tofacitinib (Figure 1). Although these trials did not assess long-term safety, the randomized Oral Rheumatoid Arthritis Trial (ORAL) Surveillance (median follow-up, 4 years) reported that MACE and malignancy occurred more often in patients ≥50 years of age with at least one additional cardiovascular risk factor who were receiving tofacitinib 5 mg or 10 mg twice daily compared with a TNF inhibitor (adalimumab 40 mg every 2 weeks or etanercept 50 mg once weekly).[45]

CONCLUSION

TYK2 plays a major role in cytokine signaling in psoriasis pathogenesis. Selective, allosteric TYK2 inhibition effectively blocks this cytokine signaling, while minimizing systemic effects associated with JAK1,2,3 inhibition. Deucravacitinib, the only selective TYK2 inhibitor approved for the treatment of plaque psoriasis, is efficacious and well tolerated in patients with moderate to severe plaque psoriasis. Further clinical evaluation of this and other TYK2 inhibitors will provide additional insights about the role of selective TYK2 inhibition in psoriasis and other IMIDs.

DISCLOSURES

LK has received research grants from AbbVie, Allergan, Almirall, Amgen, Arcutis, Boehringer Ingelheim, Breckinridge Pharma, Bristol Myers Squibb, Celgene, Cellceutix, Centocor, Combinatrix, Connetics, Coria, Dermavant, Dermira, Dow Pharma, Dr. Reddy's Laboratories, Eli Lilly, Galderma, Genentech, GlaxoSmithKline, Idera, Johnson & Johnson, Leo Pharma, Maruho, Merck, Medicis, Novartis AG, Pfizer, PharmaDerm, Promius, Stiefel, Sun Pharma, UCB, Valeant, and XenoPort, and has received honoraria from AbbVie, Allergan, Almirall, Amgen, Arcutis, Biogen Idec, Bristol Myers Squibb, Celgene, Cipher, Connetics, Dermavant, Dermira, Dr. Reddy's Laboratories, Eli Lilly, Galderma, Genentech, GlaxoSmithKline, Johnson & Johnson, Leo Pharma, Merck, Novartis AG, PharmaDerm, Promius, Serono (Merck Serono International SA), Stiefel, Sun Pharma, Taro, UCB, and Valeant. DD has served as a speaker and consultant for AbbVie, Amgen, Arcutis, Bristol Myers Squibb, Dermavant, Eli Lilly, EPI Health, Incyte, Janssen, Leo Pharma, Novartis, Pfizer, and UCB. LMA has received honoraria from AbbVie, Arcutis, Bristol Myers Squibb, Boehringer Ingelheim, Dermavant, Eli Lilly, Incyte, Janssen, Leo Pharma, Novartis, Pfizer, Regeneron, Sanofi, and UCB.

ACKNOWLEDGMENT

Writing and editorial assistance was provided by Jieming Fang MD, of Peloton Advantage, LLC, an OPEN Health company, funded by Bristol Myers Squibb.

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doi:10.36849/JDD.7748R1

August 2024 653 Volume 23 • Issue 8

ORIGINAL ARTICLE

Journal of Drugs in Dermatology

United Arab Emirates Consensus Recommendations for Management of Acne Vulgaris

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ABSTRACT

Acne in the United Arab Emirates is a common disease that causes burden to patients, has psychosocial impacts, and is associated with physical sequelae such as dyspigmentation and scarring. This guideline, which was developed from evaluation of existing international and national evidence-based acne guidelines along with live meetings of UAE acne experts, is designed to facilitate the management of acne in the UAE health care system. It discusses evaluation of acne severity, evidence-based guidance on acne treatment, and strategies for management of this chronic disease. Effective treatment of active lesions and prevention of sequela is likely to improve the health of many UAE patients with acne.

J Drugs Dermatol. 2024;23(8):653-660. doi:10.36849/JDD.7748R1

INTRODUCTION

Acne vulgaris is a chronic inflammatory disease that affects pilosebaceous units on the face and trunk requiring longitudinal patient management.[1,2] It has a multifactorial pathophysiology that involves an altered sebaceous lipid profile, inflammation, hyperkeratinization, and a dysbiosis of the skin that leads to proliferation of the bacterial commensal *Cutibacterium acnes*.[3,4] Clinical manifestations are varied, and include active acne with combinations of papules, pustules, comedones, nodules, and cysts, and its sequelae (which can occur in concurrence with active acne vulgaris regardless of severity) acne induced pigmentation (formerly known as post-inflammatory hyperpigmentation/PIH) or erythema and/or scarring.[5,6] In populations with dark skin types, the pigmentary alterations can pose significant burden to patients – sometimes causing greater distress than the primary acne lesions themselves.[7] Although there is no standardized grading scale for acnea review by Tan et al indicates the majority of acne is mild (~60%) but that there is also a substantial population of patients with moderate (~30%) or severe acne (~10%).[8]

This publication presents consensus recommendations for the management of acne in the UAE. These recommendations are not intended as a complete review of all studies in the literature, rather a synthesis of existing evidence-based guidelines, the experience of experts in the absence of evidence, and application of known data in the UAE.

FIGURE 2. Estimated distribution of acne severity.[8]

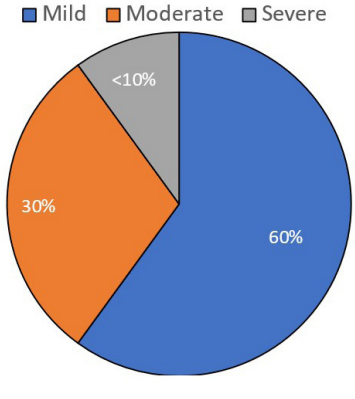
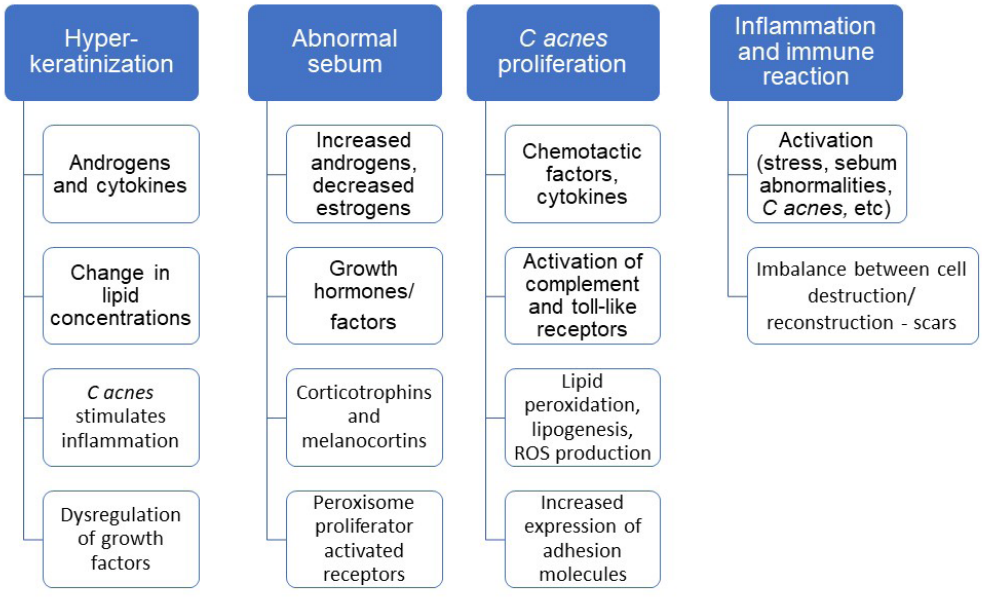


FIGURE 1. Overview of acne pathophysiology. From Oon et al.



MATERIALS AND METHODS

The Emirates Dermatology Society members represent a spectrum of institutions as well as the private sector in the UAE. The Consensus Recommendations Committee was chosen by the Society steering committee according to known expertise in acne via publications and geographic representation. These dermatologists reviewed existing acne guidelines (from various regions around the world; for detailed reviews of the evidence, readers are encouraged to consult these publications.[4,6,9-15] Then, the group held a live meeting to identify areas of agreement as well as clinical practice patterns more uniquely found in the UAE.

CONSENSUS RECOMMENDATIONS

Epidemiology of Acne

Consensus: The epidemiology of acne vulgaris in UAE is generally similar to that in other parts of the world. However, patients are more likely to have oily skin, dark skin types, and high prevalence of truncal involvement compared with other regions, and this should be factored into treatment recommendations.

There are few UAE specific studies, but existing data suggests that acne epidemiology in the UAE is generally similar to international statistics. As in other areas of the world, acne vulgaris is a widespread skin disease in the UAE among adolescents and young adults.[10,16] A prevalence study among university students (n=900) in Ajman, UAE with a mean age of 22.3 years showed approximately 65% of both young men and women had acne.[1] Many acne patients in the UAE also have dark skin types, and are at increased risk for acne-induced pigmentation even when their acne is mild.[10] While oily skin is quite common, dry skin and dermatitis can pose challenges in the UAE population during winter.[10]

Acne in adults is increasingly common in UAE.[10] Gollnick et al reported a study of 623 patients aged 25 or older treated at a private clinic in Dubai; among this group, 68% of women had acne as did 32% of men.[10] This acne had typically persisted from a younger age, and was most often inflammatory rather than comedonal acne.[10]

Classification of Acne

Consensus: A global assessment of acne (mild, moderate, severe and nodular/cystic) is recommended due to practicality, ease of use, and ability to include various anatomical locations (face and trunk) as well as subjective severity items such as degree of inflammation.

Acne has a wide range of clinical presentations, and patients often have a mixture of comedones and inflammatory lesions.[10] Assessing the severity of acne can be challenging, as there is no universally accepted grading system. Our consensus is that an overall or global assessment of acne, based on lesion type, density, and size, along with extent of involvement of the affected site is practical and familiar for clinicians. We recommend that clinicians include evaluation of chest and back with a similar classification scheme, and the overall management approach should be based on the area with the worst severity.

Typically, the diagnosis of acne is made clinically without additional need for diagnostic testing; however, we agree with the Middle Eastern acne consensus recommendations that testing may be appropriate for patients who do not have a good response to therapy and/or have an atypical clinical presentation.[10] The recognition of associated scarring and/or acne-induced pigmentation is important for selecting acne treatments. For example, topical retinoids mitigate development of some atrophic acne scars as well as improve acne-induced pigmentation while azelaic acid can be beneficial for the latter.

First and Second Line Topical and Systemic Acne Therapies

Generally, the selection of acne therapy should be guided by multiple factors such as patient experiences with any previous treatments and skin type as well as treatment factors including vehicle type, effectiveness, practicality for the patient to apply, and cost.[9,13] Efficacy, tolerability, and side effects should be assessed after 2 to 3 months, and adjustments to the treatment regimen may be made at that time as appropriate.[13] Assessments may be made more frequently in cases of severe acne.[10]

Consensus for Mild Acne: Use of topical retinoids, benzoyl peroxide (BPO), azelaic acid, and fixed-dose combinations of adapalene/BPO or tretinoin/clindamycin are strongly recommended.

Mild acne can often be treated with topical therapies, and topical retinoids, benzoyl peroxide (BPO), azelaic acid, and fixed dose combinations of topical retinoids with benzoyl peroxide or clindamycin have rigorous and extensive safety and efficacy data.[9] Figure 3 provides an overview of the approach to treatment for mild acne.

Topical retinoids (tretinoin, adapalene, and trifarotene as available in the UAE) can normalize follicular infundibular hyperkeratinization, are anti-comedogenic, have anti-inflammatory effects, and can treat/prevent pigmentation and scarring associated with acne.[10] Acne experts agree that topical retinoids are the foundation of acne therapy due to these mechanisms of action.[10] The newest topical retinoid in UAE is trifarotene, which is approved for treating acne in patients aged 12 or older, and the clinical trials of trifarotene uniquely included rigorous assessment of truncal acne in addition to facial acne.[10] Topical retinoids can be associated with skin irritation (erythema, scaling, dryness, burning, and stinging).[17] Patients should be educated about the potential for irritation, and should know that irritation usually resolves within the first few weeks of treatment.[17] Strategies such as every other day dosing and use of pH balanced gentle cleansers and moisturizers can improve tolerability of therapy initiation.[18] Sun protection should also be recommended for patients who are treated with topical retinoids.[6] Because of the multiple actions of topical retinoids against comedogenesis and inflammation, they are a good choice for maintenance therapy once clearance is achieved.[6]

BPO is a preferred antimicrobial due to its bactericidal activity against *Cutibacterium acnes* and absence of documented bacterial resistance.[10] While BPO is available in concentrations up to 10%, a comparison of 2.5%, 5%, and 10% concentrations showed that increasing concentrations offer minimal additional efficacy but are less well tolerated.[19] Lower concentrations, water-based, and wash-off products may be the best choice for patients, particularly those with sensitive skin.[10]

The fixed-dose combination of adapalene 0.1% and BPO 2.5% targets three of the four major pathophysiologic factors of acne, provides convenience, and has the potential to improve adherence.[10] It has also been shown that the fixed-combination of adapalene with BPO has synergistic effects that are superior to the additive effects that can be achieved when adapalene and BPO are applied independently.[20] The European Dermatology Foundation (EDF) guidelines give fixed-dose adapalene/BPO a high strength of recommendation for treatment of mild-moderate papulopustular acne due to its robust evidence base.[9] Adapalene/BPO is approved for use in patients aged 9 years or older.[10]

A fixed-dose combination of clindamycin phosphate 1.2% and tretinoin 0.025% (Clin/RA) was approved for management of acne in the UAE from age 12 and above in April, 2020. The EDF guidelines gave it a medium strength of recommendation as treatment for mild-moderate papulopustular acne.[9] It has shown significantly better efficacy than topical clindamycin alone and is efficacious across the spectrum of Fitzpatrick skin phototypes.[21]

Azelaic acid 20% has comedolytic, antibacterial, and anti-inflammatory actions.[6] Azelaic acid, also with a medium-strength recommendation from EDF, may be used during pregnancy and breastfeeding.[6,9] It may be useful for patients with darker skin tone due to lightening effects.[5] The most common adverse events associated with azelaic acid are skin burning, dryness, and peeling.

Topical antibiotics (clindamycin and erythromycin) should not be used as monotherapy due to the potential for antimicrobial resistance.[9] In addition, topical antibiotics should not be used together with oral antibiotics as combination therapy, since they have the same mechanism of action.[17] If electing to treat a patient with a topical antibiotic, BPO and/or a topical retinoid should be used.

Consensus for Moderate-Severe acne: Systemic antibiotics are recommended to be added to topical therapy for moderate to severe acne; oral isotretinoin is strongly recommended for severe acne, as well as for the treatment of moderate acne that is either treatment-resistant, or that produces physical scarring

FIGURE 3. Mild acne: Approach to treatment.

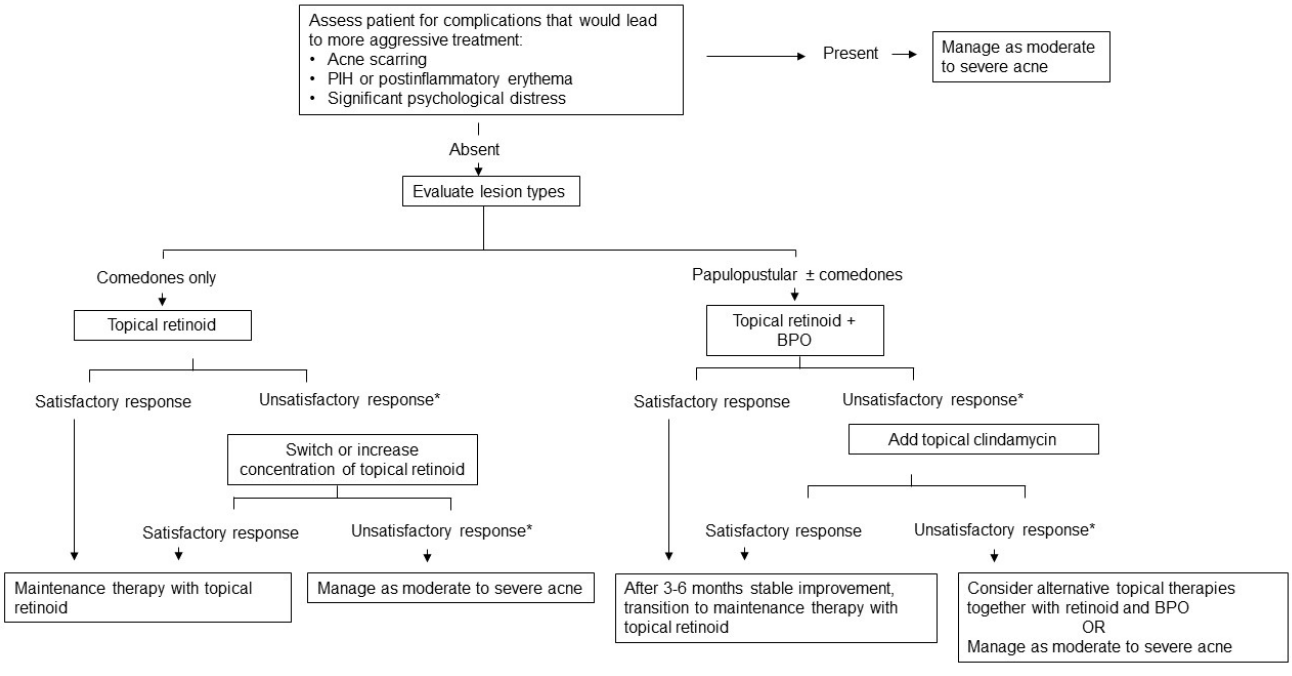
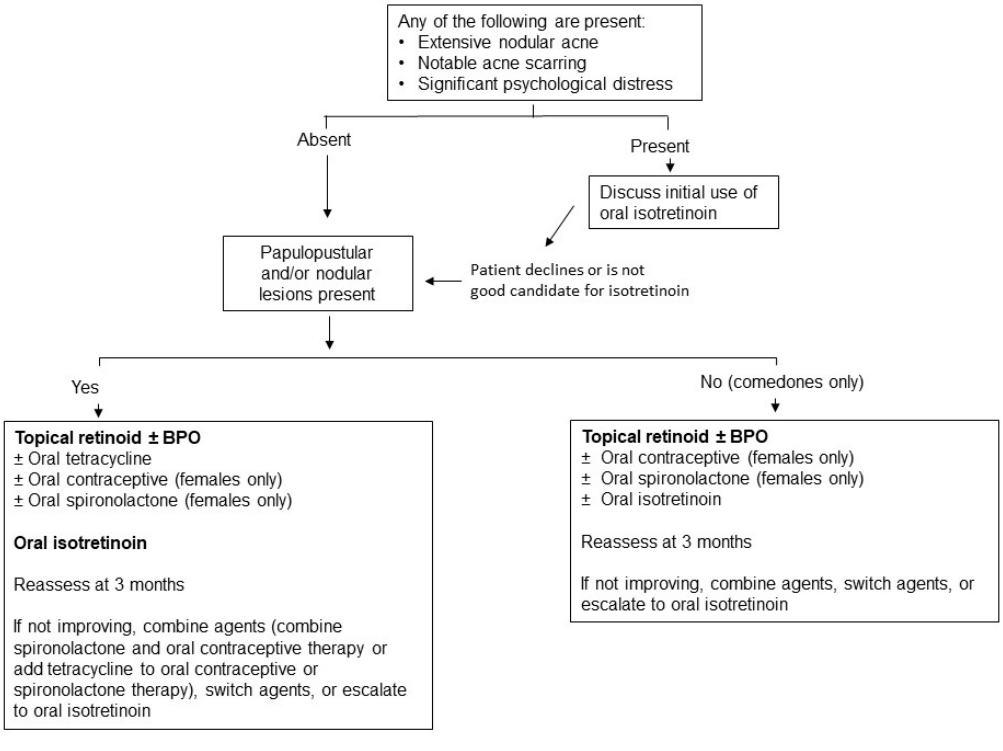


FIGURE 4. Moderate to severe acne: Approach to treatment.



or significant psychological distress; oral contraceptives may be considered for females. It is strongly recommended that concomitant topical therapy with retinoid or BPO should be used with systemic antibiotics and for maintenance after completion of systemic antibiotic therapy.

While most patients with mild to moderate acne should be treated with a combination of topical retinoid plus a topical antimicrobial like BPO, increasing acne severity warrants the addition of systemic therapy.[17] Figure 4 provides an overview of the management of moderate to severe acne.

Oral Antibiotics

For acne, first-line antibiotics are tetracyclines (doxycycline or lymecycline) except when a contraindication is present (pregnancy, lactation, or allergy); minocycline is a second line antibiotic and should be used with caution due to side effects.[22] Tetracyclines are approved for patients 12 years and older, except doxycycline is approved for those 8 years or older.[10] Antibiotics act via anti-inflammatory mechanisms, with a secondary effect on *C. acnes*.[10] The potential for antimicrobial resistance should limit use of oral antibiotics to 3-6 months duration; further, it is recommended that concomitant therapy with topical retinoid and/or BPO should be used during oral antibiotic treatment to limit local development of cutaneous flora resistance.[10] Use of systemic antibiotics other than tetracyclines and macrolides is discouraged because there are limited data in acne.[10] Azithromycin may be considered as an alternative option for patients who are allergic, women who are pregnant or lactating, although it has lower efficacy compared to the first-line antibiotics.

Hormonal Therapy

Hormonal therapy with oral contraceptives may be considered as therapy for women. As noted in the Middle Eastern consensus recommendations, societal norms in the Middle East may inhibit use of oral contraceptives for young or unmarried women.[10] We agree with Gollnick et al that dermatologists should be familiar with hormonal options and consider working together with a gynecologist to manage acne in women who could benefit from this approach.[10]

Spironolactone, an aldosterone receptor antagonist, has antiandrogenic activity that can improve acne in women in doses from 50 to 200 mg per day.[6] However, spironolactone in acne is off-label use. According to the American Academy of Dermatology acne guidelines, use of spironolactone can be considered in a select group of women who do not respond to other therapies.[6]

Oral Isotretinoin

Isotretinoin targets all of the main pathophysiologic factors in acne, and is recommended for severe acne; Table 3 presents an overview of its use.[10] It may also be used for moderate acne that is not responding to treatment or for patients who have scarring or psychological distress.[10] Isotretinoin use may be considered early for patients who have two or more of: positive family history of acne, onset of acne at a young age, hyperseborrhea, truncal acne, important psychosocial impact from acne, scarring, and persistent or late onset acne.[10] It may be initiated at a dose of 0.25 - 0.5 mg/kg/day for one month, then increased as tolerated to 1.0 mg/kg/day.[10] Isotretinoin-induced acne flaring or acne fulminans rarely occur at the start

TABLE 1.

Classification of Acne Severity (Can Be Applied to Face and Trunk)		
Severity	**Score**	**Description**
Clear	0	No lesions or very few scattered lesions
Almost clear	1	Barely visible from 2.5 m distance; few scattered non-inflammatory and inflammatory lesions
Mild	2	Easily recognizable, involving less than half of affected skin area; many acne lesions
Moderate	3	>half of affected area is involved; numerous lesions
Severe	4	Involvement of entire area; numerous lesions and nodules/cysts may be present
Very severe	5	Very inflammatory acne affecting entire skin area; nodules/cysts present

TABLE 2.

