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, and Abby Van Voorhees, MD, as they report on research results of these advances presented at the 2021 American Academy of Dermatology Virtual Meeting Experience. The faculty, and principal investigators of the research, also share their thoughts about the impact of the research findings on clinical practice.

CONTENT AREAS

- Apremilast
- Bimekizumab
- Deucravacitinib
- Guselkumab
- Risankizumab
- Secukinumab
- Tildrakizumab
- Ustekinumab
- Biosimilars
- Topical therapy

TARGET AUDIENCE

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

LEARNING OBJECTIVES

At the conclusion of this activity, participants should be better 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

Steven Feldman, MD, PhD
Professor of Dermatology, Pathology, and Public Health Sciences
Wake Forest School of Medicine
Winston-Salem, North Carolina

Abby Van Voorhees, MD
Professor and Chair
Department of Dermatology
Eastern Virginia Medical School
Norfolk, Virginia

ACCREDITATION AND CERTIFICATION

The Annenberg Center for Health Sciences at Eisenhower is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

The Annenberg Center for Health Sciences at Eisenhower designates this enduring material for a maximum of 1.25 *AMA PRA Category 1 Credits*™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

DISCLOSURE STATEMENT

It is the policy of the Annenberg Center for Health Sciences to ensure fair balance, independence, objectivity, and scientific rigor in all programming. All faculty and planners participating in accredited education activities are expected to identify and reference off-label product use and disclose any relationship with those supporting the activity or any others with products or services available within the scope of the topic being discussed in the educational presentation.

The Annenberg Center for Health Sciences assesses conflict of interest with its instructors, planners, managers, and other individuals who are in a position to control the content of CE/CME activities. All relevant conflicts of interest that are identified are thoroughly vetted by the Annenberg Center for fair balance, scientific objectivity of studies utilized in this activity, and patient care recommendations. The Annenberg Center is committed to providing its learners with high-quality CE/CME activities and related materials that promote improvements or quality in healthcare and not a specific proprietary business interest of an ineligible company.

In accordance with the Accreditation Council for Continuing Medical Education Standards, parallel documents from other accrediting bodies, and Annenberg Center for Health Sciences policy, the following disclosures have been made:

Faculty

Steven R. Feldman, MD, PhD

Chief Technology Officer: Causa Technologies

Consultant: AbbVie, Advance Medical, Almirall, Alvotech, Amgen, Arena, BMS, Caremark, Celgene, Galderma Laboratories LP, Gerson Lehrman Group, Guidepoint Global, Helsinn, Janssen, Kikaku, Leo Pharma Inc, Lilly, Merck & Co, Mylan, Novartis, Ortho Dermatology, Pfizer, Regeneron, Sanofi, Sienna, Sun Pharma, Suncare Research, Xenoport

Founder: Causa Technologies

Grant Support: AbbVie, Amgen, Celgene, Galderma Laboratories LP, Janssen, Lilly, Novartis, Pfizer, Regeneron, Sanofi

Royalties: Informa, UpToDate, Xlibris

Speaker: AbbVie, Amgen, Celgene, Janssen, Leo Pharma Inc, Lilly, Leo Pharma Inc, Novartis, Ortho Dermatology, Pfizer, Regeneron, Sanofi, Sun Pharma

Stockholder: Causa Technologies, Medical Quality Enhancement Corporation

Abby S. Van Voorhees, MD

Advisory Board: BMS, Boehringer Ingelheim, Celgene, UCB

Consultant: Amgen

Investigator: AbbVie, Celgene, Lilly

Research Support: Boehringer Ingelheim

The faculty for this activity have disclosed that there will be discussion about the use of products for non-FDA approved indications.

Additional content planners

The following have no significant relationship to disclose:
Greg Scott, PharmD, RPh (medical writer)
Eugene Cullen, MD (peer reviewer)

Annenberg Center for Health Sciences
Staff at the Annenberg Center for Health Sciences at Eisenhower have no relevant commercial relationships to disclose.

The ideas and opinions presented in this educational activity are those of the faculty and do not necessarily reflect the views of the Annenberg Center and/or its agents. As in all educational activities, we encourage practitioners to use their own judgment in treating and addressing the needs of each individual patient, taking into account that patient's unique clinical situation. The Annenberg Center disclaims all liability and cannot be held responsible for any problems that may arise from participating in this activity or following treatment recommendations presented.

This educational activity is supported by an educational grant from AbbVie, Janssen Biotech, Inc, administered by Janssen Scientific Affairs, LLC, and Novartis Pharmaceuticals Corp.

This activity is an online enduring material. Successful completion is achieved by reading and/or viewing the materials, reflecting on its implications in your practice, and completing the assessment component.

The estimated time to complete the activity is 1.25 hours.

This activity was released on June 11, 2021 and is eligible for credit through June 11, 2022.

OUR POLICY ON PRIVACY
Annenberg Center for Health Sciences respects your privacy. We don't share information you give us, or have the need to share this information in the normal course of providing the services and information you may request. If there should be a need or request to share this information, we will do so only with your explicit permission. See Privacy Statement and other information at https://annenberg.net/pages/privacyPolicy.php

CONTACT INFORMATION
For help or questions about this activity please contact Continuing Education:
ce@annenberg.net

Introduction

Steven Feldman, MD: More than seven-and-a half-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. Patients have self-reported significant quality of life issues associated with psoriasis, ranking 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 moderate-to-severe plaque psoriasis, each with its own benefits and limitations. To facilitate the selection of appropriate treatments, Dr. April Armstrong and colleagues conducted a network meta-analysis designed to evaluate the comparative efficacy of biologic and oral therapies for moderate-to-severe plaque psoriasis. Dr. Armstrong presented the results of the network meta-analysis at the 2021 American Academy of Dermatology Virtual Meeting Experience. The analysis included 13 medications in the following classes, anti-TNF, anti-phosphodiesterase type 4, fumaric acid ester, anti-IL-12/23, anti-IL-17, and anti-IL-23.

