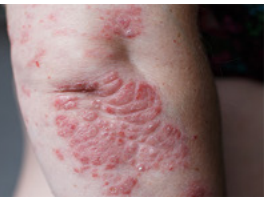
A Case-Based Roadmap for Improved Patient Outcomes in Plaque Psoriasis



OVERVIEW

Plaque psoriasis is a chronic inflammatory skin condition that impacts patient physical, social, and emotional well-being. Join Dr. Steven Feldman in an interactive case-based overview of managing patients with plaque psoriasis. Diagnosis, severity assessment, and treatment are discussed, to provide clinicians with a broad overview of optimal plaque psoriasis management. Treatment initiation, switching, and escalation are reviewed, with a focus on common clinical scenarios, such as unplanned treatment interruption, and selecting agents for patients who intend to conceive.

TARGET AUDIENCE

This activity is intended for dermatologists, primary care physicians, nurse practitioners, physician assistants and other healthcare providers who manage patients with plaque psoriasis.

LEARNING OBJECTIVES

- Utilize validated tools to assess plaque psoriasis disease burden and response to treatment
- Summarize the clinical pharmacology, including mechanism of action, as well as safety and efficacy, of evidence-based medications for plaque psoriasis
- Apply the results of clinical trials, expert recommendations, and consensus guidelines to develop treatment plans based on patient characteristics, treatment history, and comorbid conditions

FACULTY

Steven R. Feldman, MD, PhD

Professor of Dermatology, Pathology, and Social Sciences & Health Policy
Wake Forest University Health Sciences
Winston-Salem, North Carolina

Mayo Clinic Scottsdale
Scottsdale, Arizona

CE INFORMATION

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 1.0 *AMA PRA Category 1 Credit*™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Annenberg Center for Health Sciences is accredited as a provider of continuing nursing education by the American Nurses Credentialing Center's Commission on Accreditation.

A maximum of 1.0 contact hour may be earned for successful completion of this 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, Arcutis, Arena, BMS, Caremark, Celgene, Dermavant, Galderma Laboratories, LP, Gerson, Lehrman Group, Guidepoint Global, Helsinn, Janssen, Kikaku, Leo Pharma Inc, Lilly, Merck & Co, Inc, Mylan, Novartis Pharmaceuticals Corporation, Ortho Dermatology, Pfizer Inc, Regeneron, Sanofi, Sienna, Sun Pharma, Suncare Research, XenoPort
Founder:	Causa Technologies
Grand Support:	AbbVie, Amgen, Celgene, Galderma Laboratories, LP, Janssen, Lilly, Novartis Pharmaceuticals Corporation, Pfizer Inc, Regeneron, Sanofi
Royalties:	Informa, UpToDate, Xlibris
Speakers Bureau:	AbbVie, Amgen, Celgene, Janssen, Leo Pharma Inc, Lilly, Novartis Pharmaceuticals Corporation, Ortho Dermatology, Pfizer Inc, Regeneron, Sanofi, Sun Pharma
Stockholder:	Causa Technologies, Medical Quality Enhancement Corporation

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

Additional content planners

The following have no significant relationship to disclose:

Jessica Martin, PhD (medical writer)

Kam Newman, MD (peer reviewer)

Heather Jimenez, FNP-C (nurse 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 activity is supported by independent educational grants from AbbVie and UCB.

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 1.0 hour.

This activity was released on August 31, 2021 and is eligible for credit through August 31, 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

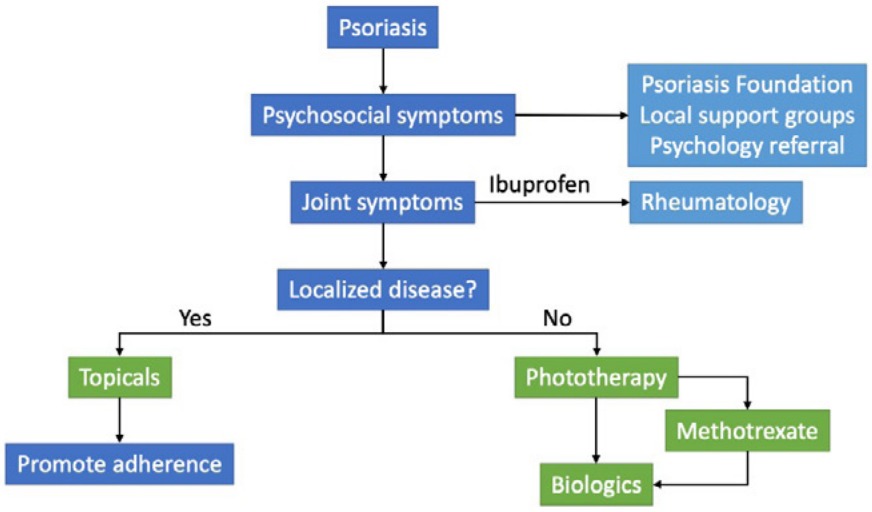
Obtain your CE/CME credit

INTRODUCTORY CONTENT

Plaque psoriasis is a complex, inflammatory disease that affects more than 7 million adults in the US.[1] Psoriasis is associated with substantial social, physical, and emotional burdens for patients, with many reporting difficulty performing daily activities, including sleeping, or embarrassment caused by the visibility of their symptoms.[2] Taken together, these factors can make psoriasis challenging to manage, particularly for those patients with moderate-to-severe disease and limited support systems. Nonetheless, untreated disease can be the source of significant morbidity among patients. Therefore, clinicians should be prepared to individualize treatment for their patients to improve outcomes.

Management of psoriasis requires a holistic approach that considers both the psychosocial and physical disease aspects (Figure 1). Assessing patient psychosocial needs is critical, and providing resources such as the Psoriasis Foundation, local support groups, or psychology referral, can help patients access information and support. Joint symptoms are also important components of psoriasis management due to the elevated risk of psoriatic arthritis among these patients. Finally, determining appropriate treatment will depend on disease severity and the extent of disease along with patient-reported information, such as symptom bothersomeness.

Figure 1. Example holistic treatment schematic for patients with psoriasis



Patient Perspective: Selli

Psoriasis Journey

My name is Selli. I'm a medical student in Philadelphia. I was first diagnosed with psoriasis when I was 10 years old. I had just moved from New York to New Jersey. And I noticed a little flake right under my eye. From there, I realized that I had more behind my ear. I told my mom. I went to my pediatrician, and they referred me out to a dermatologist.

I was treated with foams, ointments and solutions up until high school where I had psoriasis now on my arms. And my doctor had recommended I do light therapy. So I did that, on and off, a majority of my homeschool. In college is actually when it started to just continue to increase in surface area. And that's when he had suggested that I start biologic therapy. I think the reason as to why I started it in college was just because of the social impact that it had on my life. I always felt like I was covering my arms.