Use of Hormonal Therapies
Oral contraceptives containing estrogen are effective for treatment of inflammatory acne in women
Spironolactone may be useful for some women with acne
Patients with severe inflammatory acne may derive benefit from short term oral corticosteroid therapy while standard acne treatment is initiated
For patients with adrenal hyperandrogenism (documented), low dose oral corticosteroids may be useful to treat acne

TABLE 3.

Oral Isotretinoin in UAE

	Dosing Strategies	Endpoints of Treatment	Changes to Therapy	Duration of Prescription
Moderate to severe acne	Treatment initiated at 0.25-0.5 mg/kg to minimize risk for acne flare After 1 month, dose may be titrated upward to 1 mg/kg per day as tolerated Once daily isotretinoin may be considered to improve adherence	Acne clearance + 2 months	Dose of isotretinoin should be titrated if abnormalities in lipid profile or liver enzymes are detected	--

Severe acne = many inflammatory nodules extensive involvement of 1 or more body regions; Moderate acne = treatment resistant acne or acne that relapses rapidly after cessation of oral antibiotic therapy, presence of scarring, or significant psychosocial distress

of isotretinoin therapy in patients with severe inflammatory acne (eg, acne conglobata, acne fulminans) or deep comedonal acne.[6] Systemic glucocorticoids may be initiated in this condition along with a reduction in isotretinoin daily dosing.[6]

Photoprotection, including avoidance of sun exposure when possible, is recommended during isotretinoin therapy.[6] All patients of childbearing potential must select and commit to the use of two forms of birth control for at least one month prior to starting isotretinoin therapy, during therapy, and for one month after therapy. Monthly serum pregnancy tests should be performed.

Up to 40% of patients have an acne relapse after one course of isotretinoin.[10] Continuing isotretinoin therapy for two months after acne clearance is thought to reduce risk for relapse, but we feel the endpoint of treatment should be decided on a case-by-case basis.[6] Patients should be educated about the risk for severe adverse events, particularly teratogenicity, and counseled about the need for pregnancy prevention during isotretinoin therapy. The relationship between oral isotretinoin and depression is debatable; however, large studies did demonstrate an association.[24,25] In addition, patients who complete a course of isotretinoin should be counseled on how to maintain results and minimize relapse, including advice about skin care and other products used on the skin. For patients who are intolerant, unwilling, or unable to access oral isotretinoin, options include adapalene/BPO or trifarotene plus doxycycline, systemic antibiotics with adapalene or azelaic acid (medium strength recommendation from EDF); EDF gave a low-strength recommendation for systemic antibiotics with BPO, hormonal antiandrogen with systemic antibiotics (females), or hormonal antiandrogens with topical treatment (females).[9]

Consensus: The following testing is appropriate during isotretinoin therapy – baseline complete blood count, alanine transaminase (ALT), aspartate transaminase (AST), cholesterol, and triglycerides along with urine or blood testing for pregnancy. Pregnancy testing should be repeated every month and one month after discontinuation of therapy.

Patients are often followed closely with routine laboratory monitoring, although the value of this practice has been questioned.[26] For generally healthy patients with no underlying abnormalities or preexisting conditions that warrant further investigation, we recommend only to test ALT and triglycerides once at baseline, ideally within a month prior to treatment initiation, and a second time at peak dose.[27] Liver function tests (ALT and AST) are important if it increases three times the upper limit of normal and if there are signs/symptoms suggestive of hepatitis. Isotretinoin dosing should be decreased if this level of elevation occurs without symptoms and discontinued in the presence of associated symptoms. With triglyceride elevations of two to three times the upper limit of normal, monitoring should continue without further increased dose of isotretinoin. In the presence of progressive elevation, the isotretinoin dose should be modified or discontinued as appropriate in the dermatologist's judgment.

Acne in Pregnancy

Treatment selection for pregnant individuals with acne vulgaris involves consideration of risk for detrimental effects of therapy on the fetus. Common acne therapies that are contraindicated for pregnant individuals or individuals attempting to become pregnant include oral isotretinoin, oral tetracyclines and topical retinoids. The decision to treat acne in pregnant individuals warrants consideration of the severity of acne, the patient's risk tolerance, and guidance from the patient's obstetrical provider. If acne therapy is desired, reasonable options include erythromycin/azithromycin or topical clindamycin with BPO, and topical azelaic acid.

Physical Modalities

Consensus: Lasers can be used as adjunctive therapy but should not be used as monotherapy. Radiofrequency and microneedling may be helpful to improve scars and pigmentation, CO2 lasers are not indicated in Fitzpatrick skin types 4-6 due to risk of reaction and pigmentation problems.

As indicated in the Consensus statement, procedures can have a role in acne management; however, it is our belief that these interventions are best suited for improving overall skin appearance by resurfacing.[10] Options include chemical peels, laser and pulsed light therapy, photodynamic therapy, radiofrequency and microneedling. A full discussion of these procedures is beyond the scope of this publication.

Acne Sequelae

Consensus: In the UAE, acne-induced pigmentation and scarring occur frequently and early treatment to reduce clinical inflammation is recommended.

Patients in the UAE have a wide range of skin phototypes, and there are many with darker skin types that are vulnerable to developing pigmentary deposition and uneven skin tone known as acne-induced pigmentation. Patients report that acne-induced pigmentation (localized or diffuse coloration at the sites of former acne lesions) can be very bothersome, in some cases more than the acne lesions themselves, and that the uneven color frequently lasts a long time.[7,10] In the setting of acne, inflammation and inflammatory mediators stimulate melanocytes which increase melanin synthesis and pigment deposition in keratinocytes and melanophages. Excoriations can also induce or exacerbate acne-induced pigmentation as well as scarring.[10] To date, prevention is the primary treatment of acne-induced pigmentation, along with reducing acne-associated inflammation as early and effectively as possible (Table 4).[10] Topical retinoids inhibit melanosome transfer and increase epidermal turnover and thus directly affect pigmentation; and while the depigmenting action of topical retinoid therapy is not rapid, retinoids are a good therapeutic option for acne patients who have or are at risk for acne-induced pigmentation.[10] As mentioned above, azelaic acid may also be considered for patients with darker skin tones and acne-induced pigmentation. Procedures such as chemical peels and light therapies such as intense pulsed light may also be used to treat acne-induced pigmentation.[10, 31]

A full discussion of acne-related scarring and its treatment is beyond the scope of this guideline. Patients with acne are at risk for scarring, and it is generally accepted that prevention of scars by early and effective treatment of acne is optimal. Once scarring has occurred, restoring the skin to pre-scar quality is difficult and often involves also the use of multiple physical modalities which can include microneedling, laser resurfacing and surgical subcision along with additional options.[32-35]

Role of Skin Care Regimen in Acne

Consensus: A proper skin care program can improve results achieved by patients while undergoing treatment for acne vulgaris. Photoprotection is recommended, and patients taking oral isotretinoin should avoid sunlight when possible. A gentle cleanser and moisturizer regimen can enhance tolerability and adherence to treatments like topical retinoids.

Patients with acne should be educated about how to optimize their skin care regimen by using a gentle cleanser and moisturizer along with sun protection. Healthcare practitioners working with patients should discuss patient preferences for formulations, cost limitations (if any), and ability to adhere to regimen.

CONCLUSION

Acne is an important problem in the UAE, and standardizing acne care is likely to improve patient outcomes and satisfaction with healthcare. The practical recommendations presented here were developed from existing international and national guidelines that incorporated extensive review and analysis of the medical literature. We agree with those guidelines that mild to moderate acne should be treated with topical therapy, primarily topical retinoids and/or in combination with BPO. More severe acne can warrant the addition of an oral antibiotic or oral contraceptive (for women) to the retinoid/BPO regimen or use of oral isotretinoin. The prevalence of dark skin types, oily skin, and truncal acne add special considerations to acne management in the UAE.

DISCLOSURES

Dr Tan has received grants, honoraria, or served as a consultant for Bausch, Boots Walgreens, Cipher, Cutera, Galderma, La Roche Posay, Novartis, Pierre Fabre, and Pfizer; Dr Al Dhaheri, Dr Ameen, Dr Reda, Dr Alnaeem, Dr Albreiki, Dr Al Nuami, Dr Al Marzooqi, Dr Abdel Dayem, Dr Rajab, Dr Alnaqbi, Dr Al Suwaidi, Dr Al Murrawi, and Dr Hantira have nothing to declare.

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doi:10.36849/JDD.8421

August 2024 661 Volume 23 • Issue 8

ORIGINAL ARTICLE

Journal of Drugs in Dermatology

A Prospective, Multi-Center Study to Evaluate the Safety and Efficacy of a Vegan Nutraceutical to Improve Hair Growth and Quality in Females Following a Plant-Based Diet

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ABSTRACT

Hair thinning affects upwards of 50% of women by age 50, impacting their social-emotional wellbeing. It is a condition now thought to be driven by a multi-factorial etiology, including diet and nutrition. Women following vegan, vegetarian, or other plant-based diets have specific needs for nutrients traditionally sourced from animals, which could affect hair health.

To support hair growth and quality in women following a plant-based diet, a novel vegan nutraceutical (Nutrafol® Women's Vegan Capsules, Nutraceutical Wellness, Inc., New York, NY) was evaluated for its ability to support hair health. The objectives of this 6-month, multi-site, single-blind prospective clinical study was to evaluate the safety and efficacy of the nutraceutical to improve hair growth and quality in women consuming a plant-based diet. The primary endpoint in this study was an increase in terminal hair count at day 180 compared with baseline, as assessed through phototrichogram analysis. Ninety-five subjects completed the study.

Daily intake of the nutraceutical resulted in a significant increase in the number of terminal hairs at day 90 ($P<0.01$) and day 180 ($P<0.01$). There was also an increase in total hair counts ($P<0.01$), the terminal-to-vellus ratio ($P<0.01$), and a decrease in shedding ($P<0.01$). Global Investigator Ratings revealed improved hair growth ($P<0.00001$) and overall quality ($P<0.00001$). In-person hair strength and brittleness assessments significantly improved as well ($P<0.01$ for both). A significant proportion of subjects reported improved hair quality, appearance, texture, and volume. Hair problems affecting the quality of life of the subjects were also reported as improved. This study demonstrated significant improvements in hair growth and quality in a plant-based population with a vegan nutraceutical.

ClinicalTrials.gov Identifier: NCT05332743.

J Drugs Dermatol. 2024;23(8):661-668. doi:10.36849/JDD.8421

INTRODUCTION

Hair loss and thinning are common conditions affecting both men and women that are more recently recognized to be the result of multiple causes.[1] Hair loss can have a significant, detrimental impact on self-esteem, psychosocial functioning, and the overall quality of life of affected individuals.[2,3] It can also present a substantial financial burden on individuals seeking treatment.[4]

There are few United States Food and Drug Administration (FDA)-approved medical treatment options for women.[4] Conventional options include FDA-approved topical minoxidil, but most women are treated with off-label medications including spironolactone, 5-α reductase inhibitors such as finasteride or dutasteride, and, more recently, low dose oral minoxidil.[4] While these medications are effective for thinning hair, they may either have low adherence rates due to effects on hair texture and styling or be associated with side effects.[4,5] In-office procedures including Platelet-Rich Plasma (PRP) therapy and devices like Low-Level Laser therapy are also common practice, though patients are increasingly turning to more accessible, over-the-counter solutions for thinning hair, including natural therapies and dietary supplements.[4,5]

Nutrition influences hair growth and quality, as illustrated by hair conditions seen in malnutrition or specific restrictive diets.[6] For example, individuals who follow a vegan or vegetarian diet have unique dietary challenges given their limited food patterns.[7] This can lead to a risk of increased nutritional deficiencies that will impact overall hair health.[7,8] For example, collagen and keratin, both key structural proteins for hair, are typically derived from protein-rich sources, which the general population tends to source from animal-based foods.[9,10] Iron and zinc deficiencies may develop more easily on a plant-based diet and affect hair growth.[11,12] Pesticides used in plants for human consumption may alter the gut microbiome.[13] Overall, while a plant-based diet may have beneficial influences on health, they increase the chance of nutritional deficiencies that can affect hair health.

Other factors such as stress, hormonal triggers, inflammation, oxidative stress, and biological aging have compounding influence on the hair follicle.[1,14] The multifactorial nature of hair health requires a solution that, in addition to targeting these factors, also addresses the bio-specific needs of consumers following a plant-based diet.[15] Oftentimes, supplements for vegan or vegetarian consumers are formulated by simply removing animal-based ingredients, potentially leaving a gap in nutrient consumption. Current evidence suggests that there may be alternative vegan ingredients that support mechanisms traditionally targeted with animal-derived ingredients. For example, collagen consumption has been linked to improvements in skin, hair, and nail health, but is traditionally sourced from bovine, porcine, or fish.[16-18] Recent research has shown that the plant the Moldavian Dragonhead may increase the expression of type I collagen in C. elegans.[19] In vitro studies also suggest that it activates FOXO-1 and Phosphorylation of AMPK-1, both linked to stem cell longevity and aging.[19] When tested as an oral supplement, female subjects with sun-damaged skin exhibited improved skin hydration, elasticity, and skin density.[19] Another key structural component of collagen and elastin synthesis is the amino acid hydroxyproline, which is generally consumed from meat. Bamboo is reported to be up to 70% silica, which may increase tissue levels of hydroxyproline, making this a useful vegan source to combat the natural loss of collagen.[20] Silica may also be involved in GAGs (compounds that make up connective tissues) synthesis and acts as a cross-linking agent in strengthening keratin.[21]

Taken together, these data indicate that some vegan-sourced botanicals and phyto-extracts may support nutrient gaps traditionally associated with a plant-based diet, and in doing so could improve hair growth. The objective of this 6-month, multi-site, single-blind study was to evaluate the safety and efficacy of a novel nutraceutical formulated with vegan ingredients to promote hair growth in adult women consuming a plant-based diet.

MATERIALS AND METHODS

Study Design and Subjects

This was a multi-center, single-blind, single-arm study of a vegan nutraceutical in women leading a plant-based diet (ClinicalTrials.gov Identifier: NCT05332743.) Eligible subjects were healthy women aged 18 to 50 with self-perceived hair thinning confirmed by a dermatologist investigator. Selection criteria are listed in Table 1. All subjects were self-described as following a plant-based diet for at least the 3 months prior to enrollment. Plant-based was inclusive of vegetarian, lacto-vegetarian, ovo-vegetarian, lacto-ovo-vegetarian, vegan, raw vegan, pescatarian, pollotarian, or flexitarian/semi-vegetarian (defined for this study as eating red meat no more than 3X/week). Participants agreed to maintain their current diet for the duration of the study. The study was approved by an Institutional Review Board (Advarra, Columbia, MD) and conducted in compliance with good clinical practice. All participants provided written, informed consent prior to participating in the study.

Study Procedures

After subject eligibility was confirmed, subjects were instructed to take 4 capsules a day of the vegan nutraceutical (Nutrafol® Women's Vegan Capsules, Nutraceutical Wellness, Inc., New York, NY) with a meal for the 6-month duration of the study. The study consisted of clinic visits at baseline, day 90, and day 180, in addition to compliance calls on days 30, 60, and 135. Each clinic visit included a physical examination (blood pressure, heart rate, weight, and height) and a hair examination.

On the first visit during the hair exam, a region of interest (ROI) of 1 cm^2 considered to be a transitional zone between an area of thinning and healthy hair was selected along the frontalis bone where the frontal hairline and lateral hairline meet. This ROI was recorded based on a 3-point triangulation measurement between the medial canthus, lateral canthus, and preauricular skin pit. This point was identified, and the center was marked at each subsequent visit based on the recorded measurements. This ROI was used for analysis using phototrichograms (Canfield HairMetrix®) digital photography, with identified vellus and terminal hair counts based on the width of the hair. These counts were also verified by the dermatologist. The extrapolated measurements collected based on these phototrichograms included: the sum of hair widths (total scalp coverage), hair diameter (mean hair width), terminal to vellus ratio, average number of hairs per follicular unit, follicle count per 1 cm^2, and mean inter-follicular distance.

Hair shed counts were assessed by a hair pull test in 4 different regions of the scalp: the vertex area, both parietal areas, and the occipital area. Gentle traction was applied on a group of approximately 60 hairs. A hair pull test was considered positive if more than 10% or 6 hairs came out with the pull, indicating active hair shedding.[22] Subjects were instructed not to wash or

TABLE 1.

Selection Criteria	
Inclusion Criteria	
1.	Females aged 18-50, leading a plant-based lifestyle for at least 3 months and for the duration of the study.
2.	All Fitzpatrick skin types with self-perceived thinning, confirmed by a dermatologist.
3.	General good health, as determined by the Investigator.
4.	Willing to maintain the same hair length, hairstyle, and coloring practices for the duration of the study.
Exclusion Criteria	
1.	Pregnant, planning a pregnancy, or nursing.
2.	Serious complications due to COVID-19 previously or during the study as determined by the investigator.
3.	Clinical diagnosis of hair loss disorder such as alopecia areata, telogen effluvium or scarring forms of alopecia.
4.	History of acute or chronic disease that could interfere with study participation or affect study results.
5.	Current hair loss or skin disease (eg, psoriasis, atopic dermatitis, skin cancer, eczema, sun damage, seborrheic dermatitis), infections, cuts, and/ or abrasions on the scalp or condition (eg, sunburn, tattoos) on the treatment area that, in the opinion of the Investigator, might put the subject at risk or interfere with the study conduct or evaluations.
6.	History of surgical correction of hair loss on the scalp.
7.	Use of any products or devices purported to promote scalp hair growth within the 6 months prior to study start.
8.	Utilization of low-level lasers for hair growth in the last three months.
9.	Females who have started the use of hormones for birth control or hormone replacement therapy within the last 6 months.
10.	History of burning, flaking, itching, and stinging of the scalp.
11.	History of malignancy or currently undergoing chemotherapy or radiation treatments.
12.	Known allergy to any of the ingredients in the investigational product.
13.	Known history or recent blood work indicating iron deficiency, bleeding disorders or platelet dysfunction syndrome, subjects receiving anticoagulant therapy or smokers with usage >20 cigarettes/day.
14.	Use of any medications or medicated shampoos that are known to potentially cause hair loss or affect hair growth, as determined by the Investigator.

shampoo their hair for 24 hours prior to the clinic visit to ensure accurate results.

Global Investigator Assessments of change in hair growth and quality at days 90 and 180 were done via Standardized Global photography taken with Canfield IntelliStudio System®. Global ratings were done using a 7-point Likert scale, in which 0 indicated no change, negative values (-1 to -3) indicated worsened, and positive values (+1 to +3) indicated improvement. Hair quality was defined as the composite of hair brittleness, dryness, texture, strength, scalp coverage, and overall appearance. Hair strength and brittleness were further assessed in person by the site investigator. Strength and brittleness were rated on a 10-point Visual Analog Scale (VAS) with a rating of ten being the highest rating (very strong or not brittle).

Self-assessment questionnaires including perception of treatment benefit and a Quality of Life (QoL) questionnaire were administered at all timepoints, including during the compliance calls.

Study Endpoints

The primary endpoint was the increase in mean terminal hair count at day 180 relative to baseline (day 0), as measured by phototrichograms. The secondary endpoints were the change in all hair counts (total, terminal, and vellus) across all timepoints, change in terminal to vellus ratio, follicle count, and mean inter-follicular distance compared with baseline measured by phototrichograms; improvement in hair quality and growth assessed by physician ratings of global photographs; decreased hair shedding pull test compared with baseline; and perceived improvement in subject's assessment of change in hair growth and appearance measured with Subject QoL assessment and consumer perception questionnaires. Safety analyses were done, and adverse events were compiled.

Statistical Analysis

Descriptive statistics were used to compile the study population baseline demographics, distributions, and variables. The primary outcome measurement was evaluated using a one-sample t-test comparing the means for the 2 correlated samples. Continuous measurements across 3 timepoints (days 0, 90, and 180) were evaluated through analysis of variance (ANOVA) with subsequent Tukey HSD analysis. Responder rates or other assessments of proportions were evaluated using a one-sample t-test for proportions, Fisher's exact test, or Chi-Square analysis when the data were presented in contingency table format. The overall change in paired categorical contingency table greater

than 2x2 was analyzed using the McNemar-Bowker test for symmetry. Categorical data were also further categorized into groups related to the degree of change across time and analyzed using a one-sample t-test. A $P<0.05$ was considered statistically significant for clinically meaningful change.

RESULTS

Demographics and Baseline Characteristics

One hundred and ten subjects were enrolled in the study and 95 subjects completed the study per the protocol. The average age was 34.9 ± 9.7y (range:18 - 52). Fifty- two percent of these subjects considered themselves semi-vegetarian, 11% vegetarian, and 7% vegan. The rest of the population classified themselves as pollotarian, pescatarian, or lacto-vegetarian. The per-protocol population was diverse – see table of demographics for details (Table 2).

TABLE 2.

Per-Protocol Demographics	
Ethnicity	**Percentage**
Non Hispanic/Latino	80%
Hispanic/Latino	20%
Race (n=95)	**Percentage**
Caucasian	54%
Asian	20%
Hispanic	3%
African American	3%
Middle Eastern	2%
American Indian	1%
Hawaiian/Pacific Islander	1%
White/Asian	3%
White/African American	3%
White/American Indian	1%
Other (not specified)	9%

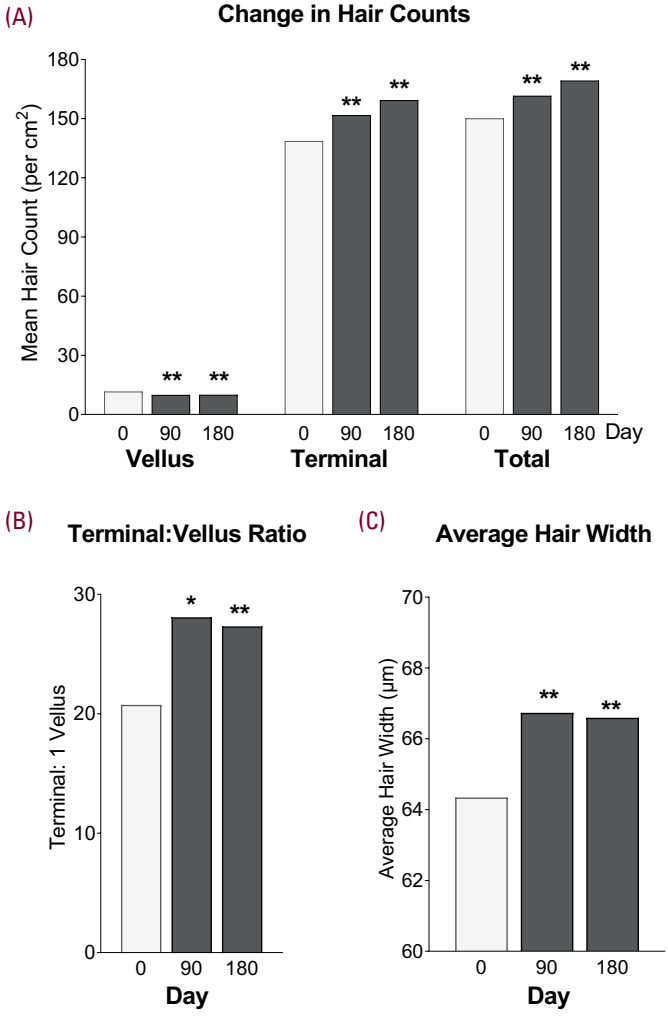
Primary Endpoint

There was a significant and progressive increase in terminal hair count from baseline (138.6 ± 37.2 hairs per cm^2) to day 180 (159.3 ± 43.9 hairs per cm^2, $P<0.0001$) meeting the primary endpoint for efficacy (Figure 1). These changes translated into a 15% increase in terminal hairs between day 0 and day 180. Test site analysis for the per-protocol population confirmed that the primary endpoint was met independently at both test sites.