The outcomes included Psoriasis Area and Severity Index (PASI) 75%, 90%, and 100% response rates at the short-term response period of 10 to 16 weeks from baseline, as well as the end of the long-term maintenance period of 48 to 52 weeks. A total of 71 eligible randomized controlled trials connecting 18 treatment regimens were included in the short-term period and 11 trials connecting 8 treatment regimens in the long-term period. The dosage regimens were generally those approved by the US Food and Drug Administration.

In the short-term analysis, calculation of the PASI 75, 90, and 100 rates revealed that ixekizumab, risankizumab, and brodalumab had the highest efficacy, while dimethyl fumarate, apremilast, and etanercept had the lowest. Dimethyl fumarate is not approved in the United States for psoriasis. In the long term, PASI 75, 90, and 100 were highest for risankizumab and lowest for etanercept, though apremilast was not included in the analysis.

The bottom line, though, is that efficacy is not everything, as apremilast efficacy may be among the lowest, but patients may still choose it because it's a pill, not an injectable. Another potential use for apremilast is for patients with milder disease, who are not getting adequate relief from topical treatment. The results of the phase 3 advanced trial investigating the safety and efficacy of apremilast in mild-to-moderate plaque psoriasis by Duffin, et al, were also reported at the AAD Virtual Media Experience in 2021. 595 patients had a static Physician Global Assessment of 2 or 3, despite treatment with 1 or more topical medications. Two-thirds had moderate disease. At the end of 16 weeks, 22% of patients treated with apremilast and only 4% treated with placebo achieved the primary endpoint of an sPGA of 0 or 1, indicating clear or almost clear skin. Quality of life was significantly improved with apremilast vs placebo. At the end of 32 weeks, improvements in physician- and patient-reported outcomes were maintained. Safety through week 32 was consistent with the known profile for apremilast. There were several other interesting studies presented.

Bimekizumab Efficacy and Safety Versus Secukinumab in Patients With Moderate-to-Severe Plaque Psoriasis: Results From a Multicenter, Randomized, Double-Blinded, Active Comparator-Controlled Phase 3b Trial Called (BE RADIANT)

The study results were presented by Dr. Kristian Reich and colleagues at the 2021 American Academy of Dermatology Virtual Meeting Experience.

Steven Feldman, MD: To summarize, interleukin 17a inhibitors, including ixekizumab and secukinumab, are some of our fastest-acting, most effective psoriasis treatments. In this phase 3b study, more patients with moderate- to-severe plaque psoriasis achieved PASI 100. In other words, complete, that's complete clearing with the dual IL-17a and IL-17f inhibitor bimekizumab vs secukinumab, a drug that only inhibits interleukin 17a. The benefits of bimekizumab were sustained through 48 weeks of treatment. Additionally, the onset of response with bimekizumab was fast, even faster than secukinumab, with a clear, statistically significant difference emerging by week 4. The safety of bimekizumab and secukinumab were similar, except there was a strikingly higher incidence of oral candidiasis with bimekizumab compared to secukinumab. The importance, bimekizumab appears to be the most effective drug for psoriasis we've seen with a high rate of patients achieving complete clearing of their psoriasis.

Let me describe the study to you. First, the methods. The patients had moderate-to-severe plaque psoriasis and were randomized1:1 to either bimekizumab, 320 mg every 4 weeks, or secukinumab, 300 mg every 4 weeks after the usual weekly secukinumab loading dose for the first 5 doses. At week 16, patients in the bimekizumab group were re-randomized 1:2, to bimekizumab, 320 mg, administered every 4 or 8 weeks. After 48 weeks patients could continue on assigned therapy for an additional 96 weeks in an open-label extension period. The primary and secondary endpoints were the percentage of patients who achieved PASI 100 response at 16 and 48 weeks.

Here are some of the key findings. First, at baseline, the mean age was 44 to 46 years, and

Lead Study Author Commentary

Important Highlights of the Study

- This is the first head-to-hear phase 3 study comparing IL-17A/F inhibition (bimekizumab) with IL-17A inhibition (secukinumab)
- Significantly more patients treated with bimekizumab achieved PASI 100 at week 16 compared with secukinumab
- Response to bimekizumab was significantly faster than with secukinumab (based on >20% difference in % achieving PASI 75 at week 4)
- Superior PASI 90 and PASI 100 response rates with bimekizumab remained stable over the 48-week study period
- Favorable benefit-risk profile seen with both medications
  - Significantly more cases of oral candidiasis with bimekizumab vs secukinumab

Impact on Patient Care

- IL-17A/F inhibition with bimekizumab is one of the fastest and most efficacious treatments for psoriasis.
- Candida infections rarely lead to drug discontinuation but may limit its use in patients at high risk.

64% to 67% of the patients were male. The mean PASI score was 20. 64% to 72% had moderate disease, an IGA score of 3. Nearly three-quarters had received systemic therapy.