In 2014, I started etanercept. And I was on that for a few months. I then quickly switched to ustekinumab, which worked great. I was on that for a couple of years, actually. The reason why I switched was because the etanercept was just more difficult to adhere to as opposed to ustekinumab, which was a lot easier to use. My last flare started in 2019. It was actually during my second year of med school. It was board season. And I was in a high stress environment. And I was placed on adalimumab due to insurance. In January of 2021, I decided to take myself off of it, because I wanted to get the COVID vaccine, and I just felt like at that point it was more important to get the COVID vaccine versus being on a biologic. And I was advised not to switch or take off your medications, but I just felt like when it came to quality of life, I was happy with where I was. My most recent flare-up was this July after not being on medication for about seven months.

CASE SCENARIO 1: Disease Severity and Treatment Response Assessment

Case 1 content: A 22-year-old man presents with erythematous plaques on his elbows and knees with an overlying silvery scale. The plaques began to appear approximately 2 months ago and have worsened recently. At this visit, he is diagnosed with mild-to-moderate plaque psoriasis.

1. Which of the following provides the most quantitative and comprehensive measure of the severity of objective skin disease in patients with plaque psoriasis?

a. Body Surface Area (BSA)
b. Clinician judgement
c. Psoriasis Area Severity Index (PASI)
d. Psoriasis Epidemiology Screening Tool (PEST)

Answer: c. Psoriasis Area Severity Index (PASI)

Rationale:

The Psoriasis Area Severity Index (PASI) characterizes plaque psoriasis severity according to the presence and severity of erythema, induration, scaling, and body surface area (BSA) affected. PASI scores range from 0 (no disease) to 72 (highest severity disease), with a score of 10 or higher indicating moderate-to-severe psoriasis.[3] PASI is recommended as a quantitative and comprehensive measure of psoriasis severity by several guidelines,[4-6] and evidence from a systematic review showed that PASI is the most extensively validated tool for determining the severity of plaque psoriasis.[7] While the PASI has high levels of inter- and intra-rater reliability,[8] it is less commonly used in clinical practice compared with other measures, due to the complexity of the measure and potentially time-consuming calculations required.[9]

BSA is one of the most commonly used assessments for psoriasis severity in clinical practice.[3,5,9] Approximately 1% BSA is represented by the area of a single handspan.[3] While BSA is a useful tool that may be quickly applied in many clinical situations to provide a quantitative measure of severity, it is prone to under- and overestimation. Additionally, BSA does not consider plaque characteristics, making it less comprehensive than the PASI.[3,9]

One limitation shared by the BSA and PASI scores, along with other physician-reported measures (eg, the Physician Global Assessment [PGA]) is the lack of consideration of patient-reported subjective outcomes, including symptoms and quality of life issues.[3,9] For example, patients with hair or nail involvement, or those with plaques in specific regions (eg, hands or groin) may have worse quality of life than others with more extensive skin involvement.[9,10] Examples of tools for measuring patient-reported outcomes that may be useful include the Psoriasis Symptom Inventory (PSI) and the Dermatology Life Quality Index (DLQI).[11,12]

Clinician judgement is not a quantitative measure of disease severity and may under- or overestimate severity. The Psoriasis Epidemiology Screening Tool (PEST) is used to screen patients for psoriatic arthritis (PsA).[13]

Case 1 content (continued): The patient's PASI score is 6, and his BSA is 3%. His DLQI score is 7. Pruritus is his most bothersome symptom, which has had a major impact on his sleep. In a shared decision-making process, the patient and his provider decide to initiate treatment with clobetasol propionate 0.05%.

2. At what point would you expect to see symptom improvement for this patient?

a. 2-4 weeks
b. 4-8 weeks
c. 8-16 weeks
d. 16-24 weeks

Answer: a. 2-4 weeks

Rationale:

Most topical corticosteroids for the treatment of mild to severe plaque psoriasis are effective within 2 to 4 weeks.[3] In a randomized controlled trial of topical clobetasol propionate 0.05%, 68% of patients had clear skin by week 2.[14,15] In contrast with topical regimens, biologic agents may take longer to exert their therapeutic effects, with studies showing that most symptom improvements occur within 4 to 13 weeks after initiation. Both the drug class and disease severity can impact the time to symptom improvement.[16]

For patients with moderate disease treated with topical agents, while it may be reasonable to schedule a follow-up appointment up to 3 months after initiation of topical therapy to monitor treatment response and discuss maintenance regimens with the patient, adherence may be improved by having an initial follow-up visit or other contact 1 week after starting a new treatment.[5]

Case 1 content (continued): Most cases of psoriasis will recur after corticosteroids are discontinued, so patients should be counseled on appropriate weaning and the use of steroid-sparing regimens to reduce the need for topical corticosteroids. Examples of corticosteroid-sparing regimens that can be considered include intermittent use of the topical corticosteroid, or use of a topical calcineurin inhibitor, vitamin D analog, retinoid, and moisturizer.[14]

The patient was instructed to use clobetasol propionate 0.05% twice daily for the first 2 weeks and then begin weaning to a corticosteroid-sparing regimen of a topical calcineurin inhibitor. In this case, the patient returns after 6 weeks of treatment.

At his return visit, the patient's PASI score has improved from 6 to 3, and his BSA has improved from 3% to 2%. His DLQI score has improved to 2, and he says that the pruritus has mostly resolved.

3. How would you classify this patient's treatment response?

a. Complete response
b. Partial response
c. Primary treatment failure
d. Secondary treatment failure

Answer: b. Partial response

Rationale:

This patient has achieved a partial response. An expert consensus suggested that the goal of psoriasis treatment is to achieve almost clear or completely clear skin (ie, close to 100% improvement in quantitative measures of disease and resolution of symptoms).[17] In clinical practice, a complete response to psoriasis treatment is often quantified as a BSA of 1% or less.[5] This patient's PASI score has improved by 50%, while his BSA has improved by less than that, with more than 1% BSA remaining. Therefore, his response would not qualify as a complete response. In general, partial responses are classified as improvements in validated scores of less than 75% but more than 50%. Treatment failure is typically defined as less than 50% improvement in PASI score requiring a change in the treatment regimen.[5]

FACULTY DISCUSSION

This patient is a young person with relatively limited disease. When we think about evaluating the severity of the disease for clinical trials, we use objective measures that are very quantitative. In real-life clinical practice, we generally use a gestalt. You know it's small areas of involvement, so topical therapy should be fine. For a clinical trial, you need to know specifically how much improvement there is. In real life, you need to know if the patients are happy and you just do that by asking them maybe on a 2-point patient global assessment, how you doing? And if they say they're doing well, typically you would continue therapy. If they're not doing well, you'd typically need to change therapy. The detailed quality of life measures we use in clinical trials aren't necessary for real-life clinical practice. That said, if you use one of these detailed quality of life measures, you may find out things that the patient didn't spontaneously report to you. They may be too embarrassed to talk about genital involvement. You may detect it in the objective measure and be able to use that.