Secondary Endpoints

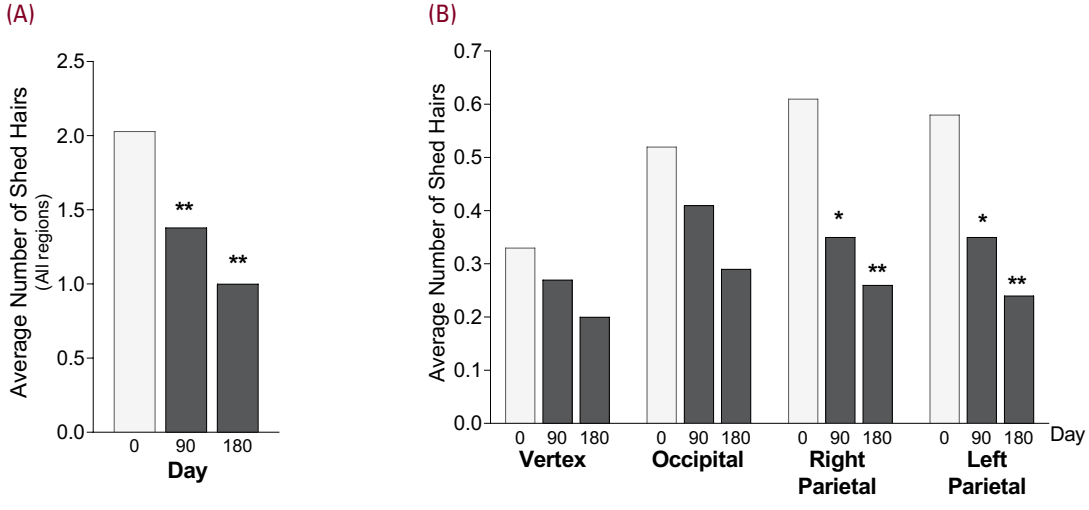
Total hair counts also progressively and significantly increased throughout the study (150.1 ± 35.8 at baseline to 161.6 ± 38.8 at day 90 to 169.2 ± 42.8 per cm^2 at day 180, $P<0.01$, Figure 1), translating into an increase of 12.8% by day 180 compared with baseline. The number of vellus hairs significantly decreased over time (11.5 at baseline to 9.9 at day 180, $P<0.01$), though there was an increase in the terminal-to-vellus hair ratio at day 90 ($P<0.05$) and 180 ($P<0.01$, Figure 1). There was also a significant increase in average hair width, increasing from 64.3 µm at baseline to 66.6 µm by day 180 ($P<0.01$). Finally, the average number of hairs per follicular unit increased from baseline to day 180 (1.2 ± 0.1 to 1.3 ± 0.2, $P<0.01$) and the inter-follicular distance decreased from 1.14 to 1.09 mm ($P<0.01$). Taken together, an increased number of hairs and smaller inter-follicular distance indicates an increase in scalp coverage.

FIGURE 1. Changes in hair parameters from baseline to day 180. (A) Terminal and total hair counts significantly increased throughout the duration of the study. Vellus hair count decreased. (B) This resulted in a significant increase in terminal-to-vellus hair ratio. (C) There was also a significant increase in the average hair width.



*P<0.05 in Tukey HSD Test compared with day 0.
**P<0.01 in Tukey HSD Test compared with day 0.
HSD, honest significant difference

FIGURE 2. Hair shedding decreases over time. (A) Average total hair shed per subject from all combined regions significantly decreased. (B) This was driven by a significantly decreased shed count in the right and left parietal regions.

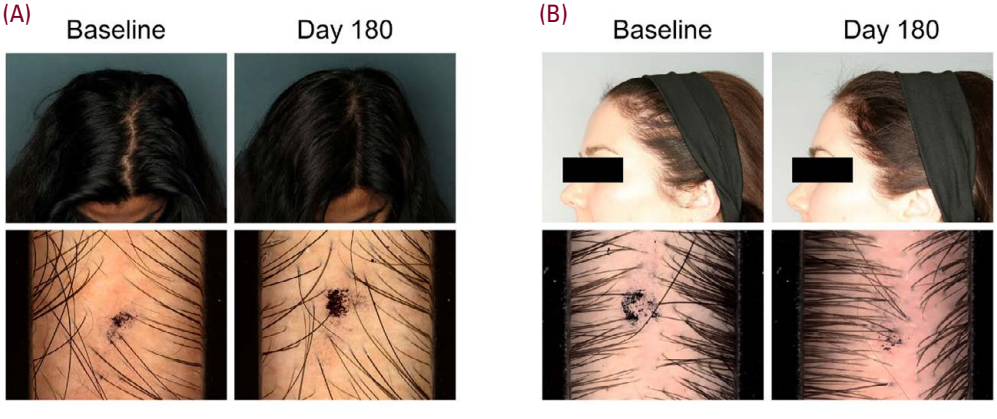


*P<0.05 in Tukey HSD Test compared with day 0.
**P<0.01 in Tukey HSD Test compared with day 0.
HSD, honest significant difference

For hair shedding counts, there were no positive hair pull tests recorded, confirming that none of the subjects was experiencing active hair shedding at any timepoint. Total hair shed combined from all regions significantly and progressively decreased throughout the study (2.0 ± 2.3 at baseline, 1.4 ± 1.5 by day 90, and to 1.0 ± 1.3 by day 180; P<0.01 at both timepoints, Figure 2). When assessed by region, the right parietal and left parietal areas of the scalp both decreased significantly compared with baseline (P<0.01 for both), while the vertex and the occipital regions did not (P=0.27 and 0.09, respectively) (Figure 2).

There were significant and progressive improvements in the Global Investigator Ratings of hair quality and growth throughout the study. The proportion of subjects rated as improved compared with neutral or negative was analyzed and found to be statistically significant for both hair quality and growth (P<0.05 and P<0.00001 respectively). For hair quality, 79% of subjects were rated as improved, and only 21% of subjects were rated as having no change at day 180. No subjects received ratings of "worsened" at either timepoint. In considering hair growth, 87% of subjects were considered improved, and only 11% were considered "no change" from baseline by day 180. Two subjects were considered "worsened". Figure 3 shows improvements in a representative subject seen through global photographs, as well as phototrichogram images of the target area for that subject. In person investigator-rated hair strength and brittleness improved during the study. Hair strength ratings increased from 7.3 ± 1.5 to 8.7 ± 1.0 (P<0.01), and hair brittleness ratings improved from 6.8 ± 1.6 to 8.2 ± 1.0 (P<0.01).

FIGURE 3. Improvement in hair growth in 2 representative subjects. (A) Thirty-five-year-old, vegetarian, mixed race/other Pacific Islander. (B) Thirty-six-year-old vegan Caucasian.



Top row: Global photographs showing visible clinical improvements.
Bottom row: Phototrichogram images of selected target area.

TABLE 3.

Subject Assessment Results	
Since the start of the study …	**Percentage of Subjects Reporting Improvement at Day 180**
My hair feels more nourished and less dry/brittle.	78%*
I have noticed an improvement in overall hair quality.	85%*
I have noticed an improvement in the appearance of hair health.	87%*
I have noticed an improvement in hair texture.	69%*
I have noticed an improvement in hair volume.	69%*
I have noticed reduced hair shedding.	67%*
I have noticed baby hairs growing out.	79%*
I have noticed an improvement in hair strength.	82%*
I have noticed an improvement in speed of hair growth.	69%*
My hair feels longer	80%*
I have noticed an improvement in fullness/thickness of hair.	72%*
I have noticed more new hairs.	76%*
I have noticed an improvement in scalp coverage.	65%*

*Indicates a significant proportion of subjects reporting a favorable response compared with the proportion of subjects reporting an unfavorable response ($P<0.01$).

Subjective assessment of changes in hair parameters and quality of life as measured by questionnaires also reflected the improvements in hair counts and ratings seen in this study (Table 3). Notably, a significant proportion of subjects reported perceiving their hair as more nourished and less dry/brittle, improved overall hair quality, and improved appearance of hair health. Quality of life parameters pertaining to hair showed that hair thinning affected day-to-day life for all subjects, and feelings of attractiveness, comfort socializing, and self-consciousness improved. Notably, at baseline, 70% of subjects reported spending much time making their hair look thicker/fuller. By day 180, this trend reversed, and 68% of subjects reported 'none' or 'just a little bit' of time making their hair look thicker/fuller. Likewise, at the beginning of the study, a majority (64%) of subjects reported that 'problems with their hair made them feel as though they appear older', but by day 180 the proportion of subjects decreased to only 32% reporting this.

Safety

In general, the product was well tolerated. No serious adverse events (AEs) were reported. A total of 10 incidences of potentially related AEs were reported by 7 subjects. Eight AEs were determined to be of mild severity and 2 of moderate severity. Most pertained to minor gastrointestinal issues (constipation 40%, abdominal pain 10%, and gastroesophageal reflux disease 10%) or to symptoms of 'head feels hot' and headache (30%). All resolved with no medical interventions.

DISCUSSION

The present study shows that daily intake of vegan nutraceuticals was safe and effective in improving hair growth and quality in women leading a plant-based lifestyle. Results showed a progressive increase in terminal and total hair counts throughout the study. Additional extrapolated measurements collected based on these hair counts, such as mean hair width, follicle count per cm^2, and the mean inter-follicular distance, all improved as well. Dermatologist ratings of global photographs for hair growth and quality, as well as in-person ratings of strength and brittleness also significantly improved. Hair shedding, along with improvements in hair appearance, volume, and growth, were also noted by the subjects and reflected in a better quality of life as it pertains to their hair.

The increase in terminal and total hair counts was coupled with a decrease in the number of vellus hairs over time. This, together with an increase in average hair diameter, may suggest that terminal hair growth is promoted compared with vellus hairs with ingestion of the supplement. Previous research suggests that thicker hair strands are associated with an increased linear hair growth rate.[23] It has also been noted that reduced hair growth rates observed in both male and female patterned hair loss are also tightly correlated to a reduction in hair diameter.[23] Thus, an increase in the number of terminal hairs seen in this study and a decrease in thin, vellus hairs could be improving hair growth by promoting the presence of thicker hair strands and providing more visible coverage.

The number of hair fibers per follicular unit and hair density are all affected by factors such as age and ethnic and/or racial background. In general, the number of hairs per follicular unit decreases with age.[24] But different ethnic or racial backgrounds have been linked to different densities.[24] Asian and Caucasian populations have been characterized as having a higher hair density than those of African descent.[24] In this study, the average number of hairs per follicular unit significantly increased from baseline to day 180 and the inter-follicular distance also decreased. Considering the diverse population of Asian, Caucasian, Hispanic, and African American subjects in this

study, an increased number of hairs and smaller inter-follicular distance may indicate an overall increase in scalp coverage irrespective of different racial or ethnic groups. Our results warrant further expanded studies in ethnic sub-populations for further characterization.

Both the investigator ratings of global photographs for hair quality and in-person dermatologist assessments of hair strength and brittleness significantly improved throughout the study. In addition, subjects reported improvements in overall hair quality, appearance of hair health, hair strength, and hair feeling less dry/brittle. Hair growth and quality have long been linked to the dietary and nutrient intake of an individual.[25] Including ingredients that support the nutritional gaps in subjects following a plant-based diet may have contributed not only to the hair growth seen in these results, but also the improvements in hair quality such as strength.

Hair growth and quality have documented impacts on the quality of life, especially in women.[26] Women are also about twice as likely than men to describe themselves as vegetarians.[27] The data presented in this study show that the subjects reported improvements in hair quality, volume, growth, and coverage. It also decreased the impact of 'problems with their hair on feelings of self-consciousness, attractiveness, and socializing'. The nutraceutical was also reported to be well tolerated and easy to incorporate into a daily routine, making this an important tool given the current landscape of hair growth solutions for women following a plant-based diet.

Current hair growth treatment options for women are limited. Considering that veganism, vegetarianism, and other animal-restrictive diets are more popular among women, this population may benefit from tailored therapies for hair thinning.[7,8] It is important to take into account the inherent differences in sources for required vitamins, minerals, and nutrients essential for healthy hair. The approach in many plant-based diets is to remove animal-based sources without providing vegan alternatives for important nutrients. By leveraging plant-based ingredients with clinical support for hair growth, the vegan nutraceutical studied here aims to fill the nutrient gaps from removing animal-sourced nutrients.[19] In doing so, the results support improved hair growth, quality, and satisfaction of the subjects' hair in a population that is plant-based. To our knowledge, this is the first study to demonstrate significant improvements in hair growth and quality in a plant-based population with these ingredients.

LIMITATIONS

This study was conducted in a large and diverse population of women leading a plant-based lifestyle. A placebo arm would have provided a control, arguably decreasing bias in the subjective assessments of the study. The results of this study warrant the development of future studies in an expanded population with a placebo-controlled design.

DISCLOSURES

Dr Sivamani has served as a scientific advisor for Nutraceutical Wellness LLC. Dr Ablon has previously received research grants from Nutraceutical Wellness LLC. Drs Maloh and Nong have no disclosures to report. Drs Hazan and Raymond are employees of Nutraceutical Wellness LLC. Funding for this study was provided by Nutraceutical Wellness LLC.

ACKNOWLEDGMENT

The authors would like to thank Elvira Cawthon at Cawthon Clinical Consulting for the statistical analyses done in this study.

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doi:10.36849/JDD.8282

August 2024 669 Volume 23 • Issue 8

ORIGINAL ARTICLE

Journal of Drugs in Dermatology

Safety and Tolerance Evaluation of a Suncare Product in Ethnically Diverse Children With Atopic Dermatitis-Prone Skin

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ABSTRACT

Atopic dermatitis (AD) is a common chronic inflammatory skin condition, with high prevalence in children. Sun protection is important for children with eczema and AD-prone skin, yet many sunscreens can cause skin irritation due to their formulations. In this study, we evaluated the safety and tolerance of an SPF 50 sunscreen in ethnically diverse children with a history of AD over 4 weeks of product use. A total of 45 children from diverse racial/ethnic backgrounds, aged 3 to 12 years old with skin phototypes I-VI, plus a history of eczema and perceived sensitive skin completed the study. All participants applied sunscreen daily on the face and body, at least 15 minutes prior to sun exposure and as needed. After 4 weeks, evaluations were performed by a dermatologist and by participants for tolerability. Product performance questionnaires were also completed by parents/guardians of pediatric participants. After 4 weeks of sunscreen application, tolerability assessments of skin dryness, peeling, erythema, and edema were all absent in children participants. Parent/guardian evaluations of sunscreen tolerability for their child also revealed no perceived skin issues. These results were consistent with no adverse event being observed throughout the study. Parents/guardians reported that sunscreen application on children was smooth and even, with the absence of a white cast appearance on children with skin of color. We conclude from this study that this SPF 50 sunscreen is safe to use in ethnically diverse children with a history of AD and sensitive skin.

J Drugs Dermatol. 2024;23(8):669-673. doi:10.36849/JDD.8282

INTRODUCTION

Atopic dermatitis (AD), commonly known as eczema, is a common chronic inflammatory skin condition, characterized by dry, itchy skin, making individuals more susceptible to skin infections and other complications.[1] This condition results in relapsing dermatosis associated with pruritus, sleep disturbance, and impaired quality of life. AD affects 10% to 20% of school-aged children.[2] The prevalence has increased two to threefold over the past three decades in industrialized countries and there is evidence to suggest that this prevalence is increasing.[4] AD affects diverse ethnic groups with varying prevalence. Despite a predominance of studies in individuals of European ancestry, AD has been found to occur more frequently in Asian and Black individuals than White individuals.[8] Clinically, there is notable phenotypic variability driven by a complex interaction between genetics, immune function, and the environment. Environmental factors such as sun exposure, temperature, and humidity contribute to both AD flares and regional prevalence variation.[3]

There are few studies on the role of photoprotection in AD. The use of adequate sunscreens in participants with AD can ensure the level of photoprotection required to prevent skin photoaging and skin cancer, mitigate skin barrier dysfunction, decrease inflammation, and neutralize facial redness.[5] Sunscreen use could play a significant role in managing AD by protecting the delicate skin of children with AD from harmful ultraviolet (UV) radiation.[3]

While sun protection is important for children with eczema and AD-prone skin, many sunscreens can cause skin irritation due to their formulations.[6] Selecting the right sunscreen for children with AD is crucial. It is advisable to choose a sunscreen specifically formulated for sensitive skin, preferably one that is fragrance-free and hypoallergenic. Fragrances and certain chemicals in regular sunscreens may trigger allergic reactions or worsen existing skin conditions. Additionally, a broad-spectrum sunscreen that protects against both UVA and UVB rays is essential for comprehensive sun protection. Therefore, the objective of this study was to evaluate the safety and tolerance of a hypoallergenic SPF 50 sunscreen in ethnically diverse children with a history of AD over 4 weeks of product use.

MATERIALS AND METHODS

Clinical Study

The study was performed in accordance with the Good Clinical Practices and the principles of the Declaration of Helsinki. The procedures used in this study were approved by Allendale Institutional Review Board (AIRB), Old Lyme, CT. Before any study procedure, the parents of the participants received the necessary written and verbal information including an informed consent form. Eligibility was determined by physical examination and confirmation of all inclusion/exclusion criteria. Participants aged 3 to 12 years old with perceived sensitive skin among all skin types (dry, normal, combination, oily; at least 10% of all skin types were represented). Participants also had a history of eczema or AD-prone skin as assessed by a board-certified dermatologist. A total of 45 children from diverse racial/ethnic backgrounds, with skin phototypes I-VI, plus a history of eczema and perceived sensitive skin completed the study.

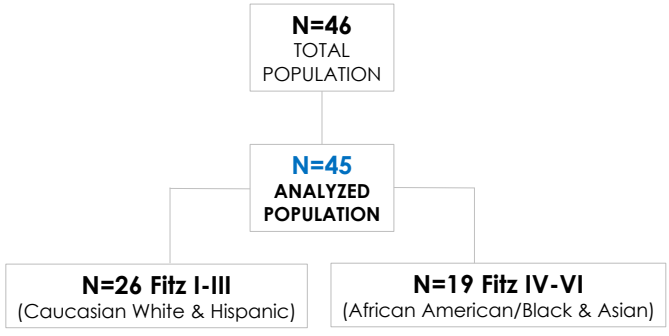
Sunscreen Product and Application

The SPF 50 sunscreen (*Anthelios Gentle Lotion Kids Sunscreen*) specially formulated for kids was a broad-spectrum UVA/UVB protection sunscreen containing *Senna alata* leaf extract as an antioxidant. In addition, it also contains glycerin, vitamin B5, niacinamide, and vitamin E as active ingredients. The sunscreen components are avobenzone, homosalate, octisalate, and octocrylene. After signing consent from the parents and dermatologist investigator evaluations, all participants were instructed to apply sunscreen daily on the face and body, at least 15 minutes prior to sun exposure and as needed. All prescription medications remained unchanged during the study.

Tolerability Evaluations

Evaluations included dermatological and subjective tolerability assessments, and product performance questionnaires to parents/guardians of pediatric participants. Dermatological/Investigator tolerability assessments were conducted using a 5-point ordinal scale (0=none, 1=minimal, 2=mild, 3=moderate, 4=severe) for dryness, peeling, erythema, edema. Subjective tolerability assessments were performed using a 5-point ordinal scale (0=none, 1=minimal, 2=mild, 3=moderate, 4=severe) for dryness, peeling, stinging, and itching. Product performance self-assessment questionnaires were completed by parents/guardians of the pediatric participant.

FIGURE 1. Patient demographics included in study.



As shown in Figure 1, 46 participants were included in the study and 45 completed the study. Twenty-six participants were Caucasian White or Hispanic ethnicity of Fitzpatrick skin type I-III; 19 participants were of African American/Asian ethnicity of Fitzpatrick skin type IV-VI. Analysis of the data was performed by determining the differences in each parameter for individual participants between the baseline and end of the treatment of 4 weeks. Statistical analysis was performed using the Wilcoxon signed-rank test and sign test for paired comparison at different time points. The change was considered significant at the alpha level of 0.05.

RESULTS

Investigator Tolerability Assessments

None of the participants at the beginning of the study demonstrated any dryness, peeling erythema, or edema at the start of the study. After 4 weeks of sunscreen application, none of the participants showed any adverse effects in any of these parameters. Tolerability assessments by an investigator for skin dryness, peeling, erythema, and edema showed absent in all the children participants. The data is summarized in Table 1.

TABLE 1.

Investigator Tolerability Assessments						
Inv Toler Long	Time Point	N	Mean (± SD)	Mean Change from Baseline (± SD)	Mean % Change from Baseline	*P*-value
Dryness	Baseline	45	0.00 ± 0.00	0.00 ± 0.00	NA	1.000
	Week 4	45	0.00 ± 0.00			
Peeling	Baseline	45	0.00 ± 0.00	0.00 ± 0.00	NA	1.000
	Week 4	45	0.00 ± 0.00			
Erythema	Baseline	45	0.00 ± 0.00	0.00 ± 0.00	NA	1.000
	Week 4	45	0.00 ± 0.00			
Edema	Baseline	45	0.00 ± 0.00	0.00 ± 0.00	NA	1.000
	Week 4	45	0.00 ± 0.00			

*denotes $P<0.05$ statistically significant different vs. Baseline; NA denotes non-applicable

TABLE 2.

Subject Tolerability Assessments						
Subj Toler Long	Time Point	N	Mean (± SD)	Mean Change from Baseline (± SD)	Mean % Change from Baseline	*P*-value
Dryness	Baseline	45	0.00 ± 0.00	0.09 ± 0.42	NA	1.000
	Week 4	45	0.09 ± 0.42			
Peeling	Baseline	45	0.00 ± 0.00	0.00 ± 0.00	NA	1.000
	Week 4	45	0.00 ± 0.00			
Stinging	Baseline	45	0.00 ± 0.00	0.02 ± 0.15	NA	1.000
	Week 4	45	0.02 ± 0.15			
Itching	Baseline	45	0.00 ± 0.00	0.00 ± 0.00	NA	1.000
	Week 4	45	0.00 ± 0.00			

*denotes *P*<0.05 statistically significant different vs. Baseline; NA denotes non-applicable

TABLE 3.

