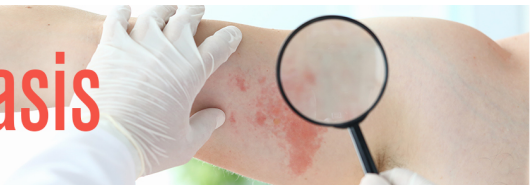
Research Developments in Psoriasis



OVERVIEW

Plaque psoriasis is responsible for a substantial burden on patients, their families, and the healthcare system. To address this burden, important treatment advances continue to be made, including a better understanding of the long-term safety and efficacy of approved medications, as well as the introduction of new classes of medications. Join Steven Feldman, MD, PhD, as he reports on research results of these advances presented at the 2022 American Academy of Dermatology Meeting. Three studies presented as posters in the meeting will be described, along with expert comments on the clinical implications of the study results by Dr. Feldman and the principal investigator.

CONTENT AREAS

- Roflumilast
- Guselkumab
- Bimekizumab
- Topical therapy
- Quality of life
- Malignancy

TARGET AUDIENCE

This activity is intended for dermatologists, pediatric dermatologists, dermatology advanced practitioners, and other clinicians who manage patients with moderate to severe plaque psoriasis.

LEARNING OBJECTIVES

At the conclusion of this activity participants should be able to:

- Summarize the latest research developments in the treatment of plaque psoriasis
- Describe how new data and recommendations can impact clinical practices to improve care
- Incorporate evidence-based research into clinical practice

FACULTY

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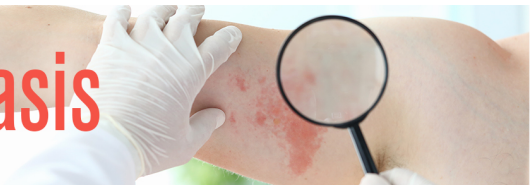

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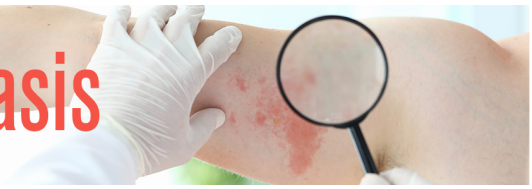

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Introduction

Psoriasis is a huge problem. More than 7.5 million adults in the United States have been diagnosed with psoriasis and the burden extends beyond the estimated $11 billion in direct and indirect costs. Some estimates put that dollar figure much higher than that. Patients have self-reported significant quality of life issues associated with psoriasis and ranked the negative psychological effects of the disease as comparable to that of heart attack, congestive heart failure, diabetes, and chronic lung disease. A variety of medications in different classes have become available in recent years for the treatment of patients with plaque psoriasis, each with its own benefits and limitations. Among the more than 100 studies related to psoriasis that were presented at the 2022 American Academy of Dermatology Meeting, I'm going to discuss 3 in this CME activity.

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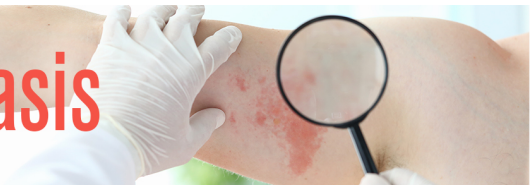


Complete Skin Clearance for Patients With Moderate to Severe Plaque Psoriasis: The Relationship Between Improvements in Psoriasis Area and Severity Index and Health-Related Quality of Life

The study results were presented by Dr. Andrew Blauvelt and colleagues at the 2022 American Academy of Dermatology Meeting.

Link to Poster: Abstract

Steven R. Feldman, MD, PhD: To summarize, incremental improvements in the psoriasis area and severity index, or the PASI score, led to higher rates of patients who achieved 0 or 1 on the Dermatology Life Quality Index, the DLQI, indicating no impact of skin disease on a patient's life. 85.5% of patients who had complete skin clearance reported a DLQI of 0 or 1, compared to 35.4% of patients who had a 75% improvement in skin clearance.