The clinical trials tell us very little about what kind of psychosocial evaluation to do or how to give patients resources. There is so much they need to know, so many treatments out there. They have so many questions about psoriasis and how it will affect their day-to-day lives. A great resource for patients is our National Psoriasis Foundation. Patients can go to www.psoriasis.org and find out pretty much everything they could want to know about the various treatments available and how to manage with psoriasis in their lives.

Patient Perspective: Selli

Burden

The most difficult symptom is the flakiness that you get with the psoriasis. I feel like, you're always leaving a mark. The hardest part for me was when the psoriasis flares were then on my face, because I felt like I was able to cover my scalp, my arms, my legs. I had done everything. I knew every trick in the book to cover up, but when it came to my face, it was very difficult to cover my face.

From an emotional standpoint, having parents from a different country, and having different cultural ideas, they really didn't understand. And 18 years after living with this they still think that there's some cure. I think probably the hardest part on an emotional level is not fully being understood by the people in your household. I came across an article that was done by the University of Pennsylvania. And it looked at the stigmatizing attitudes towards psoriasis among the general population, and among medical students. I didn't realize that medical students, soon to be doctors, would have these stigmatizing attitudes. You know, medical students that I sit in class with. So, to me, it was wow, no one will understand psoriasis unless they've lived it.

CASE SCENARIO 2: Treatment Switching

Case 2 content: A 29-year-old man with psoriasis involving the scalp, face, arms, and trunk (PASI score 9; BSA 4%) presents for first-line treatment. Although BSA and PASI scores suggest moderate severity, the patient indicates that the scalp symptoms are extremely bothersome. The patient is initially treated with a potent tumor necrosis factor (TNF) inhibitor. After 3 months, his PASI score is 8, and his BSA is 3% with good tolerability. He says that the symptoms on his face and hands continue to be extremely bothersome.

1. How would you classify this patient's treatment response?

a. Complete response

b. Partial response

c. Primary treatment failure

d. Secondary treatment failure

Answer: c. Primary treatment failure

Rationale:

This patient appears to have had primary treatment failure with this treatment regimen. Treatment failure is defined as an improvement in PASI or BSA of less than 50%. Primary failure occurs when the patient does not respond to initial treatment, while secondary failure occurs when a patient initially responds favorably to a treatment before symptoms return later. Although the reasons for loss of treatment effectiveness can vary, the development of antidrug antibodies is one potential cause.[5,18]

2. Which one of the following interventions should be considered as a next step for this patient?

a. Continuing treatment for 3 more months and reassessing response

b. Discontinuing treatment

c. Switching to a treatment with a new mechanism of action

d. Switching to a different TNF inhibitor

Answer: c. Switching to a treatment with a new mechanism of action

Rationale:

According to American Academy of Dermatology/National Psoriasis Foundation (AAD/NPF) guidelines, treatment failure with a PASI improvement less than 50% and the presence of ongoing bothersome symptoms necessitates a treatment change for this patient.[5,18] Therefore, switching to a new agent is the preferred next step. While switching both within and among drug classes could be considered reasonable options for this patients given the good tolerability of the first-line TNF inhibitor, there is evidence that switching mechanisms of action may result in slightly better response rates for patients with primary treatment failure.[18-21] In a systematic review of the efficacy of anti-TNF therapy in patients who were previously treated with a different TNF inhibitor, those who had experienced secondary treatment failure with their initial TNF inhibitor had better responses to the next treatment than those who experienced primary treatment failure.[19]

Evidence from randomized controlled trials supports the safety and efficacy of switching between biologic classes in psoriasis. In subanalyses of the UNCOVER phase 3 trials, anti-IL-17A monoclonal

antibody ixekizumab PASI75 response rates were between 73% and 78% of nonresponders to etanercept treatment.[22] Similarly, in the SIGNATURE study, nonresponders to TNF inhibitor therapy improved with secukinumab therapy, with up to 65% of patients achieving PASI75.[23]

When switching biologic treatments, the AAD/NPF recommends individualizing the switching protocol based on the treatment being discontinued, disease severity, and prior treatment response. Depending on these factors, clinicians may initiate a new biologic immediately or wait for several half-lives of the previous therapy to elapse.[18] Some experts recommend a washout period for patients who are switching due to toxicities to ensure the adverse event is resolved prior to initiation of a new therapy. For those patients switching therapies due to inadequate response, generally no washout period is necessary.[24]

3. Which one of the following pathways has been implicated in plaque psoriasis pathophysiology?

a. CRTH2
b. IL-4
c. IL-17
d. TSLP

Answer: c. IL-17

Rationale:

Several inflammatory mediators play a role in the pathophysiology of psoriasis, including IL-17, IL-12, IL-23, and tumor necrosis factor-alpha (TNF-α), among many other cytokines and immune cells. Psoriatic lesions typically develop after an initial injury to keratinocytes, which leads to the release of keratinocyte-derived DNA and other antimicrobial peptides (AMPs). These signaling molecules activate plasmacytoid dendritic cells (DCs), which are commonly found in psoriatic skin lesions, initiating an inflammatory signaling cascade involving the release of chemokines and interferon-alpha (IFN-α). In turn, keratinocytes and myeloid DCs become activated, inducing the differentiation of T cells into type 17 and type 1 helper T cells (Th17 and Th1 cells), which within psoriatic lesions. Th17 and Th1 cells drive the production of large quantities of IFN-γ and TNF-α, along with other proinflammatory cytokines (Box 1).[25]

The epithelial milieu also plays an important role in maintaining high levels of inflammation in psoriasis. Dermal DCs perpetuate inflammation by producing TNF-α and other signaling molecules as well as potentiating neutrophil, effector T-cell, and natural killer (NK)-cell responses. Keratinocytes continue to produce chemokines, cytokines, and autoantigens that recruit immune cells and promote activation, feeding into the ongoing inflammatory cycle.[25]

Box 1. Key cytokines involved in psoriatic inflammation

- IFN-α: promotes activation and maturation of myeloid DCs and stimulates pathogenic T cells
- IL-12: induces IFN-γ production
- IL-17: induces upregulation of chemokines and immunomodulatory molecules
- IL-23: stimulates the release of IL-17 and IL-22 by effector T cells
- TNF-α: induces leukocyte recruitment and stimulates production of chemokines and cytokines that maintain Th17 responses

CRTH2, TSLP, and IL-4 are molecules with roles in eosinophilic and noneosinophilic inflammation. Each of these inflammatory mediators has been implicated in airway inflammation, in particular, and is a target for the treatment of asthma.[26-28]

4. Targeting which of the following molecules is more effective than targeting IL-17A alone?

a. IL-17F alone
b. IL-17F and IL-17A
c. IL-13 alone
d. IL-13 and IL-17A

Answer: b. IL-17F and IL-17A

Rationale:

Inhibition of both IL-17F and IL-17A is more effective than targeting IL-17A alone, in both in vitro clinical models and randomized controlled trials of patients with psoriasis.[29-31]