Parent/Guardian Product Performance Questionnaires									
Product Visit - Week 4									
Q1	Applies Smooth				Q2	Applies Evenly			
Value	Frequency	Percent	Frequency	Percent	Value	Frequency	Percent	Frequency	Percent
1	0	0.0%	0	0.0%	1	0	0.0%	0	0.0%
2	1	2.2%	1	2.2%	2	0	0.0%	0	0.0%
3	0	0.0%	1	2.2%	3	0	0.0%	0	0.0%
4	5	11.1%	6	13.3%	4	6	13.3%	6	13.3%
5	39	86.7%	45	100.0%	5	39	86.7%	45	100.0%
Mean=	4.822				Mean=	4.867			
N=	45				N=	45			
Scale 4-5	44	97.8%			Scale 4-5	45	100.0%		
Q3	Does Not Feel Sticky				Q4	Does Not Leave White Marks			
Value	Frequency	Percent	Frequency	Percent	Value	Frequency	Percent	Frequency	Percent
1	0	0.0%	0	0.0%	1	0	0.0%	0	0.0%
2	0	0.0%	0	0.0%	2	2	4.4%	2	4.4%
3	0	0.0%	0	0.0%	3	0	0.0%	2	4.4%
4	3	6.7%	3	6.7%	4	11	24.4%	13	28.9%
5	42	93.3%	45	100.0%	5	32	71.1%	45	100.0%
Mean=	4.933				Mean=	4.622			
N=	45				N=	45			
Scale 4-5	45	100.0%			Scale 4-5	43	95.6%		
Q5	Does Not Feel Greasy								
Value	Frequency	Percent	Frequency	Percent					
1	0	0.0%	0	0.0%					
2	0	0.0%	0	0.0%					
3	1	2.2%	1	2.2%					
4	7	15.6%	8	17.8%					
5	37	82.2%	45	100.0%					
Mean=	4.800								
N=	45								
Scale 4-5	44	97.8%							

Participant Tolerability Assessments

At the beginning of the study and at the end of the 4 weeks of product application, no participants displayed skin dryness, peeling, erythema, or edema. After 4 weeks of sunscreen application, tolerability assessments of skin dryness, peeling, erythema, and edema were all absent in children participants. Table 2 summarizes the participant tolerability assessment data. Parent/guardian evaluations of sunscreen tolerability for their child also revealed no perceived skin issues. These results were consistent with no adverse event being observed throughout the study.

Parent/Guardian Product Performance Questionnaire

Parents/guardians were asked to fill out one questionnaire per family for the sunscreen product, for its smoothness, evenness of application, non-sticky or greasy feel, and for not leaving white marks on the skin after product application. Parents/guardians of all 45 participants rated the SPF product extremely high in terms of product performance with 95%+ of ratings in the top box defined as a rating of 4-5. The summary-frequency table is presented below in Table 3. Parents/guardians also reported that sunscreen application on children was smooth and even, with the absence of a white cast appearance on children with skin of color.

DISCUSSION AND CONCLUSIONS

The pathophysiology of atopic dermatitis is complex and multifactorial. It includes genetic disorders, a defect in the epidermal barrier, an altered immune response, and disruption of the skin's microbial balance.[7] Virtually all dysfunctions of the epidermis, whether inborn or acquired, are associated with notable modifications of the permeability barrier. It is particularly evident in dermatoses with an important inflammatory component.[11,12] In many cases, barrier dysfunction may be at the origin of a skin disease, as is the case in atopic dermatitis (AD). Clinical observations of improvement of AD lesions with topical emollient therapy alone clearly indicate that restoration of or compensation for the SC barrier helps to interrupt the vicious circle of pathogenic self-propagation.[13] Studies in neonates provide evidence that protecting the skin barrier with a moisturizer during the neonatal period prevents the development of AD and allergic sensitization. Approximately 32% fewer neonates who received a moisturizer had AD/eczema by week 32 than control participants.[9] Efficacy and the tolerability of a corticosteroid-free cream containing moisturizer, and sunscreen (zinc oxide) in the treatment of chronic mild to moderate AD in children has been demonstrated. A majority of the children in this study demonstrated a significant reduction in eczema severity score (TESS), supporting the use of sunscreens along with moisturizers for the treatment of AD.[10]

The beneficial effect of sunlight in patients with atopic eczema and AD is well established, however, excessive sunlight can also disrupt the skin barrier and generate free radicals that can damage proteins, lipids, and DNA.[5] The role of sunscreens in combination with antioxidants for the protection of skin has been demonstrated. Sunscreens protect by absorbing or reflecting UV on the skin surface. Antioxidants protect by quenching UV-induced reactive oxygen species within the skin. Complementary photoprotective benefits of formulas containing an antioxidant complex of *Cassia alata* leaf extract in combination with sunscreens on normal healthy volunteers using biomarkers of skin damage have been demonstrated.[14]

In this study, we used a sunscreen product containing a similar combination of an antioxidant complex of *Cassia alata* leaf extract along with vitamins and glycerol and a non-allergenic combination of sunscreens of SPF 50 on children who are prone to sensitive skin and who have a family history of AD. We recruited participants aged 3 to 12 years old who had perceived sensitive skin or who had a history of eczema or AD-prone skin as assessed by a board-certified dermatologist. However, none of the participants displayed any obvious skin abnormalities in terms of dryness, peeling erythema, edema stinging, or itching at the beginning of the study or at the end of 4 weeks of sunscreen product application, despite the fact that all participants recruited had a family history of AD and a history of eczema-prone skin. Since the purpose of this study was to demonstrate the safety and tolerance of this product on children, and not efficacy, the lack of active AD in the participants at the beginning of the study was not considered an issue. The sunscreen product application on children was well tolerated as reported by Parents/Guardians on all skin types, including children with skin of color, suggesting that the SPF 50 sunscreen is suitable for ethnically diverse children with a history of AD and sensitive skin. Future studies will evaluate the efficacy of the product in children who display active AD.

In addition to sunscreen use, other sun protection measures, such as protective clothing, are essential for children with AD. Sunscreens along with innovative antioxidant mixtures would complement each other and help protect the sensitive skin of these children from the harmful effects of UV radiation, reducing the risk of exacerbating their skin condition. By incorporating sunscreen into a comprehensive sun protection routine, parents and caregivers can contribute to the overall well-being of children with AD and help them enjoy outdoor activities safely.

DISCLOSURES

Dr Zoe Diana Draelos MD is a researcher and consultant for L'Oreal. All other authors are employees of La Roche-Posay Laboratoire Dermatologique.

ACKNOWLEDGMENT

We thank Dr. Kumar Pillai for his contribution to the manuscript.

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doi:10.36849/JDD.8471

August 2024 674 Volume 23 • Issue 8

ORIGINAL ARTICLE

Journal of Drugs in Dermatology

Challenges in Adult Acne and the Role of Skin Care in Managing the Condition

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ABSTRACT

Background: Acne vulgaris is a complex, multifactorial, inflammatory skin condition. Although frequently presented at dermatology clinics, the literature on adult acne is scarce, particularly concerning skin barrier function and management.
We aimed to provide insights into the role of skin barrier integrity in adult acne patients and the role of cleansers and moisturizers as adjunctive to treating and maintaining adult acne.
Methods: A panel of eight dermatologists who treat adult patients with acne developed a consensus paper on the role of skin barrier function and skin care in adult acne management. The modified Delphi method comprised a face-to-face meeting and online follow-up to discuss the results of a scoping literature review. Drawing from their experience and opinions, they agreed on seven consensus statements.
Results: Epidermal barrier dysfunction plays a vital role in acne pathogenesis and asymmetrically impacts adult female acne. Erythema, pruritus, peeling, and xerosis are common adverse effects of first-line acne treatment options and, if not appropriately counseled and managed, can exacerbate, leading to regimen nonadherence and poor patient experience and outcomes.
Conclusion: Improving patient knowledge of comprehensive acne treatments, including quality adjunctive cleansers and moisturizers, may maximize regimen efficacy and provide patients with personalized and successful acne treatment and maintenance tools.

J Drugs Dermatol. 2024;23(8):674-679. doi:10.36849/JDD.8471

INTRODUCTION

Acne vulgaris (acne) is a multifactorial skin condition affecting the pilosebaceous unit[1] and the most prevalent inflammatory dermatosis in the United States, affecting up to 50 million Americans.[2] The four central factors in acne development affect the pilosebaceous unit: hyper-seborrhea and dysseborrhea, hyperkeratinization, *Cutibacterium acnes* colonization, and inflammation.[3,4] Studies implicate skin barrier dysfunction as a material contributor to the pathophysiology of acne.[4]

Acne can occur at any stage of life but primarily affects adolescents and young adults, with over 85% of 12- to 24-year-old individuals experiencing some manifestation or sequelae of acne.[5-8] Adult acne is more prevalent among females and may have a unique presentation characterized by a predominance of inflammatory lesions on the jawline with few comedones.[9]

Acne can have significant social, psychological, and physical consequences, which can create feelings of embarrassment, humiliation, and self-consciousness.[10-12] Longitudinal and population studies showed it can lead to psychiatric disturbances, including increased risk of depression and suicide.[13-16] After the resolution of active lesions, individuals can be left with sequelae, including dyschromia and atrophic or hypertrophic scars, which can be compounded by potentially lifelong psychosocial scarring, further affecting the quality of

life.[2,15,17] Adult acne can be very isolating due to social stigma and misconceptions that acne only affects teenagers, and negative perceptions by others can have a profound socioeconomic impact, such as observed higher unemployment rates in those with severe acne.[7,8]

Despite frequent occurrences in the dermatology clinic, the literature on adult acne is scarce, particularly concerning skin barrier function and management. This manuscript aims to provide insights into the role of skin barrier integrity in adult acne management and the clinical significance of skincare with cleansers and moisturizers as adjuncts to acne treatment.

MATERIALS AND METHODS

A panel of eight dermatologists who treat adult patients with acne convened to develop consensus statements about the role of skin barrier function and adjunctive skin care in managing adult acne.

Literature Review

Before the meeting, a scoping literature review was performed on Pubmed and Google Scholar from August 20 to August 22, 2023, independently evaluated by two reviewers (JM and AA). The searches encompassed English-language, human-based data from guidelines, algorithms, consensuses, systematic reviews, meta-analyses, and clinical studies published between January 1, 2010, and August 20, 2023. Search terms used, Group 1: Adult acne* AND quality of life OR pathogenesis OR hormonal OR female. Group 2: Adult acne* AND prescription treatment OR adjunctive OR skincare OR cleanser OR moisturizer OR emollient OR ceramide-containing skincare). Duplications and publications not addressing acne or skincare were excluded (Figure 1).

Statement Development

The modified Delphi process comprised a face-to-face panel meeting on September 23, 2023, and an online follow-up to discuss the literature search results and draw from clinical experience and opinion of the panel to adopt and agree on seven statements.

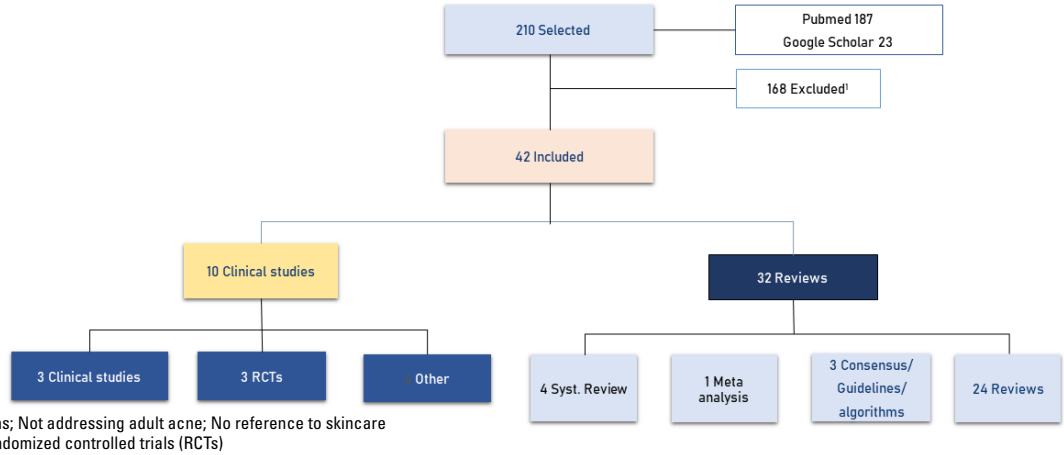
During the face-to-face meeting, the panel members split into three groups. Drawing from thirteen draft statements, each group selected the seven top statements that were modified as needed. Following the workshop, the panel reconvened, finalized and agreed on seven statements combining the feedback from each group. Follow-up and review of the manuscript took place online.

RESULTS

Statement 1: *While most common during adolescence, acne also affects a substantial number of adults, particularly women.*

Globally, in 2013, skin conditions accounted for the 18th leading cause of disability-adjusted life-years (DALYs) and, when adjusting for mortality, the fourth largest cause of morbidity-associated disability.[18] Acne vulgaris (acne) was the second largest subgrouping, accounting for over 16% of the global burden of cutaneous diseases.[18] While stereotypically considered a disease of adolescence, acne affects a material portion of the adult population, with increased prevalence among women.[2,5] A 2012 cross-sectional study found that among North American women ages 10 to 70 (n=2895), 55% had at least mild acne.[19] Subdivided by age group, 45% of women ages 21-30, 26% ages 31 to 40, and 12% ages 41 to 50 had clinical findings consistent with acne vulgaris.[19] Additional survey and population/community-based studies showed similar trends among females ages 26 to 44.[20-22] While likely multifactorial in cause, the increase in the prevalence of adult female acne may be tied to factors including changes in skin barrier function that may disproportionately affect females, altered response to classic treatment paradigms, additional psychosocial pressures

FIGURE 1. Literature search results.



[1]Excluded: Duplications; Not addressing adult acne; No reference to skincare
Systematic (Syst), Randomized controlled trials (RCTs)

affecting treatment adherence, and rising perception of acne less as a tolerant condition rather than a cutaneous dermatosis necessitating treatment.[9]

Statement 2: *Compared to adolescent acne, adult acne may present with more lesions on the lower half of the face, while comedones are less common. Adult acne patients do not typically present with endocrinopathy.*

Acne typically presents with comedones and inflammatory lesions such as papules, pustules, and nodules in areas with a high density of sebaceous glands, most commonly affecting the face, chest, and back.[3] Adult female acne may favor the lower third of the face and lateral regions of the superior neck, presenting with scattered papules, pustules, and nodulocystic lesions along the jawline and angle of the jaw.[7] Comedones are not typically dominant in adult acne, except for patients over 40 and active smokers who are more likely to develop primarily comedonal acne on the front lateral face.[25]

Androgens play a crucial role in the pathophysiology of acne lesions in all patients. Most patients, including adult women and individuals with a longitudinal history of acne starting in adolescence, do not have a concurrent or underlying endocrine disorder.[23,24] The exception is patients with polycystic ovarian syndrome (PCOS), who often present with acne as well as associated hyperandrogenism/insulin-resistance cutaneous findings, including hirsutism, acanthosis nigricans, and male-pattern alopecia.[24] The authors note that, despite normal circulating androgens in most patients, the local androgens' role in sebaceous glands drives hyper-seborrhea and dysseborrhea. These factors are part of a larger interconnected framework of epidermal barrier dysfunction and acne disease pathogenesis.[26]

Statement 3: *Acne patients may experience cosmetically disfiguring sequelae such as erythema, dyschromia, and scarring. Especially when severe, acne may lead to negative emotions such as embarrassment and self-consciousness.*

Acne vulgaris is strongly associated with psychological burden and can lower quality of life (QoL) by reducing self-confidence and self-perceived negative body image.[27,28] Even after the prototypical lesions associated with acne resolve, the physical sequelae of postinflammatory dyspigmentation, erythema, and scarring can lead to further psychosocial duress.[1,6,9,15,25] Population-based studies have found a high frequency of these sequelae.[9,25,29] Studies of the real-world experiences of adult female patients with acne have highlighted persistent themes of ongoing mental health disturbances affecting patients' professional and social lives.[30] These frustrations may be magnified in adulthood as affected individuals have fewer peers similarly affected by acne and often receive unsolicited and erroneous advice despite already taking steps to address their acne.[30] Psychosocial detriments of adult female acne can have real-world consequences, including postponing or canceling social engagements during flares and experiencing discomfort and self-consciousness that negatively impact occupational and romantic relationships.[30]

Statement 4: *Acne is associated with inherent abnormalities in skin barrier function. Acne medications can induce additional changes that further disrupt the skin barrier.*

Traditional tenants of acne pathophysiology implicate hyperkeratinization, androgen-mediated sebogenesis, colonization of the pilosebaceous unit with *C. acnes*, and inflammation.[31] Studies suggest subclinical inflammation and hormone-induced sebaceous secretory dysfunction may precede the formation of microcomedones and other prototypical acne lesions.[26,32-34] CD4+ lymphocytes and macrophages have been observed with the concurrent increase in intercellular adhesion molecules such as vascular adhesion molecules, E-selectin, and integrins.

It may also alter filaggrin, keratin (16 and 17), and interleukin (IL) 1α expression with concurrent decreases in keratin 79 and 75 expressions, leading to hyperkeratinization and the creation of microcomedones.[31] This inflammatory state may be partly driven by dysseborrhea, alterations in the normal composition of sebaceous gland excretion. In addition to the correlation between acne severity and increased sebum excretion rates, studies have found decreased levels of linoleic acid, total ceramides, free sphingosine, and higher levels of inflammatory free fatty acids (FFA). The latter are metabolic products of virulent strains of *C. acnes* (ie, clade 1A2) capable of activating nod-like receptor 3 (NLRP3) inflammasome and IL-1β.[4,26,31,32,35-37] These sebum composition and inflammation changes have been correlated with epidermal barrier dysfunction.[4,38] In a population study of young adult male Japanese patients with mild (n=25) and moderate (n=11) acne, Yamamoto et al found evidence of increased transepidermal water loss (TEWL) and stratum corneum barrier dysfunction in acne, which correlated with acne severity (TEWL g/m2/h±SD: Control 10.3±2.4; Mild acne, 14.4±2.5; Moderate acne, 16.8±3.8, $P<0.01$).[39] Furthermore, they examined the relationship between water barrier function and the lipid content of the stratum corneum, demonstrating a decrease in ceramides and free sphingosine that correlated with an increase in TEWL and a decrease in water-holding capacity of the stratum corneum. Barrier dysfunction is accompanied by hyperkeratosis of the follicular epithelium, and water barrier dysfunction may be partly responsible for comedone formation.[39]

With chronological aging, TEWL and facial skin pH increase, and stratum corneum hydration, overall barrier function, and the recovery speed of barrier function decrease.[40] Data suggest these changes may be more exaggerated in females.[41] This is partly

explained by age-related (>30%) reduction in total epidermal lipids[41] and by an age-associated decrease in ceramide NG only observed in women.[42] These findings highlight the potential significance of adrenarche and female hormones in epidermal barrier function. Ceramide-deficiency disorders such as acne directly impact epidermal barrier function and may benefit from quality skin care containing ceramides. Barrier dysfunction may translate into commonly reported symptoms of burning, pruritus, stinging, tingling, and skin tightness.[4] These symptoms are often magnified by topical acne products, most notably benzoyl peroxide (BPO) and retinoids, that may transiently increase TEWL while improving acne severity over the long term.[4,43]

Statement 5: *Once-or-twice-daily application of fragrance-free, non-irritating, and non-comedogenic cleansers, moisturizers, and sunscreen may reduce adverse events resulting from prescription oral and topical medications, such as dryness, erythema, photosensitivity, and PIH.*

Acne management includes topical retinoids and BPO, which, in addition to having documented efficacy for acne, can also increase cell turnover, induce stratum corneum thinning, and increase TEWL, often leading to xerosis, irritation, and inflammation.[4,26,44-48] Clinical evidence and expert consensuses have found that when combined with acne treatment regimens, the application of gentle moisturizers, cleansers, and sunscreen can improve patient comfort and patient-centered goals, including minimizing adverse effects of xerosis, irritation, and photosensitivity and may improve postinflammatory dyspigmentation.[3,26,49-51] A single-center, double-blinded randomized study compared the outcome of an acne treatment regimen consisting of a twice-daily skincare routine in addition to a nightly combination topical agent (adapalene 0.3%/ benzoyl peroxide 2.5%).[52] Ninety-one participants with moderate acne were randomized to use a ceramide-containing foaming cleanser and a ceramide-containing facial moisturizing lotion versus a foaming face wash gel during the 12-week study.[52] Based on both participants' subjective measures (on a 5-point Likert scale), investigator global assessment (IGA), and TEWL (right preauricular cheek 30 minutes after facial cleansing), the study found statistically significant improvement in both primary endpoints: markers of skin barrier function and acne severity.[52] Measurements of TEWL showed a material increase followed by a sustained decrease in both arms with lower TEWL in the ceramide-containing products treated arm than control.[52] IGA assessing xerosis, erythema, and scaling showed a reduction in xerosis for the ceramide-containing product-treated arm, starting at week 1 (persisting at weeks 4, 8, and 12), erythema beginning at week 4 (and continued at week 8 and 12) and a trend to decreasing scaling that was significant at weeks 1 and 8.[52] Subjectively, participants using the ceramide-containing products reported a positive experience with skin barrier function (ie, skin does not feel dry, regimen does not leave skin feeling tight, skin feels comfortable) at greater frequencies and earlier time points than their control counterparts.[52] This study demonstrated that ceramide-containing products can mitigate AE's of prescription topical agents and the importance of counseling patients on incorporating gentle cleansing and moisturizing into their treatment regimens.[52]

Statement 6: *Irrespective of the effect of a prescription acne product on skin barrier integrity, repair and support of the skin barrier should be a foundational goal of a skincare regimen in acne patients.*

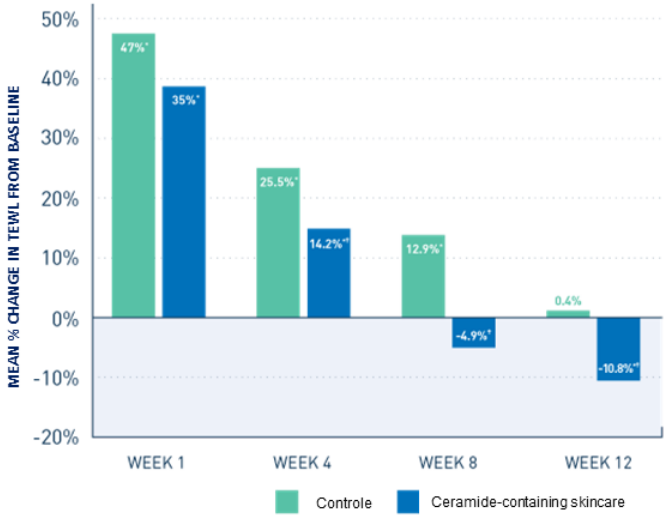
Skin cleansers utilize surfactants to solubilize and remove oils and debris from the stratum corneum. Harsh cleansers, especially those with non-physiologic pH's, may solubilize barrier lipids and disrupt skin barrier function, inducing erythema and dryness.[4] Appropriately formulated skincare as adjunctive to prescription therapy may play a role in acne management regimens. Small studies have demonstrated that daily use of a facial cleanser and moisturizer can reduce acne lesions without aggravating epidermal barrier dysfunction, thereby reducing TEWL, mitigating aberrations of cutaneous pH, and fostering the growth of a diverse microbiome.[4,45-47,49,51,53,54]

Adjunctive to prescription therapy, some studies have shown the complementary benefit of gentle cleansers and moisturizers. In a 4-week randomized controlled trial of 100 Japanese patients [mean age 25.6 years old (Standard deviation 4.7 years)] with mild (n=46) and moderate (n=46) acne were randomized to either once-daily adapalene gel monotherapy or combination therapy of adapalene gel and a once to twice daily (pretreatment) heparinoid-based lotion or ointment.[55] Although both arms had similar efficacy in reducing comedonal and inflammatory lesions, the combination therapy group had significantly greater adherence (100% versus 70%) than the adapalene-monotherapy group. The monotherapy group had a significantly higher rate of patient-reported symptoms, with the only trial adverse event of eyelid dermatitis reported in the monotherapy group.[55]

A 16-week randomized-controlled trial of 119 patients with acne on either tazarotene 0.1% cream monotherapy or tazarotene 0.1% cream plus a ceramide-containing moisturizer found similar efficacy in the reduction of all acne lesions at the end of the study with patients enrolled into the combination arm reporting significantly less facial dryness during the initial 2-week retinization period (ie, maximum skin irritation).[56]

In the 12-week randomized-controlled trial of 91 patients with moderate acne treated with once-daily adapalene 0.3% and benzoyl peroxide 2.5% topical agent daily, patients randomized to a twice-daily ceramide-containing cleanser and moisturizer had more significant improvements in inflammatory lesions,

FIGURE 2. Skincare routine restores acne treatment-induced skin barrier disruption.