At 16 weeks, 62% of the bimekizumab group and 49% of the secukinumab patients were completely clear, achieving PASI 100. At week 48, 67% of the patients treated with bimekizumab every 4 or 8 weeks achieved PASI 100 compared with 46% of the secukinumab patients. The percentage of patients who achieved PASI 100 at 48 weeks was slightly higher in the bimekizumab every-4-week group compared with the group treated with bimekizumab every 4 weeks for the first 16 weeks, then every 8 weeks after that. As expected, significantly more patients treated with bimekizumab vs secukinumab achieved PASI 90 at 16 and 48 weeks. And if you aren't familiar with what PASI 75 and PASI 90 scores look like clinically, and who is, significantly more patients treated with bimekizumab vs secukinumab achieved an IGA of 0 or 1, which means clear or almost clear skin at week 16 and 48. For example, 84% of bimekizumab patients and 74% of secukinumab patients achieved an IGA of 0 or 1 at week 48.

In terms of safety, the incidences of treatment-emergent adverse events, severe treatment-emergent adverse events, and discontinuation due to treatment of emergent adverse events, were similar in the bimekizumab and secukinumab groups. For example, over the 48 weeks of the trial, 7% of bimekizumab patients and 4% of secukinumab patients experienced a severe treatment-emergent adverse event. A fungal infection was observed in 29% of bimekizumab patients and 10% of secukinumab patients. Most of these were mild or moderate oral candidiasis. The incidences of serious infection, inflammatory bowel disease, suicidal ideation and behavior, and death, were all low for both bimekizumab and secukinumab.

There's some really interesting main points from this study. Wow! Bimekizumab is effective for psoriasis! I didn't think I'd see any new drug make another quantum leap forward in efficacy for psoriasis, but wow! Secukinumab is a very effective treatment, especially in the short run with all those doses over the first 5 weeks. Over the first 3 months of treatment, secukinumab with 10 injections over the first 4 weeks is faster than the IL-23 inhibitor guselkumab. But in this study, bimekizumab with just one dose was considerably more effective than secukinumab as early as week 4. Wow!

How will this change my current management? Probably not at all. Since bimekizumab isn't approved or available yet, I don't see how it's going to change my management now. But in the future, once bimekizumab is approved, I think it will be considered a frontline treatment by patients who want to be clear and by doctors who feel you need to completely clear psoriasis to make patients happy and to control the inflammation in psoriasis that predisposes patients to comorbidities like cardiovascular disease.

But there are unanswered questions, and a key question that remains is how safe will bimekizumab be in clinical practice? If the increased risk is truly related to something like 1-in-5 patients getting a mild yeast infection that we can control with a fluconazole pill, bimekizumab could be a major advance. But on the other hand, if there are other infections, or increases in rates of inflammatory bowel disease that we haven't observed yet, well, then bimekizumab may be more limited to patients with relatively refractory disease.

Increased Benefit of Secukinumab Versus Ustekinumab in Patients With Psoriasis Regardless of Prior Systemic Psoriasis Therapy, the Pooled Analysis of the Phase 3 CLEAR and CLARITY Trials

The study results were presented by Dr. Andy Blauvelt and colleagues at the 2021 American Academy of Dermatology Virtual Meeting Experience.

Link to poster: CLICK HERE

Abby Van Voorhees, MD: To summarize, this study analyzed the pooled data from the phase 3b CLEAR and CLARITY randomized control trials that involved patients with moderate-to-severe psoriasis. In these trials, secukinumab demonstrated superior efficacy vs ustekinumab over 52 weeks of treatment. The efficacy benefit with secukinumab was observed both in biologic naïve patients as well as in biologic experienced patients, albeit that the benefit was lower in those who were biologic experienced.

What's important about this? Well, patients with psoriasis who have prior exposures to either systemic medications or other biologic therapies may have psoriasis that's more difficult to treat than those who've not received these treatments, and this trial provides some evidence that secukinumab was more efficacious in the clearance of psoriatic lesions than ustekinumab, regardless of prior systemic or biologic therapy exposure.

Getting into the methods of this study, this was a hypothesis-generated analysis of the phase 3b CLEAR and CLARITY randomized control trials that involved patients with moderate to severe plaque psoriasis. In both trials, patients were randomized 1:1 to secukinumab 300 mg or ustekinumab as per the label. Patients were treated for 52 weeks in the CLEAR trial and for 48 weeks in the CLARITY trial.

The pooled data was grouped according to their prior exposure to either systemic therapy or biologic psoriasis therapy. And then efficacy comparisons were made between the groups at week 52, between the secukinumab 300 mg and the ustekinumab either 45 mg or 90 mg, depending on the patient's weight, using the PASI scores, PASI 75, PASI 90, and PASI 100, as well as the Investigator Global Assessment score of zero to 1.

Lead Study Author Commentary

Important Highlights of the Study

- Individuals with psoriasis may not respond well to biologics if they have prior exposure to and have failed other systemic drugs, including biologics
- Secukinumab demonstrated greater clearance of psoriatic lesions than ustekinumab, regardless of previous biologic or systemic therapy exposure
- Safety was comparable across treatment arms and subgroups

Impact on Patient Care

- Providers caring for patients with psoriasis who have had prior exposure to biologics can expect good response to treatment with secukinumab despite that prior exposure.

The key findings, there were 1,778 patients who were included in this analysis, 61% to 73% were male, mean age range from 44 to 48 years, and the mean PASI score ranged from 20 to 22. Importantly, 37% of these patients were systemic therapy naïve, and 81% were biologic

naïve. The percentage of patients who achieved the PASI 90, PASI 100, and Investigator Global of 0/1 response at week 52 was higher for patients who were treated with secukinumab than ustekinumab regardless of prior exposure to either systemic therapy or biologic therapy. For example, in the systemic therapy naïve group, 76% of the secukinumab patients achieved a PASI 90 and 65% of the ustekinumab patients achieved PASI 90 compared to 69% and 55%, respectively, of the systemic experience group. Similarly, in the biologic naïve group, 74% of the secukinumab patients and 63% of the ustekinumab patients achieved PASI 90 compared with 58% and 42%, respectively, in the biologic experience group.