There are 6 members of the IL-17 cytokine family: IL-17A, IL-17B, IL-17C, IL-17D, IL-17E (also known as IL-25), and IL-17F. IL-17A is a proinflammatory signaling molecule that drives chronic inflammation in psoriasis and is an established therapeutic target. IL-17F shares about 50% structural homology with IL-17A, and these 2 cytokines can be expressed as homodimers (ie, IL-17A/IL-17A or IL-17F/IL-17F) or heterodimers (ie, IL-17A/IL-17F). Furthermore, both IL-17A and IL-17F exert proinflammatory signaling via binding to the same complex of IL-17 receptors.[29]

IL-17F was believed to mediate lung inflammation with little role in other chronic inflammatory diseases; however, IL-17F can synergize with TNF to induce inflammation similar to that promoted by IL-17A.[32] Additionally, dysregulation of IL-17F is common in psoriatic skin lesions and synovial fluid of patients with psoriatic arthritis.[33,34]

FACULTY DISCUSSION

This case illustrates a patient who has relatively moderate-to-severe psoriasis, maybe at the mild end of moderate to severe, but still moderate disease and seemed appropriate for systemic therapy. He's treated. Clearly, he's not happy with how he's doing initially, so he needs something different to be done. And this raises all kinds of issues because we have all sorts of treatments now and sometimes it's hard to know, well, which one should we use in which situation.

When I have a patient who does well on a particular therapy and then it stops working, I often think it's probably because their body's developed an antibody against that treatment so I may switch to a different treatment from the same class since I know that class is safe and effective for the patient. If, on the other hand, a treatment doesn't work right from the beginning in a patient, I think there's a greater chance that they're probably resistant to that class of drugs and I'll probably choose a different class.

Fortunately, you know, we have multiple classes now. TNF inhibitors were revolutionary, the IL-17 inhibitors (brodalumab, ixekizumab, secukinumab) I think are generally more effective and maybe even safer. IL-23 inhibitors (guselkumab, risankizumab, tildrakizumab, ustekinumab) I think in terms of the long run option may be the safest and maybe the most effective way of treating the disease.

For many patients, the choice will not just be affected by the improvement in their skin, but also has to take into consideration whatever joint involvement they have. Some of our treatments are approved for joints; some are approved for prevention of joint progression. And I think many dermatologists might choose one therapy over another on the basis of whether there's joint involvement or not and whether the treatments are

approved for the prevention of joint progression. Me, personally, I like to treat the skin. I choose whatever I think is best for the skin because that's why they're seeing me and I'm pretty sure that most of these biologics, if not all of them that are effective for the skin, are also effective for the joints, whether they're approved for the joint disease or not. You know, many of these drugs were first approved for the skin and then they were approved for the joints. They didn't become effective for the joints when they got approved; they were already effective for the joints even before they got approval.

You know, many patients might be doing pretty well on a treatment and might feel like, gosh, I could do better if I could just take a little more of it; or, the disease is under good control for, you know, 2 months but then it starts coming back, can I take the drug more often? And typically, I don't escalate the dose. Although occasionally, for those drugs that are given every 3 months, for example, I may try to get the patient covered to take it every 2 months, if the disease starts coming back, you know, before that 3-month visit, for that 3-month dose. Typically, the guidelines for dosing are something I tend to stick with if for no other reason than I think that's what the insurer will cover. Although, you know, if you have obese patients, I think there's a lot of thought that certain drugs don't work as well in obese patients. They need a higher dose. And so using a higher dose in that situation may be appropriate. Some people believe it's helpful to go to weight-based drugs when you have very heavy patients because [with] those drugs, you can get those patients the dose they'll need.

Sometimes, one biologic alone may not be enough. We see this commonly amongst psoriatic arthritis patients where the rheumatologist will give methotrexate with a biologic. And, in fact, for those drugs that are approved for psoriatic arthritis, a lot of times the biologic was tested in conjunction with methotrexate in many of the patients in the studies. For those patients who are, you know, jumping from one biologic to another because it works for a while and then it stops working and they're developing antibodies very easily, I think combination therapy with methotrexate may be a very reasonable and good choice.

CASE SCENARIO 3: Influence of Treatment History and Other Factors

Case 3 content: A 41-year-old woman was diagnosed with moderate plaque psoriasis, localized to her elbows and forearms, 3.5 years ago. She was initially treated with a mid-potency topical corticosteroid but had minimal reduction in her pruritus. Treatment with the combination of methotrexate and a TNF inhibitor produced good results initially, but her symptoms worsened several months later and involved her knees. She was switched to an IL-17A inhibitor and achieved a PASI response of 90% reduction in symptoms (PASI90) about 5 months later. At that time, she lost her job and could not afford her health insurance, so she stopped treatment.

Now, 8 months later, she has found a new job with health insurance and presents to reinitiate treatment. She wishes to resume treatment with an IL-17A inhibitor.

1. Which of the following features of the patient's medical and treatment history may influence future efficacy of an IL-17A inhibitor?

a. Dose interruption of IL-17A inhibitor
b. Patient age ≥40 years
c. Previous switching of treatment class
d. Secondary failure of TNF inhibitor

Answer: a. Dose interruption of IL-17A inhibitor

Rationale:

In general, restarting a treatment after discontinuation has been associated with good outcomes, with more than 60% of patients recapturing disease response. However, a small proportion of patients may not reach the same level of response previously attained with the agent.[35-39] Furthermore, continuous treatment with biologics is recommended to decrease the risk of antidrug antibody formation, which can reduce treatment effectiveness.[40]

Older age, previous switching, and prior secondary failure of treatment have not been associated with nonresponse to biologic therapy. However, other medical and demographic factors can influence treatment response with biologic therapy. In a longitudinal study of more than 3000 patients initiating biologics, the following demographic and medical factors increased the risk of not achieving PASI90 at 6 months: female sex, unemployment, former and current smoking, and excess weight. Additionally, psoriasis of the palms or soles and plaque size were associated with decreased odds of achieving PASI90.[41]

2. Which of the following agents has been associated with the lowest rate of efficacy after restarting?

a. Brodalumab
b. Infliximab
c. Ixekizumab
d. Secukinumab

Answer: b. Infliximab

Relative to other treatments, infliximab has been associated with lower response rates following re-treatment after withdrawal. In a systematic review of intermittent biologic use, infliximab was associated with 25% to 38% PASI75 response along with a higher rate of infusion reactions.[35] This has been attributed to an increased risk for development of antidrug antibodies with infliximab re-treatment. In the EXPRESS II trial, anti-infliximab antibodies were detected in up to 52% of patients, with higher rates reported in patients receiving intermittent treatment compared with those receiving continuous treatment.[42]

Other biologic agents, including the anti-IL-17A agents, have higher recapture rates with reinitiation. In analyses of the UNCOVER trials, 83% to 87% of patients recaptured their response after 24 weeks re-treatment with ixekizumab.[38,43] In the phase 3 AMAGINE-1 withdrawal trial, PASI75 response was recaptured in 94% (observed data) of brodalumab responders after at least 8 weeks of nontreatment.[39] Similarly, in the phase 3 ERASURE and FIXTURE studies, re-treatment with secukinumab was associated with a 94% PASI75 recapture rate.[44] Similar results have been reported for patients restarting therapy with a TNF inhibitor (etanercept),[45] IL-12/IL-23 inhibitor (ustekinumab),[46] and IL-23 inhibitor (risankizumab).[36]

Case 3 content (continued): On assessment, the patient's psoriasis appears severe (BSA 11%; PASI23) and has spread to her hands. She says pruritus is the most bothersome symptom and frequently keeps her awake at night.