*P<0.05 vs baseline † P<0.05 vs control

TEWL, and dryness than the control (twice-daily basic foaming wash) group, by the end of the study (Figure 2).[52] Importantly, this finding highlights that a quality skin care regimen need not detract from the efficacy of prescription topical agents. Although the study did not stratify findings by patients by Fitzpatrick score, patients of all skin tones were included; this may suggest findings have a degree of generalizability to the broader population of patients with acne.

Statement 7: *Improving skin barrier function, which reduces skin irritation, may increase adherence to acne medications and, thus, improve clinical outcomes.*

Acne is a chronic inflammatory dermatosis,[3] and long-term adherence to a prescription regimen is essential to successful treatment. In a (n=3139) survey study of patients with acne, potentially mitigating factors in a multivariate analysis contributing to nonadherence included side effects, lack of knowledge about acne treatments, and lack of patient satisfaction with treatment. Improved adherence to treatment regimens was associated with using skincare comprising moisturizers and cleansers, topical therapy alone, satisfaction with therapy, and knowledge of acne treatments.[57] It is vital to dedicate time during initial and follow-up encounters to patient education regarding acne chronicity, the efficacy of treatment options, and the importance of a quality skincare regimen. In an internet survey study of patients with acne on a combination BPO-clindamycin product, between ~40-50% of patients reported experiencing dryness, flaking/peeling, irritated, or itchy skin, which resulted in poor adherence, such as deviation from recommended treatment protocol or complete abandonment of prescribed regimen.[58]

When combined with prescription therapy, gentle cleansers, and moisturizers may mitigate irritation, erythema, dryness, pruritus, and other symptoms common during the initiation phase of topical regimens[52,55,56] and may have additive or synergistic effects in achieving treatment outcomes aside from maximizing adherence.

Multiple expert panels have put forth consensus statements highlighting the importance of quality cleansers and moisturizers to minimize treatment disruption, improve the patient experience with prolonged treatment courses required to manage chronic conditions, and maximize treatment regimen outcomes.[26,46,59-61]

Limitations

There is a lack of robust, long-term randomized clinical trial data with diverse populations, including pediatric patients and patients with skin of color.

CONCLUSION

Adult acne is a common but inconclusively elucidated acne variant that presents more commonly in women. Given the role of epidermal barrier dysfunction and its asymmetrical impact on adult female acne, further studies, including the role of skin care in promoting skin barrier integrity in adult acne patients and as an adjunct to acne treatment and maintenance, are needed. While challenging to execute within the confines of a high-volume practice, improving patient knowledge of comprehensive acne treatments, including quality adjunctive cleansers and moisturizers, may be an effective way to maximize regimen efficacy and provide patients with the necessary tools for personalized and successful acne treatments.

DISCLOSURES

An educational grant from CeraVe International supported the research for this work. The authors HB, GA, VC, PF, TL, ER, TS, JM, and HWL received fees for attending the meeting. The authors contributed to the development of the manuscript, reviewed it, agreed with the final version, and have no conflict of interest with the content of the manuscript.

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doi:10.36849/JDD.7751

August 2024 680 Volume 23 • Issue 8

CASE REPORT

Journal of Drugs in Dermatology

Recalcitrant Erythrodermic Psoriasis Complicated by Septic Shock and Mycotic Aneurysm: A Call for Treatment Guidelines

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ABSTRACT

Erythroderma is characterized by diffuse erythema and scale covering over 90% body surface area that can affect individuals with inflammatory dermatoses such as psoriasis. Complications of erythrodermic psoriasis include infection and cardiovascular compromise. Here we present a case of a 68 year-old man who was hospitalized for erythrodermic psoriasis refractory to multiple immunosuppressive and immunomodulatory therapies, ultimately developing sepsis due to bacteremia and fungemia complicated by infective endocarditis and a mycotic aneurysm. Although the widespread loss of epidermal function in erythroderma increases the risk of infection by opportunistic pathogens, water loss, and electrolyte imbalances, there are very few reported cases of psoriatic erythroderma complicated by fungemia and mycotic aneurysm. Given the high mortality associated with widespread epidermal dysfunction, there is a great need for evidence-based treatment guidelines for psoriatic erythroderma.

J Drugs Dermatol. 2024;23(8):680-682. doi:10.36849/JDD.7751

INTRODUCTION

Erythroderma is characterized by a widespread erythematous rash involving >90% of body surface area (BSA).[1] It is frequently seen in the setting of pre-existing chronic inflammatory dermatoses such as psoriasis, atopic dermatitis, pityriasis rubra pilaris (PRP), and seborrheic dermatitis.[2] The estimated prevalence among psoriasis patients is reported to be approximately 1% to 2.25%.[1] Other causes include drug eruption, internal malignancy, erythrodermic mycosis fungoides, or Sezary syndrome. However, in a significant number of patients, the cause remains idiopathic despite extensive evaluation.[2]

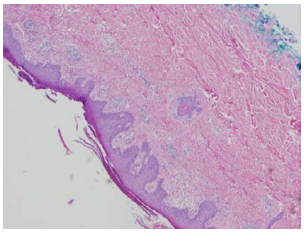
Erythrodermic psoriasis (EP) is an uncommon and severe form of psoriasis with a high morbidity and increased mortality compared to other forms of psoriasis. Erythroderma typically requires hospitalization because of its possible complications, which include infection and sepsis, fluid and electrolyte loss, thermoregulatory disturbance, high-output cardiac failure, and respiratory distress.[3] A 12-year-long prospective tertiary-care-center study of 309 erythroderma patients found that 9.1% of study participants died, most commonly due to sepsis and cardiovascular complications.[4] A larger share of deaths were observed within the Sezary syndrome and mycosis fungoides group compared to other etiologies, which is a common cause of variation in the mortality rates found in other prognostic studies of erythroderma patients.[5] Though there are several treatment options, limited evidence exists regarding the optimal treatment algorithm, which can make refractory cases challenging. Herein, we report a case of a 68-year-old patient with erythroderma secondary to severe, psoriasis, refractory to multiple first-line agents and complicated by septic shock, infective endocarditis, and a mycotic aneurysm.

Case Presentation

A 68-year-old man with no significant medical or dermatologic history was admitted for evaluation of a generalized rash. The patient reported that the rash began one year prior to presentation and was initially localized to the scalp with gradual cephalocaudal spread to the trunk and extremities. In addition to treatment with topical steroids (triamcinolone and betamethasone), mycophenolate was initiated, and a prednisone taper was completed, one week prior to presentation.

FIGURE 1. Generalized erythematous rash with fine-scale observed at first hospitalization.

FIGURE 2. Shave biopsy of the right lateral trunk during first hospitalization (H&E 10x magnification) demonstrating parakeratosis, acanthotic epidermis with sparse superficial and mid-perivascular infiltrate.



Dermatologic exam was notable for diffuse, erythematous papules and plaques with thick overlying micaceous scale and large areas of complete confluence covering a BSA of ~90% (Figure 1). There were no blisters, erosions, ulcers, or ocular, or mucosal involvement. A T-cell subset and Sezary panel were negative; HIV serology was also negative. A shave biopsy of the right lateral trunk showed psoriasiform spongiotic dermatitis (Figure 2). The patient was diagnosed with erythroderma secondary to severe psoriasis. Although initially trialed on acitretin 25 mg daily, he was readmitted within 2 weeks for worsening swelling of the hands and feet, scaling, and BSA of 95% (Figure 3). During this second hospitalization, the patient was transitioned to cyclosporine 5 mg/Kg/day in 2 divided doses.

FIGURE 3. Worsening diffuse scale and erythema on bilateral lower extremities were observed during the time of the second hospitalization.

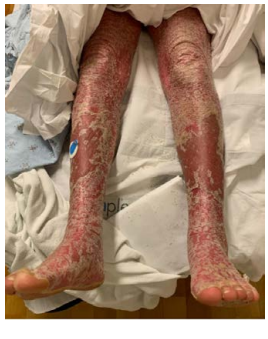


FIGURE 4. Progression of scaling and severe onycholysis were observed during the third hospitalization.

Three months later, the patient was hospitalized again for septic shock complicated by mycotic aneurysm. He was found to be septicemic with *Candida parapsilosis* and *Pseudomonas* with evidence of mitral valve endocarditis. In the intensive care unit, he developed hemorrhagic shock secondary to a gastroduodenal artery aneurysm rupture requiring embolization. He was also found to have a splenic artery embolism that was thought to represent a mycotic aneurysm in the setting of fungemia and bacteremia. The patient was transitioned to Cefepime and Fluconazole from Meropenem and Amphotericin B with Flucytosine, respectively. At this time, the patient's skin had minimally improved, with persistent fissuring and increased scale noted on the feet (Figure 4). The exam showed erythroderma with diffuse plate-like scale on the entire body and nail dystrophy. A repeat biopsy of the left abdomen showed psoriasiform dermatitis. Due to authorization issues, the patient was not able to initiate preferred treatment with Ustekinumab (Stelara), and he was instead started on methotrexate 12.5 mg weekly.

DISCUSSION

Erythrodermic psoriasis typically affects patients with long-standing and/or uncontrolled psoriasis. Rarely does it affect a patient without pre-existing psoriasis or dermatitis.[6] The differential diagnosis in this case included erythroderma secondary to psoriasis or PRP, drug eruption, and Sezary syndrome/erythrodermic cutaneous T-cell lymphoma. Overall, our patient's clinical picture of a large plate-like scale with characteristic nail changes and biopsies were consistent with a psoriasis flare. It was presumed that the patient had been flaring for weeks to months prior to presentation.

The systemic steroid rebound phenomenon has been implicated in cases of severe psoriasis flares or EP for decades and continues to be reported.[7] However, recent evidence suggests this association may not be as strong as was once thought. A retrospective cohort study of 1,970 psoriasis patients who received systemic corticosteroids found an overall psoriasis flare rate of 1.42% and a rate of erythrodermic psoriasis of 0.07% during the steroid withdrawal period.[8] It is worth noting that, in

this study, less than half of the 16 patients who experienced a flare had received tapering steroid courses. It is unclear whether, in the case at hand, the severe flare was caused by systemic or topical steroid rebound or other factors noted in the literature such as stress, substance use, or recent illness.[1] Further research may better elucidate the correlation between EP and the usage of systemic corticosteroids.

The high morbidity associated with EP stems from several complications including heat and fluid loss, high-output heart failure, and infection secondary to decreased epidermal barrier function. Severe infection and sepsis are not uncommon adverse events and are often due to Staphylococcus aureus in those with predisposing risk factors such as HIV infection or other immunocompromised states.[9] Indeed, his widespread scaling likely predisposed him to an opportunistic candida infection, and eventual septic shock, despite a negative workup for HIV infection or other underlying diseases. A study comparing fungal colonization of 1,000 psoriasis patients and 50 matched healthy controls found significantly higher rates of Candida spp. colonization in the oral cavities and psoriatic lesions of the psoriasis group.[10] Moreover, the combination of immunosuppressive and immunomodulatory treatments likely further predisposed him to the development of his fungemia and subsequent complications. Results of a study of approximately 2,000 moderate to severe psoriasis patients, comparing biologic to non-biologic systemic drugs suggested that, among the non-biologic systemic agents, cyclosporine had the highest infection risk profile.[11] Though complications of septicemia in cases of erythrodermic psoriasis have been reported and discussed in the literature, to the best of our knowledge, there is only one report in the literature of a mycotic aneurysm secondary to fungal endocarditis in an IV-drug user who coincidentally was being treated for psoriatic erythroderma with chronic systematic steroids.[12]

Treatment of EP should be dictated by the acuity of disease and patient comorbidities. Treatment includes non-biologic systemic agents such as cyclosporine, acitretin, etretinate, and methotrexate as monotherapy or in combination with biologic agents such as tumor necrosis factor (TNF) inhibitors (infliximab, etanercept, adalimumab) and interleukin-17 (IL-17) inhibitors (secukinumab, ixekizumab, brodalumab), interleukin 12 and 23 inhibitor, ustekinumab. Of these options, acitretin and methotrexate have been recommended as first-line treatment, with newer evidence supporting the role of ustekinumab for the maintenance of stable cases.[13] The joint American Academy of Dermatology-National Psoriasis Foundation granted ixekizumab a level B recommendation, versus a level C recommendation for secukinumab, as IL-17 monotherapies for erythrodermic psoriasis.[14] In this case, the patient's rapid deterioration required immunosuppressive agents that reach therapeutic levels rapidly. Moreover, cyclosporine and infliximab appear to be more rapidly acting agents and can be beneficial in unstable and more severe cases, making cyclosporine an appropriate choice for this high-acuity patient.[15] The lack of a clear treatment algorithm may be contributing to the high mortality and morbidity rates associated with EP.

Erythrodermic psoriasis is an uncommon, severe presentation of a classic dermatosis. The clinical presentation and treatment options may significantly increase a patient's risk of complications, including more opportunistic infections, and providers should have a high suspicion of infection in such cases.

DISCLOSURES

The authors have no conflicts of interest to disclose.

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doi:10.36849/JDD.8311

August 2024 683 Volume 23 • Issue 8

CASE REPORT

Journal of Drugs in Dermatology

Case Series of Acral and Mucosal Melanoma in a Diverse Patient Population

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ABSTRACT

Melanomas affecting acral and mucosal sites have distinct features and are associated with poorer prognosis. Patients of color may be disproportionately affected. Herein we discuss 6 ethnically diverse cases of acral and mucosal melanoma (AMM). More data on clinical, genetic, and environmental features of AMM are needed, but thorough physical examination can reduce the burden of disease now.

J Drugs Dermatol. 2024;23(8):683-685. doi:10.36849/JDD.8311

INTRODUCTION

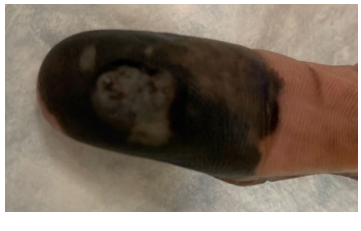
Melanoma accounts for only 1% of all skin cancers but is responsible for most skin cancer-related deaths.[1] Acral and mucosal melanoma (AMM) accounts for only 4% of all new melanomas but is associated with poorer prognosis.[2] Patients of color are disproportionately affected by AMM. Elucidating the clinical, genetic, and environmental features of AMM can guide advancements in their prevention and treatment. Herein we discuss six ethnically diverse cases.

Case Presentations

Case 1

A 48-year-old African American woman presented for evaluation of a black spot on her right thumb that had enlarged over seven years (Figure 1). The patient's past medical history was significant for multiple stab wounds to the right arm over 25 years ago. Physical examination revealed a hyperpigmented, ulcerating plaque on the volar aspect of the right thumb with a central punctum draining clear fluid. Histopathology confirmed the diagnosis revealing Breslow thickness of 2.7 mm, Clark IV (Stage cT3aN0) melanoma. Right axillary sentinel lymph node biopsy demonstrated no signs of lymph node metastasis.

FIGURE 1. Acral melanoma of the thumb in an African American female.

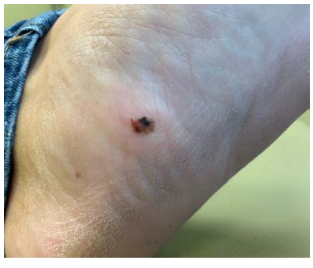


The lesion was definitively treated with right thumb amputation and close monitoring for disease recurrence.

Case 2

A 43-year-old Caucasian woman presented with a pigmented lesion on the left sole. The patient reported a change in color and morphology of the lesion over time, but denied any associated pain, bleeding, or lymphadenopathy. Past medical history was significant for hypertension and the use of tanning beds. A physical exam revealed an irregularly shaped black and brown papule on the plantar aspect of the left foot (Figure 2).

FIGURE 2. Acral melanoma of the sole in a Caucasian female.

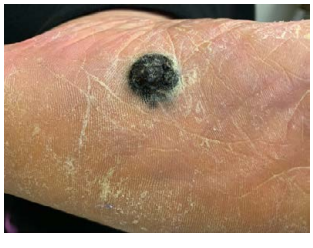


Histopathology revealed pagetoid melanocyte nests with atypical architecture and extension into the dermis, consistent with a diagnosis of acral lentiginous melanoma (ALM) with a Breslow's thickness of 0.47 mm and Clark level- III invasion. The patient was referred to surgical oncology for surgical resection.

Case 3

A 62-year-old Asian female presented for evaluation of a painful pigmented lesion on the left sole present for over four years. The plantar lesion was once flat and became nodular over time. A physical exam revealed a pigmented, friable, exophytic lesion on the plantar surface of the left foot (Figure 3). Histopathology of the nodule revealed a Breslow thickness of 7.5 mm, Clark IV (stage pT4bN0M0) with 5 mm of ulceration. Left inguinal sentinel node biopsy showed no nodal metastasis and PET scan showed no evidence of distant disease. The patient was treated with wide local excision and surveillance.

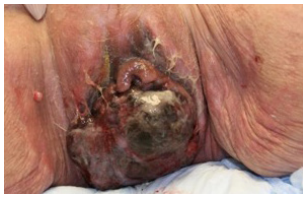
FIGURE 3. Acral melanoma of the sole in an Asian female.



Case 4

An 85-year-old Caucasian female with no past medical history presented with abnormal vaginal bleeding for one year. Associated symptoms included fatigue and lower extremity edema. A physical exam revealed left inguinal lymphadenopathy and a malodorous, hyperpigmented, hemorrhagic mass protruding from the vagina. Biopsy demonstrated pleomorphic neoplastic cells, necrosis, and fibrosis (Figure 4). Immunostaining was positive for MART-1, CD117, Vimentin, and S100, supporting a diagnosis of vaginal primary malignant melanoma. Inguinal lymph node biopsy showed neoplastic cells with nuclear hyperchromasia, enlargement, and pleomorphism.

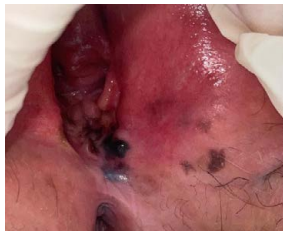
FIGURE 4. Mucosal melanoma of the vagina in a Caucasian female.



Case 5

A 62-year-old Hispanic woman presented for evaluation of a dark lesion near the vagina discovered two weeks prior. There were no associated signs or symptoms. Physical examination revealed an irregularly shaped black macule near the vaginal introitus and labia minora (Figure 5). A shave biopsy revealed atypical melanocytes with large pleomorphic nuclei, and immunostaining was positive for MART-1 and Ki67. These findings supported the diagnosis of vaginal primary malignant melanoma with Breslow's thickness of 1.1 mm. The patient was treated with wide local excision with clear margins.

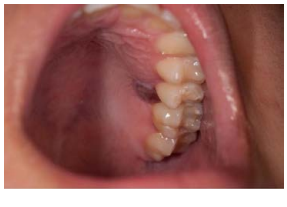
FIGURE 5. Mucosal melanoma of the vagina and labia in a Hispanic female.



Case 6

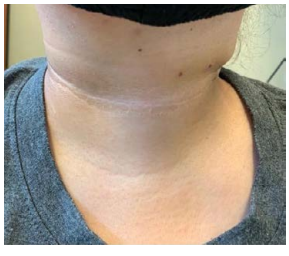
A 21-year-old Hispanic woman presented with a pigmented oral lesion and associated cervical lymphadenopathy (Figure 6). Family history was significant for multiple malignancies and germline TP53 mutations. The patient underwent genetic testing, which revealed Li-Fraumeni syndrome. Biopsy of the oral lesion demonstrated malignant melanoma and fine-needle aspiration confirmed regional nodal involvement. CT scan showed no distant metastasis. The patient was treated with surgical resection, radiotherapy, and four cycles of chemotherapy with dacarbazine, cisplatin, vinblastine, interferon alpha, and interleukin 2.

FIGURE 6. Oral mucosal melanoma in a Hispanic female.



The patient was lost to follow-up after three years of surveillance and presented eight years after the initial presentation with cervical lymphadenopathy (Figure 7). Nodal biopsy redemonstrated lesional cells. At the time of staging, MRI and CT did not reveal distant metastatic disease. The patient was

FIGURE 7. Cervical lymphadenopathy eight years after initial presentation. Note the scar from the previously performed neck dissection.



treated with three rounds of ipilimumab and nivolumab and three rounds of paclitaxel monotherapy.

DISCUSSION

The World Health Organization's melanoma classification system currently recognizes 9 melanoma subtypes, of which 6 are not associated with cumulative solar damage (CSD).[3] Included in this non-CSD division are AMM, with distinct clinical presentations, pathogenetic features, and epidemiologic characteristics separating each from other subtypes.

Acral melanoma occurs on the volar aspects of the hands and feet, as well as the nail beds.[3] These lesions usually begin as a patch, enlarge radially, and may form plaques that result in epidermal thickening.[3] However, given the thick stratum corneum on acral surfaces, the lesions often remain flat during radial growth.[3] The vertical growth phase results in ulceration or nodule formation.[3] Diagnosis of acral lesions often occurs at advanced stages leading to poor prognosis.[3]

Mucosal melanoma occurs within a mucous membrane, primarily in genital sites, oral/nasal cavities, and the conjunctiva.[3] Detection is difficult given the non-visible sites and 40% of cases being amelanotic.[4] Therefore, these lesions commonly present as bulky, invasive tumors.[3]

The role of UV radiation in the mutagenesis of classic cutaneous melanoma is well established, but the pathogenesis of AMM is poorly understood.[5] There is some evidence that previous trauma and human herpes virus DNA may play a role in the development of some acral and mucosal melanomas, respectively.[3,6]Though 40 to 60% of cutaneous melanomas have activating BRAF mutations, mutations in KIT, NRAS, and CCND1 appear to play a more significant role in the mutagenesis of AMM.[3,7] TERT translocations have been noted in 41% of cases.[3]

AMM have distinct epidemiological characteristics. AMM occurs at an approximately equal rate among all races. However, as patients of color are less prone to melanoma developing in sun-exposed sites, a greater proportion of total melanoma in these patients is AMM.[3] Difficulty in recognizing these lesions in skin of color likely contributes to advanced stage at diagnosis and poorer prognosis.