In terms of safety, among patients treated with secukinumab, what we see is that there's not really very much difference whether a person has been exposed to a prior therapy previously or not. For example, with secukinumab, in those who were systemic naïve, 73% had a treatment emergent adverse event, whereas for those who were experienced, 76% of those patients has a treatment emergent adverse event. So really, quite equivalent.

What are my thoughts about this study? I think the main point here really is looking at the response of secukinumab and ustekinumab in those who were previously treated with either systemic therapy or other biologic therapy. And this is really very important because these are the patients that we're seeing so often in the office. Often, patients are coming to us having been on 1, 2, 3 prior therapies. Understanding this kind of real-world experience is really very, very critical.

We previously knew that secukinumab was more efficacious than ustekinumab based on publications from these trials originally. But here, what we're seeing is that secukinumab was more efficacious than ustekinumab in both patients who were systemic and biologic naïve as well as in those who were systemic and/or biologic experienced. In both situations, we see secukinumab performing better than ustekinumab.

The other important points of this study are that in both cases, both with secukinumab and with ustekinumab, those who were biologic naïve or systemic naïve did better on that drug than those who were more experienced, and that was true despite the fact that they're 2 very different classes of medications. In both cases, we see that loss of effectiveness in those who've been on multiple therapies previously. The importance of this is that, first of all, it helps us understand the power of these drugs. Now, this isn't the only consideration when choosing a medication, but if we're looking to understand what the possible results of a therapy are. This data, I think, is very helpful in clarifying that.

The other thing I think is that this data is very helpful in helping us document what we've long sort of known, which is that for those patients who've been on multiple drugs before, the outcomes are not quite as good, and we see that with both of the drugs in this study. As I said, I think this is going to become increasingly important because more and more of our patients will have had these real-world experiences, and therefore I think it's really a very critical piece of information.

I think there were a couple of questions I found myself wondering about. For example, I found myself wondering whether there was any difference if people had been on multiple prior therapies. Would there have been a difference if I had looked at those who had only been on 1 prior therapy vs 2 or 3 or even more? And then, of course, there were other things that impact outcomes, such as patients' comorbid diseases,

and I would've liked to have known a little bit about that in this study. But I think this study provides us with some really useful, practical information about outcomes, especially in those who've been on either systemics or biologic therapies previously.

Efficacy and Safety of Long-term Risankizumab Re-treatment Following Drug Withdrawal, the IMMhance Trial

These study results were presented by Dr. Richard Langley and colleagues at the 2021 American Academy of Dermatology Virtual Meeting Experience.

Link to poster: CLICK HERE

Abby Van Voorhees, MD: This analysis included patients with moderate-to-severe plaque psoriasis from the IMMhance and the LIMMITLESS phase 3 trials, who were treated with risankizumab. The analysis showed that re-treatment after relapse following the withdrawal of risankizumab results in efficacy that is inferior to continuous treatment. On the other hand, re-treatment in those who didn't relapse, in other words, they maintained an intermediate to complete response, and we'll be describing what that entails in just a moment, resulted in high rates of skin clearance compared to those who relapsed and the continuous treatment groups. I think this is really very important because interruptions in treatment are really very common in those with plaque psoriasis, so it's important to understand what happens when treatments are impacted in this way.

To talk about the description of this study, so IMMhance was a multinational phase 3 randomized, double-blind, placebo-controlled trial. LIMMITLESS was also a phase 3, but an ongoing single-arm, multi-center, open-label extension study that was designed to assess the long-term efficacy of risankizumab over 5 years. Patients were initially randomized to receive risankizumab, who achieved a static Physician Global Assessment of clear or almost clear by week 28, who were subsequently re-randomized 1:2, either to receive continuous risankizumab or placebo. And what we're looking at here are only the patients who were re-randomized to placebo.

If patients relapsed, and this was determined by a static Physician's Global Assessment (sPGA) of 3 or greater after risankizumab was stopped, then they were re-treated with open-label risankizumab 150 mg every 12 weeks; but there was first the induction dose.

Patients who did not relapse during the withdrawal period were given the option to enroll in the open-label extension LIMMITLESS study, and they were re-treated with 150 mg of risankizumab every 12 weeks, but in this case, there was no induction dosing.
In total, among the patients who were switched from risankizumab to placebo in the IMMhance trial, 32% of them didn't relapse at all, and this is through week 88. 68% did relapse and were re-treated with open-label risankizumab. Amongst those 68%, what we found is that 84% achieved clear, almost clear, according to the sPGA, 76% achieved a PASI 90 and 43% achieved a PASI 100.

The key findings from this poster is that of the 201 patients who completed this trial and enrolled in the LIMMITLESS portion of it, in the observed case analysis, which is one way to look at this data, the percentage of patients who achieved clear or almost clear, according to the

sPGA, were 94% of those who remained on continuous risankizumab, and 86% of those who had a relapse and then were re-treated with the induction and then continuous risankizumab, and 96% of those who did not have a relapse, but were re-treated with risankizumab just without the induction phase.

If you compare PASI 90, it was quite similar. The numbers were just a tad lower, and there was no increase in adverse events in either the re-treated patients compared to those who had received continuous uninterrupted risankizumab. And in all cases, serious adverse events were seen in about 6% of patients in each of the arms of this study.