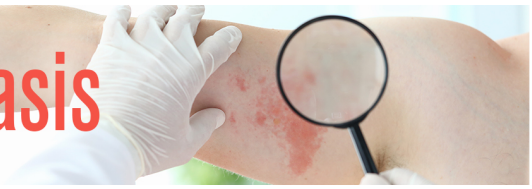
This is important. Many psoriasis drug studies show the percent improvement in skin clearance, but this has not been directly correlated with quality-of-life changes. This study showed a relationship between those incremental PASI improvements and higher rates of health-related quality of life.

The study used data from the initial 16 weeks of 4 bimekizumab phase 3 trials, BE SURE, BE VIVID, BE READY and BE RADIANT. Ustekinumab, adalimumab, secukinumab and placebo were used as the comparators to bimekizumab in these studies. DLQI is a patient-reported outcome measure used to assess the impact of skin disease on quality of life with scores ranging from 0, which indicates no detectable impact, to 30, which is very high impact on patients' lives.

A mixed effects logistic regression model was used to assess the relationship between PASI and DLQI of 0 or 1. Here's some key findings. They pooled data from over 2,000, so 2,223, randomized patients. The mean baseline score for the PASI was 20.4 and the mean DLQI was 10.7. There was an incremental increase in the percent of patients with a DLQI of 0 or 1 as the percent of PASI improvement increased. So, for patients who had 100% improvement in PASI, 85.5% of them, with a confidence interval of 83.3% to 87.4% of the patients, achieved that DLQI of 0 or 1. For the patients with a 95% PASI improvement, it was 78.6% of patients with a confidence interval from 75.9% to 81%. For those who had a 90% PASI improvement, 69.5% achieved a DLQI of 0 or 1. For 75% PASI improvement, it was only 35.4% who achieved a DLQI of 0 or 1. And for those who achieved 50% PASI improvement, but not 75% or higher, only 4.8% achieved that DLQI of 0 or 1, indicating little to no impact on their quality of life.

Itchy/sore/painful skin, embarrassment, and clothing limitations, impacted quality of life more than other DLQI items. The point of this study is that residual skin disease may still negatively impact quality of life, and the closer you get people to completely clear, the better their quality of life.

So, here's my thoughts and analysis of this study. First, we are blessed to have a lot of great treatments for psoriasis now. I feel spoiled. Second, we can get patients clearer than we used to and with less risk too. Before biologics, I wrote a paper titled "Clearance Is Not a Realistic Expectation of Psoriasis Treatment." But clearance can be a realistic expectation, now, for many patients. And this study shows that getting people clear results, results in less impact of psoriasis on their quality of life. But are those statistically significant differences meaningful? It's hard to say. A meaningful difference in



quality of life on the DLQI scale is considered to be 3 to 5 full points, and it's not clear that the small, but clearly statistically significant, differences observed in this study are really clinically meaningful.

So, how will this affect the current state of management? I think we want patients to get clear already and this study reinforces the view that we can perhaps offer that to many patients. I think this study may also encourage us to ask patients who are doing pretty well, but not clear, if they want to change course to try to do even better. Up until now, I didn't usually do that.

How will the results affect future management of our patients with psoriasis? I think, for those of us who want to offer patients the best chance of complete clearing, the findings of this study may encourage us to consider bimekizumab, when it becomes available, as it offers higher rates of getting completely clear than some of our other excellent psoriasis treatment options.
What questions remain to be answered? I think the key question is not a general one, but a patient-specific one. I think, for some patients, being almost clear makes them totally happy and they're not going to want to rock the boat. But, for others, and we need to know which ones, going from nearly completely clear to totally completely clear may be valuable and important for their quality of life.

Lead Study Author Commentary

Important Highlights of the Study

- Here, using a large group of pooled psoriasis patients participating in phase 3 trials of bimekizumab, we show that quality of life is most improved when response to a biologic drug is complete clearance (PASI 100). And, each level of skin improvement is associated with better quality of life. For example, PASI 90 response improves quality of life more than PASI 75, PASI 95 more than PASI 90 and PASI 100 more than PASI 95. Even when skin is completely clear, some patients will say psoriasis affects their quality of life. The 2 top complaints for those who are completely clear of lesions are: 1. painful, sore, itchy skin and 2. embarrassment because of their skin.