Review studies aimed at investigating the different subtypes of melanoma and their associated risk factors are underway.[8] In the meantime, encouraging regular multidisciplinary care visits can aid in early diagnosis and decrease disease burden. Performing a thorough physical at routine intervals, including examination of commonly overlooked areas such as nasal/oral cavities, hands/feet, and genitalia is essential.

CONCLUSION

AMM are rare melanoma subtypes characterized by unique clinical, genetic, and epidemiologic features. These unique characteristics are the focus of current research to better understand the etiology and mutagenesis of these subtypes. This case series demonstrates that even with limited knowledge about the etiology of AMM, performing thorough skin examinations and encouraging skin cancer awareness can aid in early detection and better patient outcomes.

DISCLOSURES

The authors have no conflicts of interest to disclose.

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doi:10.36849/JDD.8398

August 2024 686 Volume 23 • Issue 8

CASE REPORT

Journal of Drugs in Dermatology

Polymorphous Light Eruptions Treated With Roflumilast 0.3% Cream: A Case Report

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INTRODUCTION

Polymorphous light eruption (PMLE) is a photosensitivity disorder that presents as, erythematous papulovesicles in sun-exposed regions of the skin that can progress to large plaques and bullae.[1,2] While the exact mechanism of PMLE is unknown, a delayed-type hypersensitivity, involving type 1 helper (Th1) cells, immunological reaction with failure of ultraviolet-induced local immunosuppression is implicated.[1,3] Patients will typically react to ultraviolet B (UVB) rays, but lesions can be produced by any wavelength or energy source if there is sufficient exposure.[1,2] Typical treatments include sun protection, corticosteroids, systemic anti-malarial and desensitizing phototherapy.[3] However, these treatments can be ineffective and laborious, especially desensitization phototherapy. We present a case of a patient with PMLE who experienced resolution after treatment with roflumilast 0.3% cream.

A 40-year-old-female with no significant past medical history presented to the clinic with extremely pruritic, photo-distributed, edematous, erythematous pink papules and plaques on her forearms, dorsal hands, and neck of 5 months (Figures 1 and 2). A Punch biopsy of the right forearm showed papillary dermal edema and a superficial to mid-dermal perivascular infiltrate consisting of lymphocytes, histiocytes, and scattered eosinophils. Clinicopathologic correlation is consistent with PMLE. The eruptions and symptoms did not improve with strict sun protection and clobetasol ointment of 0.5% twice a day for two months. The patient declined systemic therapy, and her schedule prevented her from undergoing prophylactic phototherapy. She experienced significant improvement in symptoms and rash clearance after using roflumilast 0.3% cream once daily for 2 weeks (Figures 3 and 4). In the areas of frequent

FIGURE 1. Initial presentation of dorsal left upper extremity with slightly edematous and erythematous clusters of papules that coalesce into plaques.

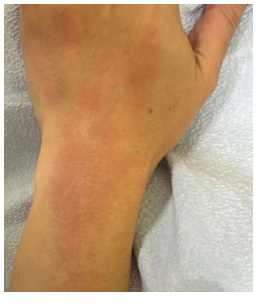


FIGURE 2. Initial presentation of lesions on the posterior neck with edematous and erythematous papules and plaques.

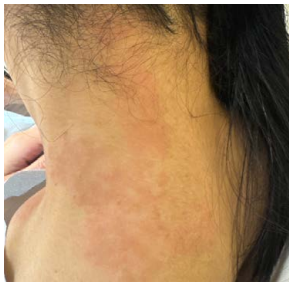


FIGURE 3. Clearance of the PMLE with roflumilast 0.3% cream with a wound from punch biopsy.

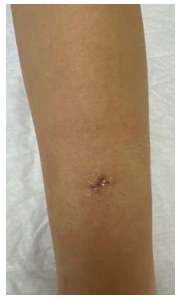
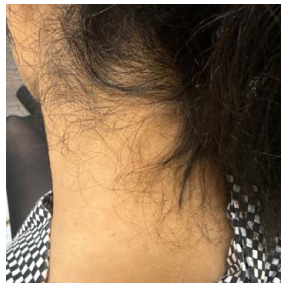


FIGURE 4. Clearance of lesions on the neck with roflumilast 0.3% cream.



recurrence of the upper extremities and neck, prophylactic use of roflumilast once a week prevented recurrence on a 3-month follow up.

Roflumilast is a PDE-4 inhibitor that results in the accumulation of cyclic adenosine monophosphate inside immune cells.[4,5] This leads to broad immunomodulation of proinflammatory cytokines by Th1, Th17, and Th2 cells, like tumor necrosis alpha (TNF-α), interferon gamma, interleukin-17 (IL-17), and IL-4.[4] Roflumilast 0.3% cream is FDA-approved for the treatment of plaque psoriasis, but to our knowledge, this is the first reported case of successful treatment of PMLE with roflumilast 0.3% cream. While not fully elucidated, aberration in TNF-α, IL-4, and IL-10 cytokines are implicated in the UVB-induced lesioned skin.[6] The mechanism of action of roflumilast cream on PMLE is not clear, but we predict its broad immunomodulatory property dampens the proinflammatory cytokine cascades that collectively triggers PMLE.

While promising, additional studies are needed to evaluate the safety and efficacy of roflumilast 0.3% cream as a treatment option for PMLE.

DISCLOSURES

Dr Leonardo Tjahjono has served as a consultant for Bristol Myers Squibb. Dr Leon Kircik has been a consultant, speaker, advisory board member, and/or investigator for and received honoraria and/or grant funding from the following companies: Abbott Laboratories, Abbvie, Ablynx, Aclaris, Acambis, Allergan, Inc., Almirall, Amgen, Inc., Anacor Pharmaceuticals, Anaptys, Arcutis, Arena, Assos Pharma, Astellas Pharma US, Inc., Asubio, Bausch Health, Berlex Laboratories (Bayer HealthCare Pharmaceuticals), Biogen-Idec, Biolife, Biopelle, BMS, Boehringer-Ingleheim, Breckinridge Pharma, Cassiopea, Centocor, Inc., Cellceutix, Cipher, Coherus, Colbar, Combinatrix, Connetics Corporation, Coria, Dermavant, Dermira, Dermik Laboratories, Dow Pharmaceutical Sciences, Inc., Dr. Reddy's Lab, Dusa , Embil Pharmaceuticals, Eli Lilly, EOS, Exeltis, Ferndale Laboratories, Inc., Foamix, Ferrer, Galderma, Genentech, Inc., GlaxoSmithKline, PLC, Glenmark, Health Point, LTD, Idera, Incyte, Intendis, Innocutis, Innovail, Isdin, Johnson & Johnson, Kyowakirin Laboratory Skin Care Inc., Leo, L'Oreal, 3M, Maruho Medical International Technologies, Merck, Medicis Pharmaceutical Corp., Merz, Nano Bio, Novartis AG, Noven Pharmaceuticals, Nucryst Pharmaceuticals Corp., Obagi, Onset, OrthoNeutrogena, PediaPharma, Pfizer, Promius, PuraCap, PharmaDerm, QLT, Inc., Quinnova, Quatrix, Regeneron, Sanofi, Serono (Merck Serono International SA), SkinMedica, Inc., Stiefel Laboratories, Inc., Sun Pharma, Taro, TolerRx, Triax, UCB, Valeant Pharmaceuticals Intl., Verrica Pharmaceutical, Warner-Chilcott, XenoPort, and/or ZAGE.

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doi:10.36849/JDD.7866

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BRIEF COMMUNICATION

Journal of Drugs in Dermatology

The Treatment of Psoriasis With Intramuscular Triamcinolone

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INTRODUCTION

Although intramuscular triamcinolone acetonide (IMT) for the treatment of numerous dermatologic conditions has been available for more than 60 years, many dermatologists continue to use it routinely while many others use it rarely or not at all, either because they are unaware of its therapeutic benefits or are concerned about its side effects. A recent survey conducted by the University of Utah Department of Dermatology (personal communication) found that of the 844 out of 2000 dermatologists who completed the survey, only 55% felt comfortable using IMT for steroid-responsive dermatoses, while 90% felt more comfortable using oral corticosteroids. If both were indicated, then 59% preferred oral corticosteroids over IMT.

In 2009, one of the co-authors (DNR) published an article describing the positive response of IMT to many chronic steroid-responsive conditions while also using a technique that minimized any significant side effects, especially when compared with a course of oral corticosteroids. We will review these findings and then discuss IMT's value in the treatment of psoriasis.[1]

Clearly, in the past two decades, there has been a huge paradigm shift with the introduction of many new systemic agents that can effectively and safely treat moderate to severe psoriasis patients. This begs the question of what IMT can do to bring therapeutic value to our patients. Psoriasis is of course a highly variable disease, and in some cases, IMT can serve as an adjunctive agent if there are significant symptomatic issues, such as pruritus and pain, not completely controlled by one of the systemic medications. In other cases, especially when the disease is localized, IMT can treat psoriasis effectively and safely without having to use one of the systemic drugs. This is important for several reasons. First, patients may have comorbidities or personal preferences which preclude the use of one of these systemic medications. Second, the cost differential between the use of one of these newer drugs and IMT is enormous. Whether insurance companies, pharmaceutical assistance programs, or out-of-pocket costs paid by patients, physicians have an ethical obligation to at least consider cost in choosing between two therapeutic options that have similar effectiveness and safety features.

MATERIALS AND METHODS

IMT is indicated in adults with chronic recalcitrant steroid-responsive dermatologic conditions that are not adequately treated with topical medications alone. Common conditions besides psoriasis include pruritus, lichen planus, atopic dermatitis as well as several types of alopecia.

Typical dosing of IMT is 80 mg at least 7 to 8 weeks apart and gradually tapered off depending on clinical response. The injection is given into the upper outer quadrant of the gluteal muscle with a 3-cc syringe and a 1 ½ inch needle. Leakage of triamcinolone into the subcutaneous tissue must be avoided to prevent localized tissue atrophy or abscess formation.

Clinical Indications for the Treatment of Psoriasis with IMT

1. Localized Psoriasis

Localized psoriasis, especially of the scalp, hands, and feet (hyperkeratotic and pustular types), may only involve a small body surface area but can be extremely symptomatic and disabling and may often be very resistant to topical medications alone. A large percentage of these patients could be adequately treated with 3 or 4 IMT injections over the course of a year which can negate the need for the use of other systemic drugs.

2. Relief of Pruritus and Pain

Pruritus and pain may often accompany moderate to severe psoriasis patients. The pain, which may or may not be due to underlying psoriatic arthritis, as well as the pruritus, will almost always improve significantly with IMT. This can be very important when patients first present or when switching from one systemic agent to another when insurance delays can take weeks or even months to resolve. Even when doing relatively well on a particular systemic medication, pain and pruritus may be present and IMT can be beneficial as adjunctive treatment.

3. Nail Psoriasis

For occasional patients, psoriasis of the nails can be quite disfiguring, and it can be very painful to treat with intralesional steroids and unresponsive to topicals. These patients will usually respond well to IMT.

4. Guttate Psoriasis
This condition usually occurs in younger patients and can be quite symptomatic but will usually respond to IMT.

IMT Side Effects
While IMT has a relatively good safety profile, there are some side effects to be aware of. Some adverse reactions seen with IMT therapy include localized lipoatrophy, petechiae and purpura, mild hyperglycemia, menstrual irregularities, and very rarely, hirsutism and sterile abscesses.

Localized lipoatrophy may occur if the full dose of steroid is not injected completely into the muscle. This side effect is typically asymptomatic and gradually resolves within a few months of injection. Petechiae and purpura may also be seen and are more common in older persons with severe sun damage. For three to five days after injection, patients may experience mild elevations (5 to 10 dL/mg) in serum glucose levels, which usually decrease within a week of treatment. This side effect does not limit the use of this treatment for patients with diabetes mellitus.

With the use of IMT, women may experience menstrual irregularities, which premenopausal women should be aware of before beginning treatment. This therapy should not be administered to females who intend to become pregnant.

Oral corticosteroids present numerous side effects that are not seen in IMT if administered every 7 to 8 weeks. Adverse reactions to oral steroids include psychiatric symptoms, muscle weakness, weight gain, increased appetite, fluid retention, bloating, moon face, insomnia, hyperactivity, increased centripetal fat distribution, and GI issues, such as nausea and bloating. Long-term use of oral corticosteroids can lead to significant health concerns, including hypertension and cataracts.

One of the concerns with the use of long-term corticosteroids is aseptic necrosis of the femur or other bones, but there is only one reported case of IMT causing that condition in the literature.[2] In addition, bone fragility and fracture are other concerns with chronic corticosteroid use, but a review of the literature as well as one of the author's experiences in treating thousands of patients over more than 40 years, that side effect is extremely rare.

Reddy et al explored the extent of adrenal suppression of IMT in 14 patients with steroid-responsive dermatological diseases. Researchers injected 30 mg IMT to patients with BMI <30 and 60 mg to patients with BMI >30. Patients received one or two doses with six weeks between doses. Morning cortisol and ACTH were measured before treatment, as well as 6- and 12-weeks post-treatment. Results showed decreased mean total cortisol levels in patients at 6- and 12-weeks post-injection but ACTH levels were not impacted. However, no secondary adrenal suppression

FIGURE 1A, 1B, 1C. These three patients have severe, symptomatic localized psoriasis (pustular and hyperkeratotic psoriasis of the palms, and psoriasis of the scalp.) These three patients had failed to respond adequately to topical medications alone but did very well receiving 3-4 IMT injections over the course of a year.

(A)
(B)
(C)

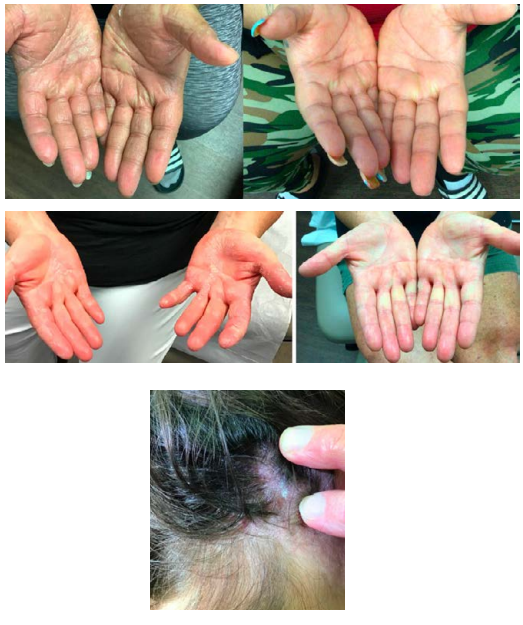


FIGURE 2A AND 2B. This patient's major concern was nail psoriasis, and he responded to a total of 4 IMT injections over the course of a year.

(A) (B)

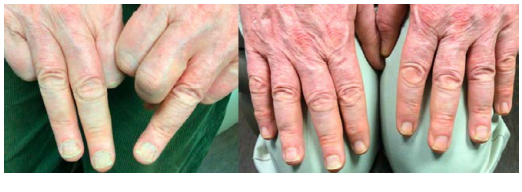


FIGURE 3A AND 3B. This 17-year-old patient presented with generalized pruritic plaque psoriasis, because insurance issues delayed his receiving systemic medications. After receiving an IMT injection on his initial visit, when he returned 2 ½ weeks later his lesions had flattened and his pruritus was gone.

(A) (B)

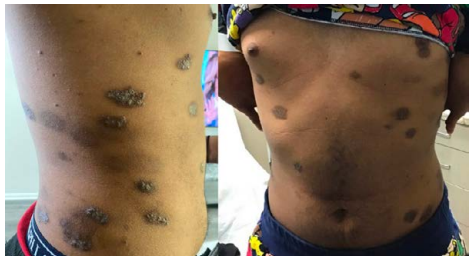
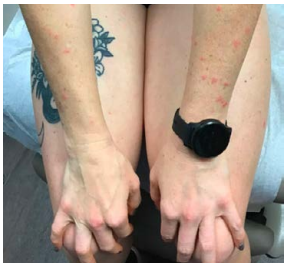


FIGURE 4. This patient developed generalized guttate psoriasis following a streptococcal infection. Within 10 days after receiving an IMT injection, her psoriasis had cleared and never recurred.



or Cushing's syndrome was noted in any patient. Researchers did not note any significant side effects of the treatment and suggested that IMT is a safe and effective way to treat multiple dermatologic conditions.[3]

One of the most important studies in the literature that helps explain the metabolism as well as the overall safety of IMT is by Kusama et al who treated 5 patients with radioactively tagged triamcinolone acetonide and measured the plasma levels and urinary excretion. They found that the peak plasma levels of triamcinolone acetonide occurred in the first one or two days, and then fell rapidly over the next 6 to 7 days to about one-third of its peak level. It was felt that this period represented an equilibrium between the slow continued release from the muscle deposit and the slow excretion because of triamcinolone's low renal clearance rate. During the next week, the plasma level decreased steadily and was gone by the end of the third week with a subsequent four to five-week break before another injection. The fact that the anti-inflammatory effects of IMT continue to be effective long after the medication has been metabolized by the body helps explain the safety of IMT if used as described in this paper.[4]

CONCLUSION

A recent editorial in the Journal of the American Academy of Dermatology[5] discussed the future of psoriasis treatment and the role of systemic agents in the treatment of limited disease, which nevertheless can have a profound impact on patients' quality of life. Since all of the systemic agents are indicated for moderate to severe psoriasis, it has become increasingly difficult to obtain insurance coverage for limited disease. As described in this paper, IMT has been very effective in treating many of these patients without the need to use other systemic agents. In addition, IMT has been very helpful as an adjunctive agent with those patients with more generalized psoriasis who require one of the systemic medications.

DISCLOSURES

The authors have no conflicts of interest to declare.

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doi:10.36849/JDD.8233

August 2024 691 Volume 23 • Issue 8

BRIEF COMMUNICATION

Journal of Drugs in Dermatology

The Burden of Melasma: Race, Ethnicity, and Comorbidities

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ABSTRACT

Introduction: In an effort to define the characteristics of populations affected by melasma, we utilized a large global health research network database from 108 health care organizations (TriNetx) to quantify the associations between race, ethnicity, and comorbidities.
Methods: We identified the cohort of all patients with melasma from the TriNetx database, and subsequently generated a control cohort. ICD-10 codes were used to identify the prevalence of various comorbidities associated with melasma.
Results: A total of 41,283 patients with melasma (93% female, mean [SD] age 48.8 [12.6] year) were identified. The most frequently associated risk factors included hypertension (25% of the melasma cohort) and hormonal contraception (24%). Rosacea (OR=5.1), atopic dermatitis (OR=3.3), lupus (OR=2.5), history of skin cancer (OR=2.5), history of internal malignancy (OR=2.1), and hormonal contraception use (OR=2.1) possessed the highest odds ratios for development of melasma (all $P< 0.01$). A statistically significant association was identified for melasma in Asian or Other/Unknown races (OR=2.0 and OR=1.7, $P< 0.01$), as well as Hispanic ethnicity (OR=1.3, $P< 0.01$). White, Black/African American, and Not Hispanic groups all revealed slightly lower odds (all 0.8, $P< 0.01$).
Conclusion: This latest global update on the etiopathology of melasma further supports findings from prior epidemiologic study reporting preference in melanized phenotypes (Fitzpatrick skin type III-V), but less so in extreme skin types (I, II, VI). Increased associations with rosacea, atopic dermatitis, and history of cancer may emphasize the importance of treating concurrent inflammatory environments and the consideration of more frequent malignancy surveillance.

J Drugs Dermatol. 2024;23(8):691-693. doi:10.36849/JDD.8233

INTRODUCTION

Melasma is a commonly acquired pigmentation disorder classically favoring young women of color or those with exacerbating factors, such as hyperestrogen states.[1] In this study, we utilized a large global health research network database from 108 health care organizations (TriNetx) to quantify the associations between race, ethnicity, and comorbidities with the prevalence of melasma. Through an enhanced understanding of those most prone to this dyschromia, dermatologists can better stratify potential surveillance and treatment plans.

MATERIALS AND METHODS

We identified the cohort of all patients diagnosed with melasma from the TriNetx database and subsequently generated a control cohort of age, sex, and race-matched patients without melasma. ICD-10 codes were used to identify the prevalence of previously reported comorbidities in both the melasma and control populations: allergic rhinitis, anticonvulsants, atopic dermatitis, diabetes, hormonal contraceptives, hypertension, hypothyroidism, lupus, malignancy, rosacea, skin cancer, and smoking. Odds ratios were subsequently generated and confirmed with Fisher's exact tests.

RESULTS

A total of 41,283 patients with melasma (93% female, mean [SD] age 48.8 [12.6] years) were identified (Table 1). The most frequently associated risk factors included hypertension (25%) and hormonal contraception (24%). Rosacea (OR=5.1), atopic dermatitis (OR=3.3), lupus (OR=2.5), history of skin cancer (OR=2.5), and history of internal malignancy (OR=2.1) possessed the highest odds ratios for development of melasma (all $P<0.01$) (Table 2). A statistically significant association was identified for melasma in Asian or Other/Unknown races (OR=2.0 and OR=1.7, $P<0.01$), as well as Hispanic ethnicity (OR=1.3, $P<0.01$). White, Black/African American, and Not Hispanic groups all revealed slightly lower odds (all 0.8, $P<0.01$) (Table 2).

DISCUSSION

This latest update on the association of skin of color and comorbidities of melasma further supports the findings from a prior epidemiologic study reporting preference in melanized phenotypes (Fitzpatrick skin type III-V), but less so in extreme skin types (I, II, VI).[2] The melasma cohort revealed very high associations with rosacea and atopic dermatitis, possibly related to increased blood flow and overactive mast cells present in both conditions, emphasizing the importance of treating concurrent inflammatory environments.[3,4]

TABLE 1.

Melasma Demographics. Patient demographic information for the melasma cohort and control cohort after propensity score matching for age, sex, race, and ethnicity (left). The overall prevalence of risk factors in the melasma cohort and each subgroup's respective demographic information (right).