3. Which of the following treatments should you initiate?

a. Initiate treatment with IL-12/IL-23 inhibitor
b. Initiate treatment with IL-23 inhibitor
c. Restart treatment with IL-17A inhibitor
d. Restart treatment with methotrexate and TNF inhibitor

Answer: c. Restart treatment with IL-17A inhibitor

Rationale:

Restarting the IL-17A inhibitor is a good treatment option for this patient. There is evidence supporting the effectiveness of re-treatment with biologics after treatment withdrawal, and no safety issues have been reported for reinitiation of IL-17A inhibition. Furthermore, IL-17A inhibition is more effective than IL-12/IL-23 inhibition. In the phase 3 CLEAR study, the IL-17A inhibitor secukinumab was associated with a higher rate of PASI90 compared with ustekinumab (76% vs 61%; *P* <0.0001) after 1 year of treatment.[47] Patient-reported outcomes, including quality of life and psoriasis-related symptoms, were also improved by secukinumab.[48] Similarly, in the AMAGINE-2 and AMAGINE-3 trials, 52 weeks of treatment with brodalumab was associated with a higher rate of PASI100 (51% vs 28%; *P* <0.0001) compared with ustekinumab.[49] IL-17A inhibition with ixekizumab led to a higher PASI75 rate than etanercept (78%-90% vs 42%).[50] Furthermore, when making treatment decisions, the AAD/NPF guidelines endorse considering patient preferences in addition to efficacy, safety, and QoL.[18]

When reinitiating therapy after discontinuation for more than 3 to 4 half-lives of the drug, loading doses can be readministered.[18] After reinitiating therapy, regular follow-up should be resumed to monitor for response and toxicity.

FACULTY DISCUSSION

This patient illustrates a common phenomenon where patients discontinue therapy for one reason or another. I hate when it happens because I have so many resources available for keeping patients on therapy. They lose their insurance, typically you can get the biologic at little to no cost for them if they will come in and tell you. Sometimes patients tell me, "I didn't come in because I didn't have insurance." And I feel so terrible because those are the patients I find easiest to treat. If they have no insurance, I probably can get them almost any treatment I want through pharmaceutical company resources.

I also worry if they stop a biologic, you know many of these biologics work pretty well when you restart them. However, I think especially for things like infliximab, there's a risk that you will lose the efficacy of the drug with prolonged stopping between therapies. I think stopping for prolonged periods may lead to greater antigenicity. You know, one of the big factors that affects treatment outcomes in general, whether we're talking about topicals or injectables, is how poorly patients use their medicine. And in the case of biologics, patients may be afraid that they're going to be at risk of infection and so if they're doing well, they may stretch out the period between doses and they may not even tell you they're doing it.

I like to ask them, "Are you keeping the extras that you've accumulated refrigerated like you're supposed to?" Now, if they say, "I don't know what you're talking about, I don't have any extras," then they're taking it regular. If they say anything else, nah, they're probably holding off on dosing between and making that interval longer. That can lead to the drug failing over time if it leads to greater antigenicity. And I don't worry about that because we've got so many options for patients with psoriasis. However, if it's a patient who's already been through a lot of those options, then I really want them to take the drug regularly, and I counsel them about the risk that if they don't take it the way it's supposed to be taken, they may lose the benefit of this drug and that we don't have that many drugs left for them.

When patients have been off therapy for a while and you're restarting it, one of the questions [that] comes up is, well, do I just get them back on their maintenance dose or do I need to reload them on the medicine? If they're restarting the drug before their psoriasis really flares up, I think just going back to the maintenance dose is fine. If they've been off the drug so long that their disease is really out of control again, then I think it makes sense to go ahead and give them a loading dose right from the get-go.

Patient Perspective: Selli

Unmet Need

I would say [an unmet need] is making sure that doctors fully understand what a patient is dealing with when it comes to managing psoriasis. Another article that I came across from the University of Pennsylvania, it was published in 2020, surveyed patients with psoriasis, and the stigma that they come across living with psoriasis. A third of those patients preferred to have another stigmatizing disease than psoriasis. And those stigmatizing diseases were obesity, depression, alcoholism, HIV, diabetes, facial disfiguring, and losing a limb. I mean, those are all, as we all know, pretty serious medical conditions. And for a third of those patients to choose one of those disorders, compared to psoriasis, just tells you that, you know, the disorder is it's more than just the skin.

CASE SCENARIO 4: Comorbidities

Case 4 content: A 35-year-old female patient is new to you, having moved into the local area a few months ago. Her medical records are unavailable, but she tells you that she was diagnosed with psoriasis while in her early thirties. She indicates that the only medication she is taking is methotrexate.

She says she has been having frequent psoriasis flares recently, and she has started to have nail involvement. At her visit, she is diagnosed with moderate-to-severe plaque psoriasis (BSA 9%; PASI21).

1. As part of educating the patient, which one of the following potential comorbidities may be important to tell the patient about?

a. Cardiovascular disease

b. Connective tissue disease

c. Thyroid disease

d. Allergic disease

Answer: a. Cardiovascular disease

Rationale:

Moderate-to-severe psoriasis has been associated with multiple comorbidities. Cardiovascular disease (CVD) is one of the most common comorbidities in psoriasis as well as one of the conditions associated with the highest risk of morbidity and mortality. Patients with psoriasis have an average life expectancy that is 6 years shorter than the general population, which has primarily been attributed to the high rate of CVD and other metabolic disorders.[51] As psoriasis severity increases, so too does the risk of CVD.[52] For example, 30-year-old patients with mild psoriasis have an estimated 1.3-fold increased risk for myocardial infarction (MI) relative to the general population, while those with severe psoriasis have about a 3-fold increased risk. Of note, since the baseline risk of a 30-year-old having an MI is quite small, a 3-fold increase results in a small increase in absolute risk.[53] Similarly, patients with psoriasis are also at elevated risk for stroke; the risk of stroke attributable to psoriasis in patients with mild and severe disease was 1 in 4115 and 1 in 530 per year, respectively.[54]

The reason for the elevated risk of CVD among patients with psoriasis is likely multifactorial. Chronic, systemic inflammation has been linked to arteriosclerosis and metabolic abnormalities. Patients with immune diseases, including psoriasis, often have higher rates of cardiovascular risk factors, including obesity, hypertension, dyslipidemia, and type 2 diabetes.[55,56]

According to AAD/NPF guidelines, dermatologists should discuss the risk for CVD with their patients with psoriasis to ensure that they are receiving appropriate monitoring and treatment. Additionally, adequate treatment of psoriasis using biologics—and specifically with TNF inhibitors—may decrease the risk of developing MI by up to 50%,[57] underscoring the role of the dermatologist in maintaining optimal health for their patients.