Impact on Patient Care

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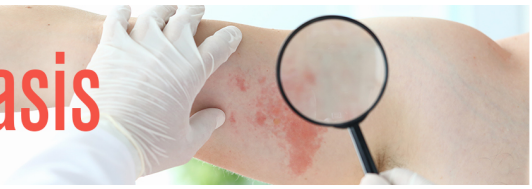


Malignancy Rates Through 5 Years of Follow-up in Guselkumab-treated Patients With Moderate to Severe Psoriasis: Results from the VOYAGE 1 and 2 Trials and Comparisons to General Populations

The study results were presented by Dr. Andy Blauvelt and colleagues at the 2022 American Academy of Dermatology Meeting.

Link to poster: Abstract

Steven R. Feldman, MD, PhD: To summarize, this study shows the malignancy rates after 5 years of guselkumab treatment were low, and similar to rates in the general US population, and to other patients with psoriasis.

This is important. Psoriasis and other immune-related diseases are associated with an increased risk of malignancy. Additionally, inhibition of interleukin-23, which is a key signaling molecule in the immune system, perhaps, in theory, might affect tumor growth rate. While we don't expect interleukin-23 blockade to have a significant effect on cancer rates, empirical effects on cancer from psoriasis therapy in humans is not well defined. This study confirms our impression that IL-23 blockade does not have a significant effect on cancer rates, and this should be reassuring to doctors and patients.

In this study, they included 1,721 patients from the VOYAGE-1 and -2 studies. Patients were treated with guselkumab, GUS, for up to 5 years, and then divided into the following groups: patients randomized to GUS at baseline and those randomized to placebo, but then transferred to GUS at week 16 was 1 group. There were participants randomized to adalimumab at baseline and then transferred to GUS at or after week 28, 500 of those. Then there were combined participants from the 2 groups above, that made up the 1,721 subjects.

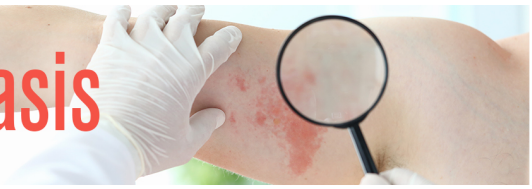
Rates of malignancy were calculated per 100 patient-years through 5 years, and per year, to evaluate trends. Participants treated with GUS were compared to the general psoriasis population who qualify for systemic therapy using a representative sample from the Psoriasis Longitudinal Assessment and Registry, the PSOLAR study. Comparisons to the general US population used a sample from the Surveillance Epidemiology and End Results, or SEER, database.

Overall rates of malignancy, excluding nonmelanoma skin cancer, were compared with rates from PSOLAR. Standardized incidence ratios were used to compare malignancy rates between the GUS groups and the SEER group.

Here are the key findings. The rate of non-nonmelanoma skin cancers in the GUS group was 0.45 per hundred patient-years compared to 0.68 per hundred patient-years in PSOLAR. The rate of cancer, excluding cervical and nonmelanoma skin cancer, was similar between the GUS group and the SEER group, with a standardized incidence ratio of 0.93, with a 95% confidence interval going from 0.64 to 1.31. That standardized incidence ratio is the ratio of observed vs expected number of patients with malignancy.

Over time, there was year-to-year variability in malignancy rate, but there was no trend towards an increasing rate of cancer over time. And the cancers that were most commonly reported were breast, colorectal, melanoma, and prostate. These rates were similar to the general US population.

So, here are my thoughts on this. You know, when etanercept was approved, it was revolutionary. I thought I'd never see another



quantum leap forward in psoriasis treatment of that magnitude in my lifetime. Then came more effective treatments, adalimumab and ustekinumab. Then, IL-17 blockers and then the IL-23 blockers, like guselkumab. The efficacy of the IL-23 blockers is terrific. The dosing regimen of guselkumab, once every 2 months, is great, although to tell you the truth, I don't care about the number of shots as much as my patients do! But on top of all that, we seem to be targeting immune function in such a narrow way that the safety is outstanding too, and this study supports that safety.