	Melasma and Control Cohorts			Prevalence of Comorbidities in Melasma Cohort					
	All Melasma (n=41,283)	Control Cohort (n=41,283)	*P*-value	Allergic Rhinitis (n=6344)	Anti-convul-sants (n=9293)	Atopic Dermatitis (n=1909)	Diabetes (n=4697)	Hormonal Contraception (n=10216)	Hypertension (n=10683)
Age, mean [SD] years	49 (13)	49 (13)	1	57 (14)	53 (13)	51 (14)	59 (13)	42 (8)	58 (13)
Sex, no (%)									
Female	38524 (93)	38527 (93)	1	6027 (95)	8735 (94)	1794 (94)	4274 (91)	10216 (100)	9722 (91)
Male	2738 (7)	2738 (7)	1	317 (5)	558 (6)	115 (6)	423 (9)	0 (0)	961 (9)
Race, no (%)									
White	21338 (52)	21893 (52)	1	3363 (53)	4833 (52)	840 (44)	1597 (34)	6845 (67)	4273 (40)
Black/AA	4983 (12)	5053 (12)	1	1142 (18)	1766 (19)	363 (19)	1409 (30)	715 (7)	2884 (27)
Asian	2560 (6)	2562 (6)	1	444 (7)	465 (5)	191 (10)	376 (8)	511 (5)	748 (7)
Other/Unknown	12040 (30)	12038 (30)	1	1332 (21)	2137 (23)	496 (26)	1221 (26)	2043 (20)	2671 (25)
Ethnicity, no (%)									
Not Hispanic	23218 (56)	23218 (56)	1	3806 (60)	5762 (62)	1336 (70)	2630 (56)	6845 (67)	6303 (59)
Hispanic	6514 (16)	6514 (16)	1	1269 (20)	1487 (16)	267 (14)	987 (21)	1839 (18)	1933 (18)
Unknown	12040 (28)	12040 (28)	1	1269 (20)	2044 (22)	306 (16)	1081 (23)	1532 (15)	2457 (23)

	Melasma and Control Cohorts			Prevalence of Comorbidities in Melasma Cohort					
	All Melasma (n=41,283)	Control Cohort (n=41,283)	*P*-value	Hypo-thyroid (n=5740)	Lupus (n=345)	Malignancy (n=2681)	Rosacea (n=3576)	Skin Cancer (n=1078)	Smoking (n=3078)
Age, mean [SD] years	49 (13)	49 (13)	1	53 (13)	52 (12)	58 (14)	49 (12)	57 (14)	52 (12)
Sex, no (%)									
Female	38524 (93)	38527 (93)	1	5568 (97)	335 (97)	2520 (94)	3469 (97)	970 (90)	2740 (89)
Male	2738 (7)	2738 (7)	1	172 (3)	10 (3)	161 (6)	107 (3)	108 (10)	338 (11)
Race, no (%)									
White	21338 (52)	21893 (52)	1	3157 (55)	148 (43)	1582 (59)	2360 (66)	776 (72)	1693 (55)
Black/AA	4983 (12)	5053 (12)	1	631 (11)	79 (23)	429 (16)	215 (6)	43 (4)	677 (22)
Asian	2560 (6)	2562 (6)	1	459 (8)	17 (5)	134 (5)	143 (4)	22 (2)	92 (3)
Other/Unknown	12040 (30)	12038 (30)	1	1435 (25)	93 (27)	536 (20)	823 (23)	216 (20)	586 (19)
Ethnicity, no (%)									
Not Hispanic	23218 (56)	23218 (56)	1	3559 (62)	214 (62)	1877 (70)	2289 (64)	765 (71)	2031 (66)
Hispanic	6514 (16)	6514 (16)	1	918 (16)	72 (21)	375 (14)	536 (15)	76 (7)	462 (15)
Unknown	12040 (28)	12040 (28)	1	1263 (22)	59 (17)	429 (16)	751 (21)	237 (22)	585 (19)

AA=African American. ICD-10 codes used: Melasma=L81.1, Allergic rhinitis=J30.9, Anticonvulsants=CN400, Atopic Dermatitis=L20, Diabetes=E08-E13, Hormonal contraceptives=HS200, Hypertension=I10-I16, Hypothyroid=E03, Lupus=L93, Malignancy=Z85, Rosacea=L71, Skin Cancer=C43-C44, Smoking=F17.

Cutaneous malignancies were more frequently seen in melasma patients (778 (72%) nonmelanoma, 300 (28%) melanoma cases), leading us to speculate several plausible explanations, from higher sun exposure, hormonal stimuli, altered oxidative status, and impaired skin barriers, which promote melasma and may also predispose the development of skin cancer.[3] Similarly, a history of internal malignancy (most commonly lymphoproliferative (1268, 47%) and breast (208, 8%)) possessed a high odds ratio (2.1). This association remains more difficult to explain, possibly related to higher inflammatory states or hormonal milieu changes, whether disease-specific or iatrogenic.[1] These findings lead us to suggest that melasma patients may benefit from increased skin cancer surveillance and age-appropriate cancer screening.

TABLE 2.

Melasma Risk Factor Analysis			
Risk Factor, no (%)	**Melasma (n = 41,283)**	**Control (n = 41,283)**	**OR***
Race			
White	21337 (52)	26744 (65)	0.8
Black/AA	4983 (12)	5895 (14)	0.8
Asian	2559 (6)	1283 (3)	2.0
Other/Unknown	12040 (29)	7163 (17)	1.7
Ethnicity			
Not Hispanic	23216 (56)	28612 (69)	0.8
Hispanic	6514 (16)	5157 (12)	1.3
Comorbidities			
Rosacea	1704 (3.9)	332 (0.8)	5.1
Atopic Dermatitis	960 (2.3)	309 (0.7)	3.3
Skin Cancer	629 (1.5)	263 (0.6)	2.5
Lupus	222 (0.5)	89 (0.2)	2.5
Malignancy	1589 (3.8)	777 (1.8)	2.1
Hormonal Contraception	7923 (19)	3752 (9)	2.1
Allergic Rhinitis	4742 (11.5)	2581 (6.2)	1.9
Hypothyroid	4088 (9.9)	2276 (5.5)	1.8
Anticonvulsants	5907 (14.3)	3886 (9.4)	1.5
Hypertension	7731 (18.7)	5771 (13.9)	1.3
Diabetes	3230 (7.8)	2858 (6.9)	1.1
Smoking	2332 (5.6)	2533 (6.1)	0.9

Incidence of risk factors in melasma cohort compared to control cohort. Age, sex, and comorbidities held constant for race and ethnicity analysis. Age, sex, race, and ethnicity held constant for comorbidity analysis. AA=African American. OR=odds ratio. *=all *P*-values <0.05.

CONCLUSION

Understanding the potential associations between these risk factors and melasma will better improve the management and monitoring of the most susceptible patients. Limitations of this study include the retrospective nature of data collection, the potential for misclassification of diagnoses using ICD-10 codes, and the correlative, not causative, nature of our analysis.

DISCLOSURES

The authors have no conflicts of interest to disclose.

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doi:10.36849/JDD.8381

August 2024 694 Volume 23 • Issue 8

BRIEF COMMUNICATION

Journal of Drugs in Dermatology

Rapid Remission of Plaque Psoriasis With Bimekizumab Treatment

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ABSTRACT

Bimekizumab is a novel humanized bispecific monoclonal immunoglobulin G1 (IgG1) antibody that dually inhibits both IL-17A and IL-17F. Investigation of the pivotal role of IL-17A, and more recently, IL-17F, in the pathogenesis of psoriasis has underscored the utility of biologics targeting these cytokines in the treatment of the disease. Treatments include the anti-IL-17 biologics specifically targeted against IL-17A (secukinumab and ixekizumab) or its receptor (brodalumab). Recent clinical trials proved the efficacy and safety of bimekizumab in the treatment of moderate-to-severe plaque psoriasis and even showed it to be superior to other psoriasis biologic treatments in regards to efficacy and rapidity of response. These are important factors to consider when discussing treatment options with patients as psoriasis patients commonly desire fast-acting results. In this case, we describe clearance of moderate-to-severe plaque psoriasis within 72 hours of treatment with bimekizumab, one of the fastest reported clearance times in the medical literature.

J Drugs Dermatol. 2024;23(8):694-696. doi:10.36849/JDD.8381

INTRODUCTION

Some psoriatic disease topical treatments, such as coal tar and salicylic acid, have stood the test of time, being used consistently over the past century.[1] However, the landscape of systemic medications used to treat psoriasis has undergone significant evolution in a fraction of the time. Since their first approval by the US Food and Drug Administration (FDA) in 2003, biologics have transformed the treatment of moderate-to-severe psoriasis because of their high degree of efficacy.[1] These include T-cell targeted agents, tumor necrosis factor (TNF)-α inhibitors, interleukin (IL)-17 inhibitors, IL-12/23 inhibitors, and IL-23 inhibitors. The newest approved biologic in the United States is bimekizumab, a selective inhibitor of both IL-17A and IL-17F, which has shown significant, long-term clinical efficacy in randomized clinical trials.[2,3,4] In fact, it has even been shown to be superior to other psoriasis biologic treatments, including IL-17A, IL-12/23, and TNF-α inhibition.[5–7]

The choice of psoriatic disease therapy is patient-dependent and involves the consideration of many factors, including patient preference. When queried on what aspects of treatment they valued, many psoriasis patients value effectiveness, rapidity of response, and longevity of response the most.[8] As such, dermatologists should focus on providing patients with treatment options that are rapid acting, effective while safe, and long-lasting. Two studies investigating the rapidity of the response of biologic treatments for moderate-to-severe psoriasis found that IL-17 inhibitors brodalumab and ixekizumab yielded the overall fastest response rate.[9,10] Utilizing Bayesian and Frequentist network meta-analyses of phase 3, double-blind, randomized, controlled trials testing IL-17, IL-12/-23, IL-23, and TNF inhibitors for the treatment of moderate-to-severe psoriasis, Warren et al found more rapid therapeutic effects on Psoriasis Area and Severity Index (PASI) 75 and 90 response rates at weeks 2, 4, and 8 with ixekizumab and brodalumab.[9] Egeberg et al similarly found that brodalumab and ixekizumab yielded the shortest time to achieve PASI 90 in 25% and 50% of patients in their systematic review of phase 3 clinical trials of IL-17 and IL-23 inhibitors for moderate-to-severe psoriasis in adult patients.[10] However, it is important to note that these studies were performed prior to the approval of bimekizumab. Since then, bimekizumab has shown in head-to-head clinical trials to be more rapid-acting than other psoriasis treatments.[5-7] Herein, we describe a case of treatment naïve moderate-to-severe plaque psoriasis with significant clearance within 72 hours of treatment with bimekizumab.

Case Description

A 38-year-old skin of color male presented with a 2-year history of treatment naïve plaque psoriasis. He reported moderate pruritus of the affected areas which interfered with his daily activities and quality of life. On physical exam, he had 20% body surface area involvement, including the trunk, bilateral lower extremities (Figure 1A), upper extremities (Figure 2A), and forehead (Figure 3A). The patient shared his desire for an effective systemic treatment and did not want to pursue topical therapy. Bimekizumab treatment was initiated. He reported his itch to be negligible approximately 6 to 12 hours after the injection. Within 72 hours after the initial dose (given as two subcutaneous syringes of 160 mg each, both injected into the arms), the patient experienced a remarkable clearance of his psoriasis (PASI 90) (Figure 1B, 2B, and 3B). He achieved PASI 100 at day 7 (1 week) and rated his itch score as 0 with only post-inflammatory hyperpigmentation remaining (Figure 1C, 2C, and 3C).

FIGURE 1. Psoriasis of the lower extremities at (A) day 0 (B) day 3 (72 hours after treatment with two subcutaneous injections of 160 mg bimekizumab into the arms), and (C) day 7.

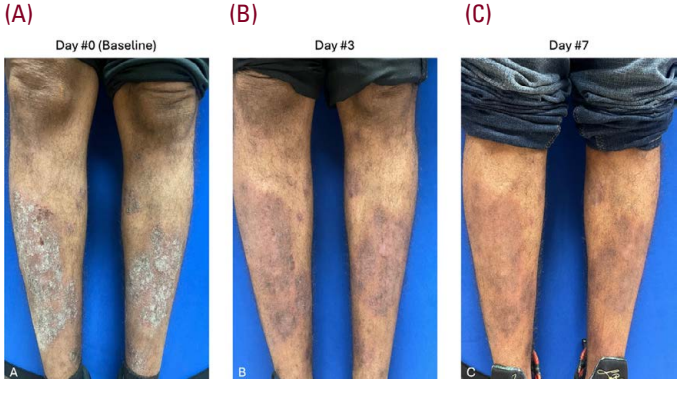


FIGURE 2. Psoriasis of the left forearm at (A) day 0 (B) day 3 (72 hours after treatment with two subcutaneous injections of 160 mg bimekizumab into the arms), and (C) day 7.

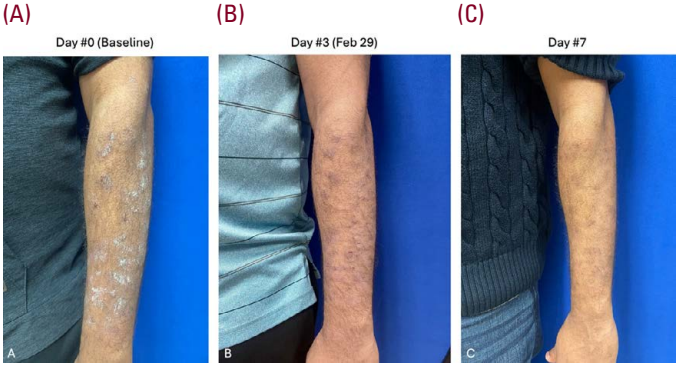
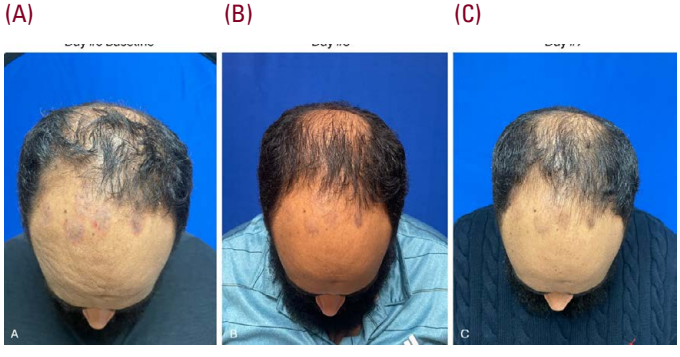


FIGURE 3. Psoriasis of the forehead at (A) day 0 (B) day 3 (72 hours after treatment with two subcutaneous injections of 160 mg bimekizumab into the arms), and (C) day 7.



DISCUSSION

Bimekizumab is a novel humanized bispecific monoclonal immunoglobulin G1 (IgG1) antibody that dually inhibits IL-17A and IL-17F.[2,11] Historically, the role of IL-17A in the pathogenesis and treatment of psoriasis has been the point of focus; as such, prior to the approval of bimekizumab, the anti-IL-17 biologics specifically targeted only IL-17A (secukinumab and ixekizumab) or its receptor (brodalumab).[2,11] However, there has been recent interest in the role of IL-17F in the pathogenesis and treatment of the disease given its structural homology with IL-17A. Indeed, both IL-17 isomers bind to the same complex of IL-17RA and IL-17RC.[11] Although IL-17F has been regarded as less biologically active than IL-17A, given its decreased binding affinity for the IL-17RA/RC complex, it is ~30-fold more abundant than IL-17A in the skin and its role in the pathogenesis of psoriasis has been described.[11,12] Therefore, it is not surprising that the dual inhibition of IL-17A and IL-17F offered by bimekizumab provides more effective and rapid-acting clinical results than its biologic comparators. The molecular and structural basis for bimekizumab inhibition of IL-17A and IL-17F was also recently reported.[13]

Regarding the specific studies on bimekizumab, BE ABLE 1 (NCT02905006) is a 12-week multicenter, randomized, double-blind, placebo-controlled, parallel-group, dose-ranging, phase IIb study investigating the efficacy of bimekizumab compared to placebo in patients with moderate-to-severe psoriasis. Patients were randomized to receive bimekizumab every 4 weeks at doses of 64 mg, 160 mg, 160 mg (with 320 mg loading dose at baseline), 320 mg, 480 mg, or placebo over 12 weeks. A statistically significant dose-response was noted in regards to PASI 90 response at week 12 (primary endpoint), and this was achieved by significantly more bimekizumab-treated patients compared to placebo-treated patients (46.2% to 79.1% vs 0%, $P<0.0001$ for all dose comparisons).[2] Given its proven clinical efficacy, the next question was how bimekizumab fared compared to other IL-17 inhibitors. BE RADIANT (NCT03536884) is a 48-week multicenter, randomized, double-blind, secukinumab-controlled, parallel-group, phase IIIb study comparing the efficacy of bimekizumab versus secukinumab in

the treatment of moderate-to-severe plaque psoriasis.[6] Patients were randomized to receive bimekizumab 320 mg every 4 weeks or secukinumab 300 mg weekly to week 4 followed by once every 4 weeks. At week 16, patients in the bimekizumab group underwent rerandomization to receive a maintenance dose of bimekizumab (320 mg) either once every 4 weeks or once every 8 weeks to week 48; patients in the secukinumab group continued to receive secukinumab to week 48. By week 16, 61.7% of patients treated with bimekizumab achieved PASI 100 response (the primary endpoint) compared to 48.9% of those treated with secukinumab (adjusted risk difference, 12.7 percentage points; 95% confidence interval (CI), 5.8 to 19.6, $P<0.001$ for noninferiority and superiority). In addition, after just one dose of bimekizumab (week 4), 71.0% of patients achieved a PASI 75 response compared to 47.3% of secukinumab-treated patients at this time point (adjusted risk difference, 23.7 percentage points; 95% CI, 17.0 to 30.4, $P<0.001$). The superiority and noninferiority of bimekizumab compared to control was maintained through the period of 48 weeks. The authors postulate two theories as to why better response rates were observed. One theory suggests a higher binding affinity of bimekizumab for IL-17A than secukinumab in vitro. The second theory is that dual inhibition of IL-17A and IL-17F is superior to IL-17A inhibition alone. Either one of these two theories is plausible, but likely it is a combination of the two that explains the observed differences in response.[6] Treatment with bimekizumab in clinical trials was associated with oral candidiasis; however, our patient has not experienced candidiasis to date.[2,6]

CONCLUSION

In conclusion, our case presents one of the fastest documented clearances of moderate-to-severe plaque psoriasis in the medical literature. Our patient received bimekizumab loading doses and achieved PASI 90 and PASI 100 at 72 hours and 1 week, respectively, with associated itch resolution. One other report highlights rapid clearance albeit at two weeks.[14] These findings have real-world implications, as our patient's quality of life benefited immensely in the clearance of his disease and associated symptoms after the initial dose of bimekizumab. Notably, there is no formally reported data on PASI scores with any biologic at time points less than 1 week. Given the dramatically effective and rapid clearance in our treatment-naïve patient, we encourage other investigators to report their experience with bimekizumab as a rapidly effective treatment for moderate-to-severe plaque psoriasis.

DISCLOSURES

NTI has received funding from the following entities either as a speaker, consultant, advisor, or investigator: Abbvie, Bristol Myers Squibb, Castle Biosciences, Dermavant Sciences, DermTech, Galderma, Incyte, Journey, LEO Pharma, Lilly, National Eczema Association, Ortho Dermatologics, Pfizer, RBC Consultants, Verrica Pharmaceuticals, and WebMD. CGB has served as an investigator for AbbVie, Almirall, Daiichi Sankyo, LEO Pharma, Ortho Dermatologics, Sun Pharma, Timber, and Palvella; a consultant for AbbVie, Almirall, Apogee, Arcutis, Eli Lilly, EPI Health/Novan, LEO Pharma, Novartis, Ortho Dermatologics, Pfizer, Sanofi-Regeneron, and UCB; and a speaker for and received honoraria from Allergan, Almirall, LEO Pharma, and UCB. RG discloses consulting, speaking, and clinical trials for Abbvie, Amgen, Pfizer, Mindera, Sanofi, Regeneron, Cara Therapeutics, Argenx, BMS, Galderma, Arcutis, AstraZeneca, Leo, Lilly, UCB, and Incyte.

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doi:10.36849/JDD.7956e

August 2024 e167 Volume 23 • Issue 8

BRIEF COMMUNICATION

Journal of Drugs in Dermatology

TikTok and Dermatology: Questioning the Data

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INTRODUCTION

TikTok is a wildly popular social media application with over 1 billion users. With its ever-growing popularity, it has also become a source of dermatological information and misinformation for the public. A call has been made to encourage dermatologists to join the platform to combat the spread of misinformation. The dissemination of dermatological information on TikTok is important and needs to be studied. Such studies published to date rarely account for TikTok's content algorithm and how it will impact their results. The information currently published on TikTok's algorithm reveals that it caters videos towards each user, based on perceived viewing preferences. In this commentary, we propose various mechanisms by which the features of the algorithm may bias data collection, leading to results that lack objectivity, reproducibility, and reliability. We suggest authors acknowledge how the nature of TikTok's algorithm can lead to variability in results. Currently, we do not believe there is an effective method to obtain representative, reliable, and reproducible data regarding dermatology content on TikTok.

The social media app TikTok has amassed over 1.6 billion users since its inception in 2016 and boasts over 1.7 billion monthly active users this year alone.[1] In 2022, it generated $9.4 billion in revenue.[1] To date, public academic search engines report over 240,000 results with the keyword "TikTok." Many dermatologists, dermatology residents, and medical students have joined the platform and posted content regularly. Understanding TikTok and its value in dermatology is important, especially since medical misinformation is exceedingly common on the app. In recent years, a call was made for medical dermatologists to join social media to combat dermatological misinformation.[2] With its ever-increasing popularity, research is needed to assess information disseminated on the application. Numerous studies have been published analyzing various dermatological concepts on TikTok.[3-5] However, investigators rarely consider the unpredictable nature of TikTok's algorithm, and how it may produce unrepresentative, inconsistent, and unreliable results.

Although much of the algorithm remains elusive, a leaked document provides some information.[6] Additionally, the company has released reports on how it uses data, mainly covered by news outlets. TikTok reports that content recommendations are based on a variety of factors including user interactions with content (likes, shares, comments), content previously created by the viewer, and device data.[6] Accounts the user follows and watch time are utilized as well.[6] The algorithm also predicts what type of content a user will like, even before the user indicates with the previous specifications that they do. The app presents users with videos it believes they might enjoy and then gauges their responses.[7] In this way, the TikTok algorithm manipulates the user's experience from the instant they open the app.

A survey of dermatological-based studies focusing on TikTok revealed various ways of measuring data. Some study methods focused on the first "X" number of videos under a hashtag, others analyzed "top" videos by searching a specific term, and some analyzed the most popular videos under a hashtag but did not specify what metric they used to determine which videos were most popular. Notably, the top "X" amount of videos under a hashtag are not sorted according to popularity; this is made evident by the random variation in number of views, likes, and shares from video to video. There is no consensus about the best way to obtain and sort data on the app. Additionally, many studies do not account for algorithmic intervention in which content is served to the investigator, or that the act of data collection itself may be biasing the results by altering which content is subsequently presented. For example: if an investigator spends longer amounts of time analyzing videos containing misinformed content, they are likely to be served more similar content by the app, skewing the data toward misinformation. The moment a user opens the app, TikTok caters videos to the user. Interestingly, even if a user is not logged into their account, TikTok will still collect data on the user.[8]

Inspired by previous study methods, we investigated variation in user experiences due to the algorithm by comparing in-app search results between users. It appears the search categories "top," "videos," and "shop" differ between users. The categories "users," "sounds," and "hashtag" seem to be the same from user to user. Although not much information is available about how content under "users," "sounds," and "hashtag" is generated, TikTok states that, "the hashtag page displays the videos that started the trend first, and then other popular videos relevant to the trending hashtag."[9] After our informal investigation,

doi:10.36849/JDD.7956e

we noted that as new and popular videos are created, the "hashtag" page changes over time, although the frequency of these changes is unknown. In this way, data collected via TikTok's hashtag system is unreliable. Additionally, it is important to consider that each time a new feature is added, the algorithm might be altered drastically. Examples of new features include TikTok Stories, TikTok Now, TikTok Shop, and TikTok Music.