2. Which one of the following patient characteristics increases her risk of developing psoriatic arthritis?

a. Infrequent psoriasis flares
b. Hypertension
c. Nail involvement
d. Obesity

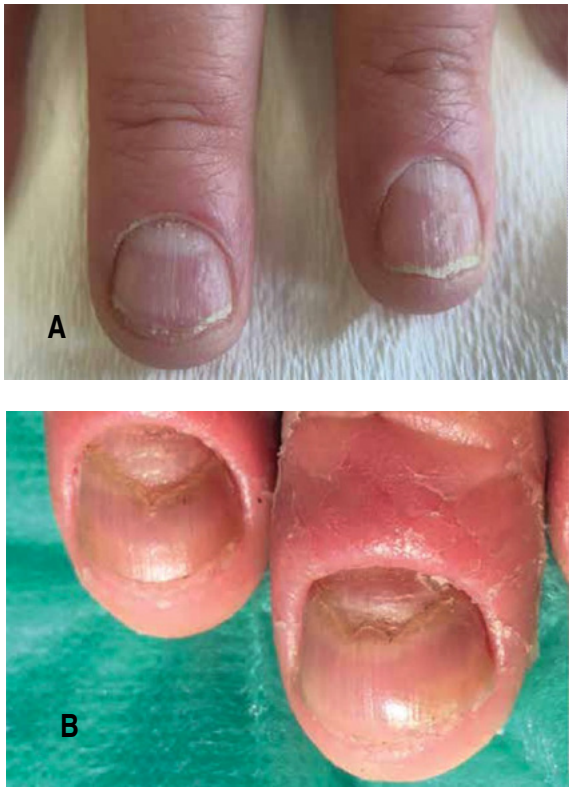
Answer: c. Nail involvement

Rationale:

Psoriatic arthritis (PsA) is an inflammatory arthritis that occurs in about 3% of patients with psoriasis, with higher rates reported in patients with longer durations of skin symptoms.[58,59] Nail lesions have been identified as a risk factor for the development of PsA. While nail changes are reported in about 40% of the general psoriasis population, they occur in up to 90% of patients with PsA.[60,61] The most common nail sign for patients with PsA is pitting (depressions in the nail plate; Figure 1A) followed by onycholysis (separation of the nail plate from the bed; Figure 1B).[60]

The correlation between psoriatic nail changes and PsA has been linked to anatomical relationship between the nail matrix and the distal interphalangeal joint enthesis.[60]

Figure a. Examples of nail pitting (A) and onycholysis leading to complete shedding of the nail (B). Images courtesy of Sobolewski P, Walecka I, Dopytalska K. Nail involvement in psoriatic arthritis. *Reumatologia*. 2017;55(3):131-135. CC BY-NC-SA 4.0.



3. How might joint pain be assessed in this patient?

a. Body Surface Area (BSA)
b. Dermatology Life Quality Index (DLQI)
c. Psoriasis Area Severity Index (PASI)
d. Psoriasis Epidemiology Screening Tool (PEST)

Answer: d. Psoriasis Epidemiology Screening Tool (PEST)

Rationale:

Delayed diagnosis and treatment of PsA can lead to substantial morbidity and irreversible joint damage. As such, patients with psoriasis should be screened for joint pain at every visit.[3] The Psoriasis Epidemiology Screening Tool (PEST) is a validated tool for assessing joint pain in patients. The PEST tool requires the patient to answer 5 yes or no questions and indicate on a diagram which joints have caused them discomfort. A score of 3 or more on the PEST has 92% sensitivity and 78% specificity for diagnosis of PsA.[62]

Other PsA screening tools include the Toronto Psoriatic Arthritis Screen, the Psoriatic Arthritis Screening and Evaluation, and the Early Arthritis for Psoriatic Patients questionnaire, all of which have good reliability and validity.[63]

Case 4 content (continued): The patient says she wants to discontinue methotrexate, as she and her partner are planning to begin trying for their first child soon.

4. Which of the following treatment options would you recommend for this patient?

a. Certolizumab pegol
b. Continuing methotrexate
c. Acitretin
d. Isotretinoin

Answer: a. Certolizumab pegol

Rationale:

According to AAD/NPF guidelines, TNF inhibitors, including certolizumab pegol, are safe in pregnancy and lactation.[18] Previous studies of TNF inhibition during pregnancy have shown no increase in adverse maternal, pregnancy, or neonatal outcomes. In a meta-analysis of patients exposed to TNF inhibitors during pregnancy, the rates of congenital malformations, low birth weight, and preterm birth were similar to those of the general population.[64]

Because anti-TNF antibodies (such as adalimumab and infliximab) can cross the placental barrier, infants exposed in utero should be considered immunosuppressed for the first 3 months of their lives, particularly when exposed in the third trimester of pregnancy. Certolizumab pegol, however, is an exception, as the absence of the Fc binding region of this drug leads to minimal (if any) placental transfer.[18]

Although the most robust evidence regarding psoriasis biologics in pregnancy stems from TNF inhibition, data also suggest that IL-17 inhibition is safe during pregnancy. Safety of IL-23 and IL-12/IL-23 inhibitors during pregnancy is not well characterized.[42]

Methotrexate, acitretin, and isotretinoin are contraindicated in pregnancy due to the risk of potential harms to the fetus. Women of childbearing potential should not initiate any of these drugs unless pregnancy is excluded and contraception is planned during sexual activity.[3,65]

FACULTY DISCUSSION

Psoriasis is more than just a skin disease. It's a systemic immunologic problem and it commonly gets in the joints. And I think it's important for dermatologists to screen patients for psoriatic arthritis because, that way, patients' arthritis can be addressed early and they may not know that their arthritis is coming from their psoriasis. And because psoriatic arthritis can cause permanent deformities, catching it early, getting patients treated, it makes really good sense. So, I like to ask patients pretty much at every visit, are you having any joint pain? Are you having any joint stiffness? Because they may not realize stiffness is arthritis. And are you having any back pain? Because they may not realize their back is full of joints and that the back pain may be a manifestation of psoriatic arthritis.

And then, if I detect any sign of an inflammatory arthritis, I refer to the rheumatologist for further evaluation. Personally, I don't think I meet the standards of a rheumatologist for managing the joints. I asked a rheumatologist, "What physical exam should I do when I see somebody who has possible psoriatic arthritis?" And they said, "Oh, it's easy, Steve, just do a complete musculoskeletal examination including measurement of range of motion, palpation of all the joints and assess their gait." And when they said that, I was like, no, that's okay, I'm just going to refer them to rheumatology to get that evaluation.