Lead Study Author Commentary

Important Highlights of the Study

- Long-term safety of biologics is important. Here, we examine cancer types and cancer rates over the course of 5 years in psoriasis patients receiving guselkumab, an IL-23 blocker. Cancers occurred, yes, but the types of cancers and the rates at which they occurred in this large cohort were not different than what would be expected from cancer types and rates in healthy individuals, patients with psoriasis, and psoriasis patients on other types of long-term systemic medications. In other words, there were no clear cancer "signals" in psoriasis patients receiving guselkumab over the course of 5 years.

I think the main points of the study is that when you're blocking aspects of immune function, we worry about infection and malignancy. This study supports the notion that there is not a meaningful increased risk of malignancy with IL-23 blockade. Considering the increased risk of lymphoma from having an immune disease with a billion, trillion T-cells dividing and multiplying, I suspect that drugs like guselkumab lower overall malignancy rates.

How will this study impact the current state of patient management for patients with psoriasis? Well, I think this study supports current management of psoriasis more than it will change our management. I believe we already have a sense that IL-23 blockade is very safe. Interleukin-17 blockade seems very safe, even though there is some small increased risk of candidiasis and even smaller increased risk of inflammatory bowel disease with IL-17 blockade. But blocking IL-23 with guselkumab doesn't have even those IL-17 risks. This study supports the general perception of the safety of interleukin-23 inhibition.

How will these results impact future management? I think IL-23 blockade is going to continue to be a favored treatment for psoriasis. The IL-23 genes are linked to psoriasis and so blocking interleukin-23 may be getting to some of the root cause of having psoriasis. IL-23 blockers aren't oral, and patients prefer oral therapy over injection treatments. IL-23 blockade may not be the fastest acting psoriasis treatment, but they're close, and when you look at the overall risk and benefit profile, IL-23 blockade seems to be an excellent first-line option for managing patients with moderate to severe psoriasis.

What questions remain to be answered? Well, when it comes to safety, more experience is always better, but I have the sense that there aren't a lot of unanswered questions when it comes to blocking interleukin-23. The efficacy and safety are excellent. Perhaps 1 unanswered question is how long patients will continue to need the treatment once they're clear. Might there be long-term remissions? I'm not sure.

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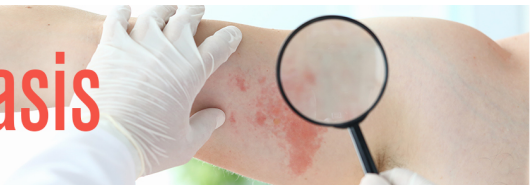


Pooled Efficacy and Safety Results from the DERMIS-1 and DERMIS-2 Phase 3 Trials of Once-Daily Roflumilast Cream 0.3% for Treatment of Chronic Plaque Psoriasis

These study results were presented by Dr. Mark Lebwohl and colleagues at the 2022 American Academy of Dermatology Meeting.

Link to poster: Abstract

Steven R. Feldman, MD, PhD: To summarize, this was a safety and efficacy analysis using pooled data of 2 large, phase 3, vehicle-controlled trials of the topical phosphodiesterase-4 inhibitor roflumilast cream, in patients with mild to moderate psoriasis. After 8 weeks, the results showed that once-daily roflumilast cream, 0.3%, provided superior improvement and favorable safety and tolerability compared to the control vehicle.

This is important. You know, we have topical agents, such as corticosteroids, vitamin D analogs, and calcineurin inhibitors, and they're considered first-line therapies for mild to moderate psoriasis. But no novel topical medications have been approved for mild to moderate psoriasis in 20 years. Many of the existing agents have some safety concerns with long-term use. Roflumilast is a highly-potent and selective phosphodiesterase-4 inhibitor that appears to be safe and effective.