Even though it is important to perform studies evaluating TikTok and its effect on dermatology, investigators need to consider the algorithm when drawing conclusions. To date, very few studies have included that the algorithm played a part in their search and results.[10,11] This is important because due to the personalized nature of the TikTok algorithm, another investigator using the same research method may reach a completely different outcome. These findings are not objective and may not even be representative. Additionally, due to the ever-changing nature of the algorithm, frequent updates, and constant new video uploads, data gathered on the app can quickly become outdated. Until TikTok creates methods to sort videos based on objective measures, authors should exercise caution in data collection and consider how the algorithm plays a role in their findings. To do this, we suggest authors acknowledge how the nature of TikTok's algorithm can lead to variability in results. At this time, we do not believe there is an effective method to obtain representative, reliable, and reproducible data regarding dermatology content on TikTok.

DISCLOSURES

The authors have no conflicts of interest to disclose.

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doi:10.36849/JDD.7815R1e

August 2024 e169 Volume 23 • Issue 8

LETTERS TO THE EDITOR

Journal of Drugs in Dermatology

The Impact of At-Home Narrow-Band UVB Phototherapy for Mild-to-Severe Psoriasis: A Retrospective, Multicenter, Observational Study

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INTRODUCTION

Narrow band-ultraviolet B (NB-UVB) light therapy has been shown to be one of the safest, least expensive, and most effective treatments for psoriasis.[1] Traditional clinic-based phototherapy is time-consuming, expensive, and inconvenient, causing significant patient dropout. This study aims to assess adherence, patient-reported outcomes, and satisfaction with a comprehensive at-home NB-UVB phototherapy system.

Thirty-six patients with mild to severe psoriasis (mild n=14, moderate n=17, severe n=2, unknown n=3) who had been prescribed topical corticosteroids (Group 1, n=25) or systemic or biologic therapy (Group 2, n=11) were treated with adjuvant at-home NB-UVB phototherapy accompanied by a smartphone application with integrated dosing controls, adherence reminders, and one-to-one coaching and monitoring by a care coach (Zerigo Health Solution). The treatment period ranged between 86 to 286 days (three treatments per week, per AAD guidelines[1]). Adherence and treatment satisfaction (5-point scale) were collected. Dermatology Life Quality Index (DLQI) and Psoriasis Symptom Inventory (PSI) surveys were administered at baseline and 12-week follow-up. Normality of the data was determined by the Shapiro-Wilk test, and statistical significance was determined by the Wilcoxon signed-rank test. Results were considered significant at a *P*-value <0.05.

Median adherence was 70.4%, 68.3%, and 86.7% for all patients, Group 1, and Group 2, respectively, with average patient satisfaction ratings of 4.27, 4.33, and 4.11 out of 5, respectively. Average treatment time per patient was 16.7 minutes per week. Average treatment time by disease severity at the initiation of the study was 19.1, 13.4, and 25.4 minutes per week for mild, moderate, and severe disease, respectively. Twenty patients completed both the baseline and week 12 PSI (range 0 to 32, the higher the score, the more severe of symptoms) and DLQI (range 0 to 30, the higher the score, the more quality of life is impaired). There was a 3.9-point average improvement in PSI at week 12 compared to baseline (*P*=0.007; Table 1). DLQI scores improved by an average of 1.8 points at week 12 compared to baseline (*P*=0.038), with 30.0% of patients achieving the minimal clinically important difference (≥ 4 points improvement; Table 2). As part of the treatment protocol per AAD-NPF guidelines,[1] two patients experienced mild erythema as they attempted to reach minimal erythema dosing levels. They paused treatment until the erythema resolved. Events were evaluated and were not reportable to the Food and Drug Administration.

Previous studies have found that at-home NB-UVB phototherapy is at least as effective and safe as NB-UVB phototherapy offered in the outpatient clinic setting for the treatment of mild to severe psoriasis.[2-4] Koek et al reported that for patients treated at home, the median PASI score decreased by 74% compared with 70% for patients treated in an outpatient setting and that the treatment effect was similar (*P*>0.3).[4] Importantly, our current study shows notable improvement in psoriatic symptoms and quality of life. A potential reason for the improved quality of life

TABLE 1.

Psoriasis Symptom Inventory Among Patients Who Received At-Home Narrow-Band UVB Phototherapy		
PSI (n=20)		
Average reduction from baseline	3.9 points	
Scoring Category	**Baseline (n)**	**Week 12 (n)**
0-8 None/Mild	8	15
9-16 Moderate	7	3
17-24 Severe	4	1
25-32 Very Severe	1	1
Change in PSI		
Worsened (n, %)	1 (5%)	
No change (n, %)	10 (50%)	
Improved by 1 category (n, %)	7 (35%)	
Improved by 2 categories (n, %)	2 (10%)	
Improved by 1 or 2 categories (n, %)	9 (45.0%)	

Abbreviations: PSI: Psoriasis Symptom Inventory, UVB: Ultraviolet B light

doi:10.36849/JDD.7815R1e

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TABLE 2.

Dermatology Life Quality Index Among Patients Who Received At-Home Narrow-Band UVB Phototherapy		
DLQI (n=20)		
Average reduction from baseline	1.8 points	
Patients who achieved MCID* (%)	30.0%	
Score (Effect on patient's life)	**Baseline (n)**	**Week 12 (n)**
0-1 (None)	3	2
2-5 (Small)	8	13
6-10 (Moderate)	6	4
11-20 (Very large)	2	1
21-30 (Extremely large)	1	0
Change in DLQI		
Worsened (n, %)	3 (15%)	
No change (n, %)	9 (45%)	
Improved by 1 category (n, %)	7 (35%)	
Improved by 2 categories (n, %)	1 (5%)	
Improved by 1 or 2 categories (n, %)	8 (40.0%)	

*Change in DLQI of at least 4 points.
Abbreviations: DLQI: Dermatology Life Quality Index, MCID: Minimally clinically important difference, UVB: Ultraviolet B light

is the overall low treatment time at just under 17 minutes per week, in addition to the one-on-one coaching provided. When considering travel time and actual appointment time, the burden on one's daily life is significantly reduced by offering at-home treatment. An additional benefit other studies have identified is the cost-effectiveness of at-home phototherapy since the cost of at-home treatment is comparable to outpatient treatment and significantly less expensive than biologic therapy.[3,5] In conclusion, hand-held, at-home NB-UVB phototherapy with proactive coaching and monitoring can improve outcomes and quality of life for patients.

DISCLOSURES

Justine Schneider has no disclosures. Tina Bhutani and Ronald Moy are members of the Zerigo Medical Advisory Board.

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doi:10.36849/JDD.8449e

August 2024 e171 Volume 23 • Issue 8

LETTERS TO THE EDITOR

Journal of Drugs in Dermatology

Comparison of Characteristics Influencing Patient Selection of Sunscreen Between Urban and Rural Regions in the United States

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ABSTRACT

Sunscreen greatly reduces the risk of skin cancer and is recommended as a critical component of sun protection. There is limited literature on patient preferences for sunscreen characteristics. A cross-sectional survey was administered to patients in an urban city and rural area in the United States. Sun Protection Factor (SPF) was consistently the most important factor for patients when selecting sunscreen. However, numerous preferences for sunscreen characteristics vary between the 2 regions, including dermatologist recommendation, texture, ingredients, cost, broad-spectrum, and brand. Gaps in patient knowledge of sunscreen recommendations may be present and further educational programs may be necessary.

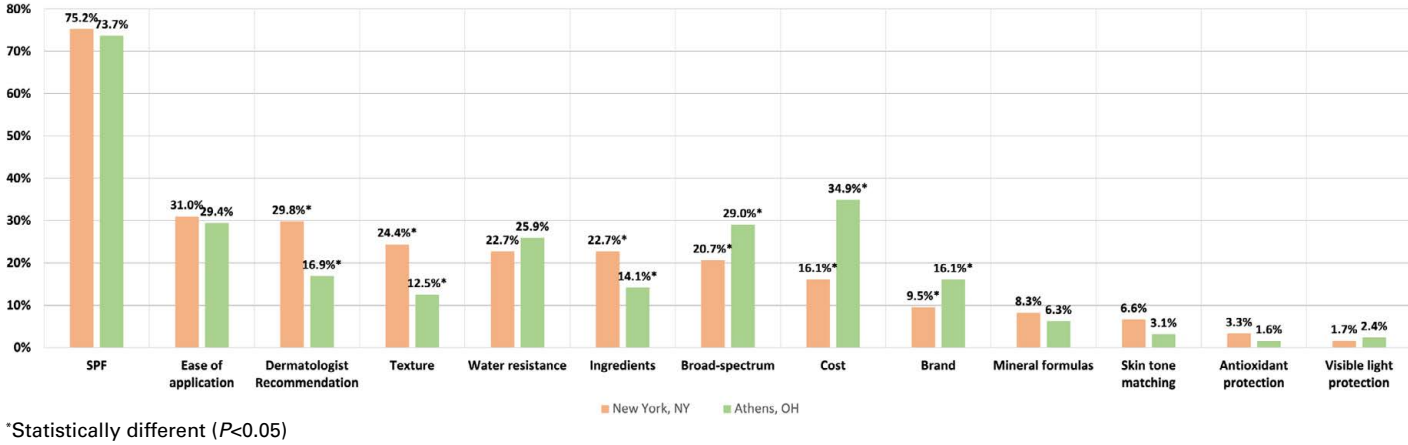
J Drugs Dermatol. 2024;23(8): doi:10.36849/JDD.8449e

INTRODUCTION

Sunscreen greatly reduces the risk of skin cancer and is recommended as a critical component of sun protection by the American Academy of Dermatology (AAD).[1,2] One study found that dermatologists most commonly used several recommendation criteria for sunscreen, including Sun Protection Factor (SPF) level (96%), board spectrum protection (98%), cosmetic feel (85%), and photostability (68%).[3]

While there is a diverse selection of sunscreen types and formulations available, a recent survey study in an urban metropolitan city found that patients valued SPF levels significantly more than any other sunscreen characteristic.[4] In addition, this study reported that other preferred characteristics were ease of application and dermatologist recommendation, while features such as cost, brand, visible light protection, and others were selected less frequently.[4] The purpose of this study was to assess the differences in factors that influence patient selection of sunscreen in urban compared with rural regions in the United States (US).

FIGURE 1. Factors influencing patient selection of sunscreen: Manhattan, NY vs Athens, OH.



*Statistically different ($P<0.05$)

doi:10.36849/JDD.8449e

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MATERIALS AND METHODS

A cross-sectional survey study was performed in 2 dermatology offices: Manhattan, New York (NYC) in November 2023 and Athens, Ohio (Athens) in February 2024. The survey was voluntary and offered to all patients >18 years. This study was exempted by the Institutional Review Board (IRB). Respondents were asked to circle the 3 most important characteristics (out of 13 listed) they use to choose sunscreen (Figure 1). Data were analyzed using SPSS v29.0.1.0.

RESULTS

A total of 497 patients completed the survey (NYC=242, Athens=255), of which 203 were male and 294 were female. The average age was similar between locations (NYC=53.6 vs Athens=52.2 years, respectively). Patients in NYC and Athens both selected SPF as the most preferred characteristic (75.2% vs 73.7%, P=0.71). For patients in NYC and Athens, SPF selection was significantly higher than all other characteristics (P<0.001 for both). Patient preferences for sunscreen characteristics in NYC and Athens are displayed in Figure 1.

Patients in NYC had a significantly greater number of selections for dermatologist recommendation (29.8% vs 16.9%, P<0.001), texture (24.4% vs 12.5%, P<0.001), and ingredients (22.7% vs 14.1%, P=0.01). On the other hand, patients in Athens had significantly more selections for the cost (16.1% vs 34.9%, P<0.001), broad-spectrum (20.7% vs 29.0%, P=0.03), and brand (9.5% vs 16.1%, P=0.03). Ease of application, water resistance, mineral formulas, skin tone matching, antioxidant protection, and visible light protection all had similar rates of preference between NYC and Athens.

DISCUSSION

SPF is consistently the most important factor for patients when selecting sunscreen across urban and rural areas. However, several preferences for sunscreen characteristics vary in different regions of the US.

As reported in a recent survey, SPF was chosen significantly more than any other sunscreen characteristic for patients in NYC.[4] Our data demonstrate that this factor was also significantly greater than all other characteristics for patients in a rural region. This is consistent with the most commonly used recommendation criteria by dermatologists.[3] Notably, there was significantly greater importance placed on cost for Athens compared with NYC. One reason may be due to variations in income, as the median household income for NYC is $70,663 while in Athens it is $33,524.[5,6] Despite this difference, there are highly rated sunscreens available for low prices,[7] and patients should be informed of this accessibility to improve rates of sunscreen usage.

AAD guidelines recommend sunscreens with broad spectrum protection, SPF >30, and water resistance.[2] An analysis of the top one percentile of sunscreen products on Amazon.com found that 40% did not adhere to AAD guidelines.[7] The results of our study reveal that although patients are aware of the importance of SPF in choosing a sunscreen, other AAD recommended features are less frequently emphasized. However, patients in Athens had a higher rate of selection for the broad spectrum compared with NYC, demonstrating that a gap in patient education may be present. Additionally, studies have recognized the importance of visible light coverage, particularly in skin of color.[8] As visible light protection was the lowest selected characteristic in both regions, patient education may be required to improve awareness.

Limitations of this study include that all respondents were patients from dermatology offices in two US regions that may not reflect the general public. Strengths of this study include a large number of participants and an equal number at both study locations.

CONCLUSION

There are significant differences in patient preferences for sunscreen characteristics between urban and rural regions in the US. Despite this, SPF is consistently selected as the most important sunscreen characteristic for patients. Gaps in patient knowledge of sunscreen recommendations may be present and further educational programs may be necessary.

DISCLOSURES

The authors have no conflicts of interest to disclose.

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doi:10.36849/JDD.2024.NVRN0824

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FEATURED CONTENT

Journal of Drugs in Dermatology

NEWS, VIEWS, & REVIEWS

Applications of Bruton Tyrosine Kinase Inhibitors in Dermatology

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INTRODUCTION

A member of the tyrosine-protein kinase Tec (TEC) family of tyrosine kinases, Bruton's tyrosine kinase (BTK) is a cytoplasmic, nonreceptor kinase essential to myriad immunological pathways.[1] Activity of BTK most notably underlies B cell development, migration, and activation through B cell receptor (BCR) activation.[1] BTK is also critical for its role in receptor-mediated signal transduction of Fc receptors, toll-like receptors (TLRs), and chemokine receptors.[1] For its dual activity in both adaptive and innate immunity, inhibition of BTK is a potential therapeutic target for autoimmune and allergic dermatologic diseases.[2,3] Emerging applications of BTK-inhibiting drugs in dermatology will be reviewed herein, with a focus on chronic spontaneous urticaria (CSU) and pemphigus vulgaris (PV).

Mechanism of Action

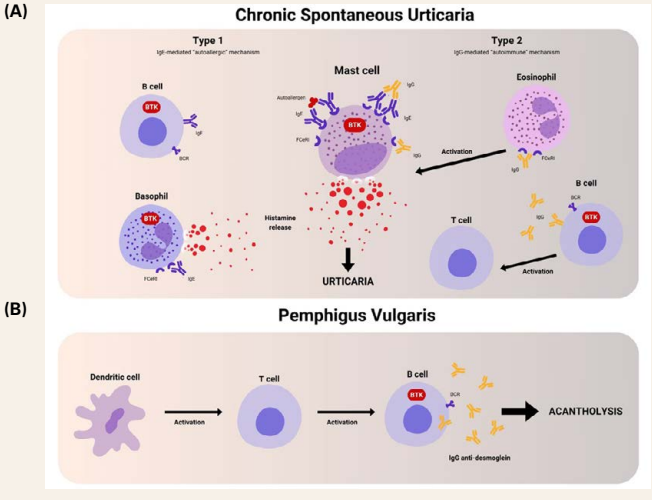
The first-in-class BTK inhibitor, ibrutinib, arrests the enzymatic activity of BTK by forming a covalent, irreversible bond to the cysteine residue C481 of the kinase domain. By preventing downstream activation of BCR pathways, B cell growth, proliferation, and survival is halted. Although effective for the treatment of several lymphoproliferative disorders, ibrutinib inhibits other kinases causing several concerning adverse effects; the development of mutations conferring resistance to ibrutinib is also an arising problem.[1]

Second-generation BTK inhibitors such as acalabrutinib and zanubrutinib also bind irreversibly and covalently to C481 but with higher selectivity, exhibiting less off-target toxicities than ibrutinib.[1,4] To further limit undesired toxicities and resistance, next-generation BTK inhibitors utilize novel mechanisms, such as employing reversible inhibition and targeting alternative binding sites, thus expanding their clinical potential to treat chronic, non-oncological conditions.[1,4]

Chronic Spontaneous Urticaria

Chronic spontaneous urticaria (CSU) is a common and increasingly prevalent condition worldwide that imparts a profound burden on patient quality of life.[5,6] For patients with disease inadequately controlled using first-line H1-antihistamines then anti-IgE monoclonal antibody biologic therapies, BTK inhibition is an emerging yet currently off-label treatment strategy as its activity is essential to the IgE-mediated activation of human mast cells and basophils underlying CSU.[3] Through BTK inhibition, the signal cascade initiated by cross-linking of the high-affinity receptor FcεRI is arrested, preventing subsequent cellular degranulation, leukotriene and prostaglandin production, and cytokine synthesis.[3] Currently two distinct pathophysiologic mechanisms promoting mast cell (MC) activation in CSU are recognized: type 1 (autoallergic) mediated by IgE molecules directed against self-antigens, and type IIb (autoimmune) mediated through IgG molecules directed against the Fc region of IgE or the FcεRI (Figure 1A).[7] Although less common, type IIb CSU is associated with more severe disease and poor response to H1-antihistamines and omalizumab.[7,8] With the ability to address both IgE- and B cell-mediated sources of MC degranulation, BTK inhibitors have the potential for greater efficacy than currently available treatments for CSU, even the more treatment-resistant autoimmune type.[7]

Figure 1. Role of BTK in the pathophysiology of CSU and pemphigus. Figure adapted from Mendes-Bastos et al.[2] **(A)** CSU: Mast cell degranulation is the key pathogenic driver of CSU, with two pathogenic endotypes accepted: type 1 CSU (autoallergic) due to crosslinking of FcεRI via IgE directed at autoallergens, and type IIb CSU (autoimmune) due to IgG directed at the Fc region of IgE or the FcεRI. Eosinophils may also promote MC degranulation. BTK is required for IgE-mediated activation of basophils and FcεRI-initiated cytokine secretion. **(B)** Pemphigus: Presentation of desmoglien antigens by dendritic cells activates T cells thus inducing BTK-mediated anti-desmoglien antibody production by B cells. BCR, B-cell receptor; BTK, Bruton's tyrosine kinase; CSU, chronic spontaneous urticaria; IgE, immunoglobulin E; IgG, immunoglobulin G.



Several clinical trials are investigating three new generation BTK inhibitors as potential therapies for CSU refractory to antihistamines.[3] Remibrutinib, an oral BTK inhibitor drug, is

leading in development with two global, double-blind, placebo-controlled phase 3 trials (REMIX-1 and REMIX-2) completed and awaiting final analyses of results. Primary pooled analyses of the parallel trials (2:1 randomization; remibrutinib 25 mg twice-daily n=613 for up to 52 weeks; placebo n=312 for up to 24 weeks) found both primary endpoints met by achieving superior improvements vs placebo across three disease severity scores as early as week 2 and revealed favorable safety profiles.[9] Further analysis found remibrutinib remained efficacious vs placebo independent of prior exposure to anti-IgE biologic therapies.[10] Another selective BTK inhibitor, fenebrutinib, also demonstrated efficacy in treating antihistamine-refractory CSU in a phase 2a trial and notably showed reductions in autoantibody titers in patients with autoimmune disease; however, further development of fenebrutinib has been halted due to transient elevation of liver transaminases in these trials.[11-13] A final next-generation BTK inhibitor, rilzabrutinib, showed promise as an effective treatment for CSU in phase 2 trials although with a greater incidence of non-life threatening adverse effects compared to placebo.[14]

Pemphigus Vulgaris

Management of moderate to severe PV flares typically involves high-dose systemic corticosteroids and/or intravenous rituximab. While PV is primarily mediated by B cell and plasma cell autoantibodies against desmoglein antigens, activation of the innate immune system plays a role in pathogenesis (Figure 1B); thus, optimal therapeutic regimens should target both innate and active immunological pathways.[15] Rilzabrutinab imparts a favorable mechanism of action by targeting both pathways without directly affectingT cells or depleting B cells. In the phase II BELIEVE study which involved 27 patients with newly diagnosed or relapsing, mild-severe PV, control of disease activity with 400-600 mg twice daily rilzabrutinab monotherapy or concurrent low-dose corticosteroids was achieved in 52% of patients after 12 weeks.[15] At the 24-week follow-up, 22% of patients achieved complete remission, providing compelling evidence in support of rilzabrutinab's rapid clinical efficacy. Notably, treatment-related adverse events were largely mild-moderate, though 3 patients with complex medical histories experienced serious adverse events including cellulitis and pneumonitis. Part B of this trial confirmed and expanded on previous findings by implementing 24 weeks of treatment and more dosing options.[16] By week 4, 60% of patients demonstrated control of disease activity (n=15). Complete healing of all lesions and absence of new lesions was achieved in 40% of patients who were concurrently on low-dose corticosteroids on at least one visit.Thirteen patients experienced mild-moderate, transient treatment-emergent adverse events. Treatment failure was observed in one patient, who discontinued the study.

Additional Applications

BTK inhibition is also actively being investigated in clinical trials for the treatment of atopic dermatitis[3] and systemic lupus erythematosus,[13] and may be a future therapeutic strategy for the treatment of hidradenitis suppurativa given B cells and plasma cells are key pathogenic players in this disease.[17]

CONCLUSION

BTK inhibition is an emerging strategy for allergic and autoimmune dermatologic diseases. Advances in drug design have propelled BTK inhibition from being a solely oncologic therapy with severe side effects to a potentially pivotal treatment strategy in dermatology.

DISCLOSURE

CW's work is funded through an independent fellowship grant from Galderma; SAA's work is funded through independent fellowship grants from Lilly and Pfizer.

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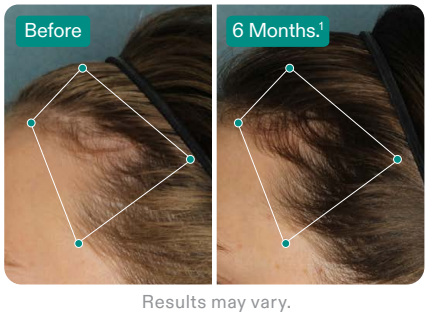

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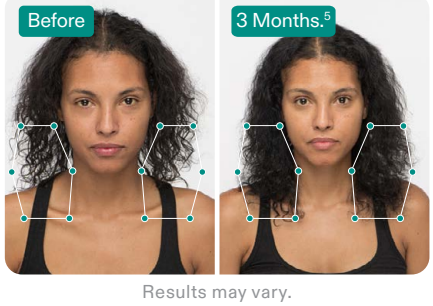

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