The main points of this poster, there were several, actually. I thought this was a really provocative poster. I think the first thing to say is that re-treatment after relapse is poor ... These patients have a poorer outcome than those who remain on continuous treatment. We often are wondering, since these medications are very expensive, is there a way to dose somebody for a period of time, it might be a year, it might be 2, and then stop? And would they stay in remission? And I think this poster speaks to that point, suggesting that patients, when there's a stop, if they flare, as defined by a greater than 3 sPGA, they do not do as well as those who continue treatment. What's also really interesting is that those who stopped treatment, but didn't relapse as severely, so they may have gotten a little bit worse, but they never got an sPGA of 3, but they didn't necessarily stay at a clear status, these patients had the same efficacy as those who remained on continuous treatment.

I think the other issues that are really important from this poster are that the quality-of-life scores really correlated very closely with response so that we see, when we re-treat, patients' quality of life scores really doing very nicely as well, assuming that they have a response. And we did not see any safety signals when it came to re-treatment, and this is important because we all have known with the other medications, such as infliximab, there are safety signals if there's a gap in treatment, if we go back to the same drug. This was very nice to see and an important point that, I think, comes out of this study.

If you say, "Well, how will this impact what I do in my clinic?" I think that's a very interesting point about when that point is of no return, if there's a gap in treatment before a patient really goes over the edge, if you will, and starts to truly lose efficacy, because clearly this poster is suggesting that for some patients, there is a little bit of a wiggle room where they can be off treatment a little bit before they deteriorate too far and that, in that situation, if you then dose them, you can recapture that really excellent response.

I think this gives us a peek into how to skip treatments or how to prolong the intervals between patient dosing. And I think this requires, really, more study because I think, obviously, this would be very helpful. It would be helpful in guiding patients when they just ... For example, if insurance issues have come up and they've had to miss doses, it would be important for guiding them. It would be important for potentially allowing the cost of treatment to be a little less if we didn't have to dose people as frequently. I think this is really important and very provocative.

The other thing I think that I took away from this poster is I'd really like to know who that 32% of patients were who never lost response despite being off treatment for 88 weeks. That's up to 100 weeks. That's a huge amount of time to be able to be off treatment and not flare. I know people have questioned, "What is the definition

of cure?" And we could debate that for a prolonged period of time, what the criteria should be. But people who can stay off of drug for prolonged periods and still remain disease free, boy, that's coming pretty close to what that could look like. Very exciting, I think, in terms of what the future state of patient management might look like.

Obviously, there were a lot of questions. Where is that optimal point we could've intervened to have saved those who relapsed? I think that would be really important, and I would've liked to have known, of the people who were PASI 100 responders, what percentage of them were in that group that never lost response vs in the group that truly relapsed by the definition. I think there's a lot that could be explored further, but I thought this poster had a lot of exciting stuff in it. I hope you agree.

Sustained Improvement in General Health-Related Quality of Life and Work Productivity in Patients With Moderate to Severe Psoriasis Treated With Guselkumab. The 5-Year Data From the Clinical Trial, VOYAGE 2.

The study results were presented by Dr. Kristian Reich and colleagues at the 2021 American Academy of Dermatology Virtual Meeting Experience.

Link to poster: CLICK HERE

Abby Van Voorhees, MD: This trial demonstrated that treatment with guselkumab resulted in sustained improvement in measures of health-related quality of life, depression and anxiety, and work through up to 5 years in adults with moderate-to-severe psoriasis.

I think this trial extends the results of previous investigation that looked at 16 weeks and 24 weeks, showing that the quality of life and work productivity benefits experienced by patients treated with guselkumab are sustained long-term.

Let's talk about the description of the study for a moment. Adult patients with moderate-to-severe psoriasis were initially randomized to guselkumab 100 mg administered at weeks zero, 4, and then every 8 weeks. Placebo at week zero, 4, and 12, followed by guselkumab, 100 mg at weeks 16 and 20, and then every 8 weeks. And adalimumab 80 mg at week zero, 40 mg at week 1, and then 40 mg every 2 weeks through week 23.

Patients entered a randomized withdrawal phase from weeks 28 to 72. During this time, patients were restarted on guselkumab if they lost 50% of their improvements in their PASI at week 28. From week 76 to week 252, patients then were treated with open-label guselkumab 100 mg every 8 weeks. And this analysis reports on the weeks from week 100 to week 252.

So, the patients were grouped into 3 groups. Group A was those who received guselkumab throughout the entire course of the study. Group B are those 203 adults who started with adalimumab at baseline, and then crossed over to guselkumab at week 28, and then group C was a combination of those patients who were in group A as well as those in group B.

Lead Study Author Commentary

Important Highlights of the Study

- The IL-23/p19 inhibitor guselkumab provides stable and high levels of quality-of-life improvement alongside high levels of clinical response
- Improvement of health-related quality-of-life correlates with positive effects on work productivity
- High overall drug survival rates contribute to sustained improvement in general health-related quality-of-life and work productivity

Impact on Patient Care

- The study data adds to the favorable long-term profile of guselkumab in patients with moderate-to-severe psoriasis in terms of efficacy, safety, quality-of-life, work productivity

At week 100, nearly half of the patients in group C, so all of the patients, achieved clinically meaningful improvement in both the SF-36, which was defined as improvement of 5 or more points. For example, clinically meaningful improvement of the SF-36 physical component score was achieved by 47% of adults in group C at week 100, and 45% at week 252. Just to remind you, the SF-36 has both a mental score and a physical component part of it. That's why that's divided that way.