There are other comorbidities. Depression is common. Of course, depression's common in all Americans and so if I see a patient who kind of looks like this, paucity of movement, you know, poor eye contact, whether they have psoriasis or not, I want to pursue issues of depression and ask about suicidality. If there's suicidality, then it's emergent to get them seen by a psychiatric professional.

The other area of comorbidity that's really exciting is all the research being done on the cardiovascular manifestations of psoriasis. If you have especially severe psoriasis, that inflammation appears to be predispose you to cardiovascular disease. And if you're between the ages of 20 and 30 and you have severe psoriasis, you're at like 2- to 3-fold increased risk of having a heart attack. Which sounds really bad until you ask yourself, well wait a minute, what's the baseline risk that a 20- to 30-year-old is going to have a heart attack, and it's roughly zero. Two to 3 times that is still roughly zero. So, there is an increased relative risk of cardiovascular disease in young people, but it doesn't amount to much. But it's probably cumulative over time and if you're lucky enough to get to be as old as I am, well then maybe a 20% increased risk of cardiovascular disease is an enormously greater increased risk than that increased risk in a 20- to 30-year-old.

I think it's reasonable to counsel people not to smoke. You know, make sure their blood pressure's okay, keep their weight, you know, within reason, exercise regularly, eat a healthy diet - whether they have psoriasis or not. Do psoriasis patients need special cardiovascular screening? I don't think so, but they need at least the standard recommendations for their age and it may be helpful to make sure they're seeing somebody to get that done.

Patient Perspective: Selli

Patient / Physician Relationship

I would say expressing sympathy and giving hope to your patients goes a long way. Especially your young patients. Build a strong relationship with your chronic patients. I've had the same dermatologist for 18 years, and you know, I'll have him for another 18 years. So, that strong patient physician relationship is probably the biggest support that I've had. I have always looked forward to seeing my dermatologist every 3 to 6 months, only for 15 minutes, but those 15 minutes go a long way, especially when you have a good relationship with your patients.

REFERENCES

1. Rachakonda TD, Schupp CW, Armstrong AW. Psoriasis prevalence among adults in the United States. *J Am Acad Dermatol*. 2014;70(3):512-516. doi:10.1016/j.jaad.2013.11.013
2. Feldman SR, Goffe B, Rice G, et al. The challenge of managing psoriasis: Unmet medical needs and stakeholder perspectives. *Am Health Drug Benefits*. 2016;9(9):504-513.
3. Elmets CA, Korman NJ, Prater EF, et al. Joint AAD-NPF Guidelines of care for the management and treatment of psoriasis with topical therapy and alternative medicine modalities for psoriasis severity measures. *J Am Acad Dermatol*. 2021;84(2):432-470. doi:10.1016/j.jaad.2020.07.087
4. Gisondi P, Talamonti M, Chiricozzi A, et al. Treat-to-target approach for the management of patients with moderate-to-severe plaque psoriasis: Consensus recommendations. *Dermatol Ther (Heidelb)*. 2021;11(1):235-252. doi:10.1007/s13555-020-00475-8
5. Armstrong AW, Siegel MP, Bagel J, et al. From the Medical Board of the National Psoriasis Foundation: Treatment targets for plaque psoriasis. *J Am Acad Dermatol*. 2017;76(2):290-298. doi:10.1016/j.jaad.2016.10.017
6. Mrowietz U, Kragballe K, Reich K, et al. Definition of treatment goals for moderate to severe psoriasis: a European consensus. *Arch Dermatol Res*. 2011;303(1):1-10. doi:10.1007/s00403-010-1080-1
7. Puzenat E, Bronsard V, Prey S, et al. What are the best outcome measures for assessing plaque psoriasis severity? A systematic review of the literature. *J Eur Acad Dermatol Venereol*. 2010;24 Suppl 2:10-16. doi:10.1111/j.1468-3083.2009.03562.x
8. Berth-Jones J, Grotzinger K, Rainville C, et al. A study examining inter- and intrarater reliability of three scales for measuring severity of psoriasis: Psoriasis Area and Severity Index, Physician's Global Assessment and Lattice System Physician's Global Assessment. *Br J Dermatol*. 2006;155(4):707-713. doi:10.1111/j.1365-2133.2006.07389.x
9. Svoboda SA, Ghamrawi RI, Owusu DA, Feldman SR. Treatment goals in psoriasis: Which outcomes matter most? *Am J Clin Dermatol*. 2020;21(4):505-511. doi:10.1007/s40257-020-00521-3
10. Dopytalska K, Sobolewski P, Blaszczak A, Szymanska E, Walecka I. Psoriasis in special localizations. *Reumatologia*. 2018;56(6):392-398. doi:10.5114/reum.2018.80718
11. Bushnell DM, Martin ML, McCarrier K, et al. Validation of the Psoriasis Symptom Inventory (PSI), a patient-reported outcome measure to assess psoriasis symptom severity. *J Dermatolog Treat*. 2013;24(5):356-360. doi:10.3109/09546634.2012.742950
12. Finlay AY, Khan GK. Dermatology Life Quality Index (DLQI)--a simple practical measure for routine clinical use. *Clin Exp Dermatol*. 1994;19(3):210-216. doi:10.1111/j.1365-2230.1994.tb01167.x
13. Karreman MC, Weel A, van der Ven M, et al. Performance of screening tools for psoriatic arthritis: a cross-sectional study in primary care. *Rheumatology (Oxford)*. 2017;56(4):597-602. doi:10.1093/rheumatology/kew410
14. Gottlieb AB, Ford RO, Spellman MC. The efficacy and tolerability of clobetasol propionate foam 0.05% in the treatment of mild to moderate plaque-type psoriasis of nonscalp regions. *J Cutan Med Surg*. 2003;7(3):185-192. doi:10.1007/s10227-002-0114-5
15. Rajabi-Estarabadi A, Hasanzadeh H, Taheri A, Feldman SR, Firooz A. The efficacy of short-term clobetasol lotion in the treatment of scalp psoriasis. *J Dermatol Treat*. 2018;29(2):111-115.
16. Johnson MC, Heron CE, Ghamrawi RI, Balogh EA, Feldman SR. Speed of Psoriasis Treatment Response for Biologic Agents: A Review of Phase III Clinical Trials. *J Psoriasis Psoriatic Arthritis*. 2021;6(2):99-105. doi:10.1177/2475530321999087
17. Strober BE, van der Walt JM, Armstrong AW, et al. Clinical goals and barriers to effective psoriasis care. *Dermatol Ther (Heidelb)*. 2019;9(1):5-18. doi:10.1007/s13555-018-0279-5
18. Menter A, Strober BE, Kaplan DH, et al. Joint AAD-NPF guidelines of care for the management and treatment of psoriasis with biologics. *J Am Acad Dermatol*. 2019;80(4):1029-1072. doi:10.1016/j.jaad.2018.11.057
19. Yamauchi PS, Bissonnette R, Teixeira HD, Valdecantos WC. Systematic review of efficacy of anti-tumor necrosis factor (TNF) therapy in patients with psoriasis previously treated with a different anti-TNF agent. *J Am Acad Dermatol*. 2016;75(3):612-618 e616. doi:10.1016/j.jaad.2016.02.1221
20. Ozkur E, Kivanc Altunay I, Oguz Topal I, et al. Switching biologics in the treatment of psoriasis: A multicenter experience. *Dermatology*. 2021;237(1):22-30. doi:10.1159/000504839
21. Gottlieb AB, Lacour JP, Korman N, et al. Treatment outcomes with ixekizumab in patients with moderate-to-severe psoriasis who have or have not received prior biological therapies: an integrated analysis of two Phase III randomized studies. *J Eur Acad Dermatol Venereol*. 2017;31(4):679-685. doi:10.1111/jdv.13990
22. Blauvelt A, Papp KA, Griffiths CEM, et al. Efficacy and safety of switching to ixekizumab in etanercept non-responders: A subanalysis from two phase III randomized clinical trials in moderate-to-severe plaque psoriasis (UNCOVER-2 and -3). *Am J Clin Dermatol*. 2017;18(2):273-280. doi:10.1007/s40257-016-0246-9
23. Warren RB, Barker J, Finlay AY, et al. Secukinumab for patients failing previous tumour necrosis factor-alpha inhibitor therapy: results of a randomized open-label study (SIGNATURE). *Br J Dermatol*. 2020;183(1):60-70. doi:10.1111/bjd.18623
24. Kerdel F, Zaiac M. An evolution in switching therapy for psoriasis patients who fail to meet treatment goals. *Dermatol Ther*. 2015;28(6):390-403. doi:10.1111/dth.12267
25. Albanesi C. Immunology of Psoriasis. In: Rich RR, Fleisher TA, Shearer WT, Schroeder HW, Frew AJ, Weyand CM, eds. *Clin Immunol*. Elsevier; 2019:871-878.e871. https://www.sciencedirect.com/science/article/pii/B9780702068966000648
26. Singh D, Ravi A, Southworth T. CRTH2 antagonists in asthma: current perspectives. *Clin Pharmacol*. 2017;9:165-173. doi:10.2147/CPAA.S119295
27. Junttila IS. Tuning the cytokine responses: An update on interleukin (IL)-4 and IL-13 receptor complexes. *Front Immunol*. 2018;9(888):888. doi:10.3389/fimmu.2018.00888
28. West EE, Kashyap M, Leonard WJ. TSLP: A Key Regulator of Asthma Pathogenesis. *Drug Discov Today Dis Mech*. 2012;9(3-4):10.1016/j.ddmec.2012.1009.1003. doi:10.1016/j.ddmec.2012.09.003
29. Adams R, Maroof A, Baker T, et al. Bimekizumab, a novel humanized IgG1 antibody that neutralizes both IL-17A and IL-17F. *Front Immunol*. 2020;11(1894):1894. doi:10.3389/fimmu.2020.01894
30. 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. *Lancet*. 2021;397(10273):475-486. doi:10.1016/s0140-6736(21)00126-4
31. Reich K, Warren RB, Lebwohl M, et al. Bimekizumab versus secukinumab in plaque psoriasis. *N Engl J Med*. 2021;385(2):142-152. doi:10.1056/NEJMoa2102383
32. Hot A, Zrioual S, Toh ML, Lenief V, Miossec P. IL-17A- versus IL-17F-induced intracellular signal transduction pathways and modulation by IL-17RA and IL-17RC RNA interference in rheumatoid synoviocytes. *Ann Rheum Dis*. 2011;70(2):341-348. doi:10.1136/ard.2010.132233
33. Johansen C, Usher PA, Kjellerup RB, Lundsgaard D, Iversen L, Kragballe K. Characterization of the interleukin-17 isoforms and receptors in lesional psoriatic skin. *Br J Dermatol*. 2009;160(2):319-324. doi:10.1111/j.1365-2133.2008.08902.x
34. van Baarsen LG, Lebre MC, van der Coelen D, et al. Heterogeneous expression pattern of interleukin 17A (IL-17A), IL-17F and their receptors