In this study, they did an analysis that included all data from the 8-week, phase 3, randomized, double-blind, vehicle-controlled DERMIS-1 and DERMIS-2 trials. Patients received either once-daily roflumilast, 0.3% cream or a vehicle cream. The inclusion criteria were age greater than 2 years, a disease duration of greater than or equal to 6 months for adults or 3 months for children. Investigator global assessment, or IGA, had to be greater than or equal to mild in severity. The psoriasis needed to cover 2% to 20% of the body surface area, and the psoriasis area and severity index, or PASI score, had to be greater than or equal to 2.

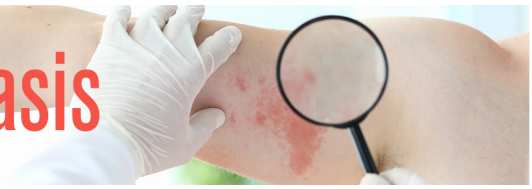
The primary endpoint was that investigator global assessment or IGA success at week 8 and secondary endpoints included an intertriginous IGA, PASI 75 scores, and the worst itch numeric rating scale. The IGA success was defined as clear/almost clear with 2-grade or better improvement from baseline. Safety and tolerability endpoints included rates of application-site adverse events, treatment-related adverse events, and discontinuation due to adverse events.

Lead Study Author Commentary

Important Highlights of the Study

- Roflumilast is a nonsteroid that works by blocking PDE-4. It is effective for psoriasis and is safe and effective for intertriginous psoriasis.

Here are the key findings. So, they pooled data from 881 patients with similar demographics and disease characteristics across the different treatment groups. 39.9% of patients in the roflumilast group achieved IGA success compared to just 6.5% for the vehicle. And that was, had a *P*<.0001. 69.7% of the patients in the roflumilast group achieved that intertriginous IGA success compared to 16.1% in the vehicle group. That was also statistically significant with a *P*<0.01. 40.3% of patients in the roflumilast group achieved a 75% reduction in PASI score compared to just 6.5% in the vehicle group. That



was highly statistically significant. 68.5% of the patients in the roflumilast group achieved at least a 4-point improvement in that itch rating scale compared to 31.3% in the vehicle group. Again, highly statistically significant, *P*<.0001.

There was a low incidence of adverse events with no significant difference between roflumilast and vehicle groups. The rates of treatment-related adverse events were 4% and 3.6% in the roflumilast and vehicle groups.

Here are my thoughts. Most of the unmet need that we have in psoriasis is from a huge fraction of patients who just have limited psoriasis. We already have a host of great treatment options for patients with extensive psoriasis. But, for the limited psoriasis, not so much, and lots of patients fail our current topical treatment options for limited psoriasis. And much of that failure is because the patients don't put topicals on very well.

Here are the main points of this study from my perspective. This study showed that topical roflumilast is very safe and effective in the clinical trials. Unfortunately, the study doesn't show whether our real-life patients will use the drug more often than they do our current treatments that aren't working.

How will this study affect the current state of patient management? I think the results of the study are exciting. I think dermatologists are going to want to have patients try this drug when it's approved because it's so safe and effective in the clinical trials. But I fear that we dermatologists, and our patients, are going to be disappointed when the drug doesn't work as well in real-life practice as it did in the clinical trial because patients tend to use their medicines much better in clinical trials than they do in real-life practice.

How do the results of this study impact the future state of patient management? In the future, we need to do a better job getting patients to use their topical medications. It's like a Vietnamese philosopher once said, "If the lettuce isn't growing well, you don't blame the lettuce." If we want our topical treatments to work in the future, new topical treatments may not be the answer unless, maybe, they're a once-a-week or once-a-month topical. We need to find ways to get patients to use the topical treatments better. If we can get them to use topical roflumilast, that's great.

What questions remain to be answered? I think the big question when it comes to topical treatment is whether we will change the way we use it, the way we practice. Telling patients to put a medicine on every day and see you in 3 months would be a lot like a piano teacher saying, "Yeah, practice the piano every day, I'll see you at the recital in 3 months. No, we're not going to have weekly lessons." You know that recital would sound execrable. If that's how we continue to follow up patients on topical therapy, I suspect we'll continue to have topical treatment failures, and we'll end up putting patients on easier-to-do systemic treatment options.