Clinically meaningful improvement was slightly greater in Cohort A than in B. Those are the patients on guselkumab continuously vs those who started on adalimumab and then rotated to guselkumab. At week 100, slightly more than half of the adults in Cohort C, so the total group, experienced significant improvement in anxiety and depression as assessed by the Hospital Anxiety and Depression Scale, otherwise known as HADS. For example, of the adults with a HADS anxiety subscale of 8 or greater at baseline, 56% had a score of less than 8 at week 100. At week 252, 60% achieved a HADS anxiety subscale score of less than 8. And similar findings were found when it came to depression.

With respect to work productivity, the mean change from baseline in each of the 4 domains measured by the work limitations questionnaire showed improvement at week 100 with an improvement sustained through week 252.

What are the main points of this poster? I think the first is that we see that at week 100, 46% of those being treated continuously with guselkumab had improvement of their SF-36, and this was persistent as determined by this study design.

I think the second point I want to highlight is that the anxiety and depression scores, as defined by the HADS score, that also improved both at week 100 and week 252. And about 50% of patients did much better on that score as well. And then lastly, we're seeing that work productivity score as well, about half, a little more than half, of patients demonstrating improvement based on these subscales.

I think how this impacts our current management … I think to a large extent, in my mind, what this poster does is it really reminds all of us of the tremendous impact that having psoriasis has on our patients, and I think it very clearly demonstrates that for those patients on guselkumab, and to a slightly lesser extent, but still quite strong effect, those on adalimumab, we see all of these patients having quite substantial improvements in all of these measures. Their SF-36, we see it in the HADS

score, and we see it in the work productivity scale.

I think it reminds us that our treatments truly are making an impact, not just in what we can see, but in also how our patients feel, how they feel about their skin, how uncomfortable it is, how they feel about their life, their outlook. We see it in how anxious they feel, how depressed they feel, and in just their ability to function and to work and do the things that we all need to do. I think that's really very, very important. It reminds us, sometimes we're busy looking at their skin and we don't take the next step and say, "How are our patients functioning in the real world?" And this reminds us that our treatments are really working in more than just what we can see.

I think that there are still, though, some questions that I believe remain unanswered. In all of these cases, we saw about a 50% improvement in these scores. I found myself wondering, and I'm not an expert in, for example, work productivity scales, but I found myself wondering how quickly patients lose those numbers, how sensitive these measures are because I'd like to know more about those who didn't respond and why, and how did this correlate with those patients who are having great clinical outcomes or not. Were patients who were still anxious, were they the ones who did not do as well in terms of their clinical efficacy or not? Maybe their skin responded very well, but they still were feeling really anxious.

I think I'd like to know more about the failures because, obviously, the success is terrific, but I'd like to see even higher numbers than 50%. And are these tools good enough to be sensitive, or do we need other, newer tools? I think there are still some questions, but I think this study really does help us think outside of our normal box and really expand our thinking about how our patients are really suffering in a bigger way, and how important our medications are to them and what impacts they can have beyond just to their skin.

Efficacy and Safety of Deucravacitinib, an Oral-Selective Tyrosine Kinase 2 (TYK2) Inhibitor, Compared with Placebo and Apremilast in Moderate-to-Severe Plaque Psoriasis: Results From the Phase 3 POETYK PSO-1 Study

The study results were presented by Dr. April Armstrong and colleagues at the 2021 American Academy of Dermatology Virtual Meeting Experience.

Steven Feldman, MD: To summarize, deucravacitinib is an investigational oral-selective tyrosine kinase inhibitor. The findings from the 2 phase 3 POETYK trials in patients with moderate-to-severe plaque psoriasis were reported by Armstrong, et al, showing that deucravacitinib was superior to placebo and to apremilast for both co-primary endpoints of 75% improvement in Psoriasis Area and Severity Index, commonly called PASI 75, and static Physician Global Assessment, or sPGA, of 0 or 1 at week 16 and week 24. The therapeutic efficacy was maintained through week 52. Deucravacitinib was well tolerated. The results of these 2 phase 3 trials confirm earlier safety and efficacy findings from phase 2 trials that deucravacitinib is well tolerated and more effective than apremilast in moderate-to-severe plaque psoriasis and active psoriatic arthritis.

Let's talk about the methods. The POETYK PSO-1 and PSO-2 trials included adults with moderate-

Lead Study Author Commentary

Important Highlights of the Study

- Deucravacitinib is a novel, oral, selective tyrosine kinase 2 (TYK2) inhibitor that binds to the TYK2 regulatory domain with high selectivity and inhibits TYK2 via an allosteric mechanism
- Deucravacitinib was superior to placebo for both coprimary endpoints (PASI 75 and sPGA 0/1) at week 16 in each trial
- Superiority vs apremilast demonstrated for PASI 75 and sPGA 0/1 at weeks 16 and 24
- Superiority vs placebo and apremilast was demonstrated for multiple ranked secondary endpoints
- Therapeutic effect was maintained through week 52
- Deucravacitinib was well tolerated and had a similar safety profile in both trials
  - Safety profile was consistent with the mechanism of action of deucravacitinib
  - Most common adverse events (≥5%) were nasopharyngitis and upper respiratory tract infection
  - Overall adverse events and serious adverse events, and adverse events leading to discontinuation were similar across 3 treatment groups
  - No clinically meaningful changes were observed in multiple laboratory parameters over 52 weeks

Impact on Patient Care

- Deucravacitinib, a once-daily oral investigational drug, has the potential to become an efficacious and well-tolerated treatment of choice for patients with moderate-to-severe plaque psoriasis

to-severe plaque psoriasis. To get in the study, you had to have a PASI of greater-than-or-equal-to 12 and an sPGA greater-than-or-equal to 3 with psoriasis involving 10% or more of the body surface area. In POETYK PSO-1 and PSO-2, patients were randomized 1:2:1 to placebo, to deucravacitinib 6 mg per day, or apremilast 30 mg twice a day. After 16 weeks, placebo patients were switched to deucravacitinib. It wouldn't be humane to leave patients with moderate-to-severe psoriasis untreated longer than that. Psoriasis is not a short-term illness. Treatment was continued for 52 weeks, giving us a better sense of long-term treatment efficacy.

The key findings. There were 663 adults with a mean age of 46 years who were randomized in PSO-1 and 1,020 adults with mean age 47 years in PSO-2. 75% to 85% of adults had moderate disease. The mean PASI ranged from 21 to 22 in all groups in both studies. For the coprimary endpoint of PASI 75 at week 16, this endpoint was achieved by 59% of deucravacitinib patients, 35% of apremilast patients, and 13% of placebo patients in the PSO-1 trial. In the PSO-2 trial, the rates were 54% for deucravacitinib, 40% for apremilast, and 9% for placebo. At week 24, the rates increased slightly in both trials with deucravacitinib and increased slightly in PSO-1 and decreased slightly in PSO-2 for apremilast.

For the other coprimary endpoint of static PGA, the percentages achieving the endpoint at weeks 16 and 24 were slightly lower than observed with PASI 75, but the trends were similar. Statistical significance was achieved for deucravacitinib vs placebo and vs apremilast for multiple ranked secondary endpoints in both trials, such as PASI 90, PASI 100, and quality of life. Significantly greater improvements from baseline for deucravacitinib vs apremilast were seen at week

16 and 24 in both trials. The therapeutic effect was maintained through week 52.

The most common adverse events were nasopharyngitis and upper respiratory tract infections. The rates of serious infection for deucravacitinib and apremilast were similar and slightly lower than 2 events per 100 patient-years. None of the serious infections associated with deucravacitinib led to treatment discontinuation.

Here are my thoughts. From my perspective, the main point of this study is that, well, many patients with severe psoriasis would prefer a pill over an injection. Apremilast is available, but it isn't particularly effective. Deucravacitinib is considerably more effective with an efficacy that approaches that of adalimumab and ustekinumab, and deucravacitinib is, at least in these trials, well tolerated.

Will this study have a big impact on the current state of patient management? I don't think so.

Now, how about the future state of patient management? The study findings could portend that deucravacitinib will become a first-line treatment for moderate-to-severe psoriasis. Deucravacitinib has a high level of efficacy. It's not quite what we see with IL-17 and IL-23 inhibitors, but patients are often happy to sacrifice some efficacy to avoid injections, and patients wouldn't need to sacrifice nearly as much efficacy with deucravacitinib as they do when they choose apremilast.

What remains unanswered? Well, it's hard to know at this point what the long-term safety of deucravacitinib is. In these trials, it looked quite safe, but the trials have a limited size, and we don't know what safety signals might be seen once tens of thousands of patients are treated.

Gastrointestinal Adverse Events Related to Study Drug and Leading to Discontinuation Through 5 Years of Tildrakizumab Exposure in 2 Phase 3 Clinical Trials

The study results were presented by Dr. Jennifer Connor and colleagues at the 2021 American Academy of Dermatology Virtual Meeting Experience.

Link to poster: CLICK HERE

Steven Feldman, MD: To summarize, this was a post hoc analysis of 2 large phase 3 trials of the high-affinity, humanized, anti-IL-23p19 monoclonal antibody tildrakizumab in patients with moderate-to-severe plaque psoriasis. The results showed that through 5 years of treatment with tildrakizumab, 100 mg or 200 mg, gastrointestinal (GI) serious adverse events, including inflammatory bowel disease, leading to treatment discontinuation, occurred at very low rates. Overall, the GI safety profile was as expected.

This is important, because a limitation of many biologic medications used for the treatment of patients with plaque psoriasis, particularly medications that affect IL-17 levels, are associated with an increased risk of fungal infections and inflammatory bowel disease. The low incidence of these adverse events with tildrakizumab in this analysis provides some

reassurance as to its long-term safety in patients with moderate-to-severe plaque psoriasis.

Let me describe some of the study details to you. This analysis includes data from all patients with moderate-to-severe plaque psoriasis in the 3-part double-blind randomized placebo-controlled phase 3 64-week reSURFACE 1 and 52-week reSURFACE 2 trials, who received at least 1 dose of tildrakizumab, 100 mg or 200 mg, during the optional long-term extension periods. Patients received tildrakizumab 100 mg or 200 mg monotherapy at weeks zero and 4 and every 12 weeks thereafter, or they got placebo. Patients could be re-randomized or reassigned to a different treatment based on prescribed prespecified efficacy criteria.

Here are the key findings. These are good-sized studies. Over 500 patients entered the extension phase of reSURACE 1 and over 700 entered the extension phase of reSURFACE 2. The mean age ranged from 44 to 47 years in the 2 trials. 67% to 76% were male. Now, these were typical patients with moderate-to-severe psoriasis. Can I just call it bad psoriasis with baseline Psoriasis Area and Severity Index (PASI) scores ranging from 19 to 21? Patient exposure to tildrakizumab ranged from about 1200 to 1400 patient years in reSURFACE 1, and nearly 1600 to 1700 in reSURFACE 2.

Pooled exposure-adjusted incidence rates for all drug-related serious adverse GI events across both trials were 0.1 per 100 patient-years. That's another way of saying one in a thousand patient-years. A drug-related GI adverse event leading to discontinuation occurred in 1 patient in the reSURFACE 2 trial, and it was due to dysphagia, trouble swallowing. They were 2 treatment-emergent adverse events of inflammatory bowel disease in patients on the lower dose, 100 mg, of tildrakizumab, 1 due to ulcerative colitis and the other due to Crohn's disease. The ulcerative colitis patient had a previous history of ulcerative colitis. The adverse event was considered moderate in severity and resolved after about a month. The Crohn's disease patient had no prior history of Crohn's disease. The event was considered mild and did not even lead to treatment discontinuation.

Here's some thoughts of mine and analysis of this study. The main point is that on the one hand, the low rate of GI side effects is very reassuring. On the other hand, until this study, I associated a risk of psoriasis patients developing inflammatory bowel disease pretty much exclusively with IL-17 inhibitors, not with drugs that block IL-23, like tildrakizumab.

How do the results of this study impact the current state of patient management? Well, tildrakizumab is not the most widely used IL-23 inhibitor. It's only approved for office use. I think that's a great niche for nonadherent patients and for patients whose insurance makes office administration a more accessible route for getting the drug.

The low rate of GI side effects with tildrakizumab may be reassuring. On the other hand, seeing even one IBD case with an IL-23 blocker makes me begin to wonder, at least a little bit, how different IL-23 blockers are from IL-17 drugs when it comes to IBD. Will this affect our future management? I think this study will do very little to change the impression that IL-17 drugs have a bit more of an IBD risk associated with them than the IL-23 drugs have.

What's left to know? Well, very little seems to remain unanswered with respect to the safety of IL-23 blockers. Even with 5-year follow-up, we don't see much, if any, safety risk. Still, we don't know if something unknown will happen after 10, 20, or 50 years of treatment, but I feel pretty well assured of their safety.

Additional Discussion of Psoriasis Poster

Steven Feldman, MD: I just want to share with you some additional thoughts. Some of the additional posters presented at the 2021 American Academy of Dermatology Virtual Meeting Experience were worth noting. Two of these related to topical therapies and 1 to biosimilars.

In the first poster related to topical therapy, Gold, et al, presented the results of 2 phase 3 double-blind vehicle-controlled trials of tapinarof cream, 1% given once daily for 12 weeks for the treatment of patients with mild-to-severe plaque psoriasis. Tapinarof is an investigational, nonsteroidal, topical, aryl hydrocarbon receptor modulating agent. Response rates for the primary endpoint of Physician Global Assessment (PGA) were significantly higher in the tapinarof group vs the vehicle group at 12 weeks.

For example, 38% to 44% of tapinarof patients and 8% to 10% of vehicle patients achieved a PGA score of 0 or 1. Similarly, significantly more patients treated with tapinarof vs vehicle achieved Psoriasis Area and Severity Index (PASI) scores of 75 or 90 at 12 weeks. Most of the treatment-emergent adverse events were mild or moderate in severity and did not lead to study discontinuation. If confirmed in further investigations, tapinarof would provide an alternative to topical corticosteroids for plaque psoriasis.

Another poster, also presented by Gold, investigated the efficacy of roflumilast cream in relieving itch associated with chronic plaque psoriasis. Roflumilast is a phosphodiesterase-4 inhibitor. Itch is extremely important to patients with psoriasis, as shown by the Multinational Assessment of Psoriasis and Psoriatic Arthritis Survey, because of itch's profound impact on

patient quality-of-life. Over 12 weeks, patients treated with roflumilast 0.15% or 0.3% achieved significantly greater improvement in itch compared with patients treated with the vehicle. This resulted in significantly greater reduction in itch-related sleep loss and improved quality of life with roflumilast compared with vehicle.

The findings in these 2 posters are encouraging, since these topical therapies might help avoid some of the challenges experienced with topical corticosteroids. But as much as I love these drugs and love having new options for my patients with psoriasis, I'm not enthusiastic about how much benefit these new products will bring. And I may be uniquely pessimistic, but adherence to topical treatment is often abysmal, and if insurers require prior authorization for these new topicals and require failure of other topicals first, it seems likely that the only people who will get the new treatments will be relatively nonadherent patients, and even these new drugs will fail if patients don't put them on.

A third poster, presented by Menter and colleagues, reported on the results of studies of BI 695501 as a potential biosimilar to adalimumab for patients with moderate-to-severe chronic plaque psoriasis. Now, biologics are so large and so complicated they cannot be exactly duplicated, so BI 695501 is not identical to adalimumab, but it's very similar. BI 695501 is biosimilar to adalimumab in patients with moderately to severely active rheumatoid arthritis, and by biosimilar, I mean that in every

clinically meaningful way, it appears to work the same. Menter's study looked at how similar it performed for psoriasis, and in his study, BI 695501 was noninferior to the adalimumab reference product with respect to pharmacokinetics, immunogenicity, efficacy, and safety, meaning that it met the criteria for biosimilarity. Also, BI 695501 was noninferior in patients who switched between it and the adalimumab reference product, vs those who received continuous treatment with the adalimumab reference product.

Listen, the bottom line is that biologics are so large, they are so complicated, they cannot be exactly duplicated by anyone, and that means that even the reference product, adalimumab from the brand name company, varies from

batch to batch. BI 695501 and other biosimilars give us a lot of data, more than we have for the batch-to-batch variation in the reference product, that they're going to perform similar to the reference product. So, on the one hand, I'm glad that biosimilars are coming in order to help control the cost of medication. On the other hand, I don't get too excited about it, because they're not going to help me help patients that I can't already treat with the available treatment options.