in synovium of rheumatoid arthritis, psoriatic arthritis and osteoarthritis: possible explanation for nonresponse to anti-IL-17 therapy? *Arthritis Res Ther*. 2014;16(4):426. doi:10.1186/s13075-014-0426-z

35. Al-Hammadi A, Ruszczak Z, Magarinos G, Chu CY, El Dershaby Y, Tarcha N. Intermittent use of biologic agents for the treatment of psoriasis in adults. *J Eur Acad Dermatol Venereol*. 2021;35(2):360-367. doi:10.1111/jdv.16803
36. Blauvelt A, Leonardi CL, Gooderham M, et al. Efficacy and safety of continuous risankizumab therapy vs treatment withdrawal in patients with moderate to severe plaque psoriasis: A phase 3 randomized clinical trial. *JAMA Dermatol*. 2020;156(6):649-658. doi:10.1001/jamadermatol.2020.0723
37. Gordon KB, Armstrong AW, Foley P, et al. Guselkumab efficacy after withdrawal is associated with suppression of serum IL-23-regulated IL-17 and IL-22 in psoriasis: VOYAGE 2 study. *J Invest Dermatol*. 2019;139(12):2437-2446 e2431. doi:10.1016/j.jid.2019.05.016
38. Umezawa Y, Torisu-Itakura H, Morisaki Y, et al. Long-term efficacy and safety results from an open-label phase III study (UNCOVER-J) in Japanese plaque psoriasis patients: impact of treatment withdrawal and retreatment of ixekizumab. *J Eur Acad Dermatol Venereol*. 2019;33(3):568-576. doi:10.1111/jdv.15292
39. Papp K, Menter A, Leonardi C, et al. Long-term efficacy and safety of brodalumab in psoriasis through 120 weeks and after withdrawal and retreatment: subgroup analysis of a randomized phase III trial (AMAGINE-1). *Br J Dermatol*. 2020;183(6):1037-1048. doi:10.1111/bjd.19132
40. Kim B, Maverakis E, Raychaudhuri SP. Is it possible to discontinue tumor necrosis factor antagonists after psoriasis remission? *Ann Dermatol*. 2019;31(5):495-501. doi:10.5021/ad.2019.31.5.495
41. Warren RB, Marsden A, Tomenson B, et al. Identifying demographic, social and clinical predictors of biologic therapy effectiveness in psoriasis: a multicentre longitudinal cohort study. *Br J Dermatol*. 2019;180(5):1069-1076. doi:10.1111/bjd.16776
42. Menter A, Feldman SR, Weinstein GD, et al. A randomized comparison of continuous vs. intermittent infliximab maintenance regimens over 1 year in the treatment of moderate-to-severe plaque psoriasis. *J Am Acad Dermatol*. 2007;56(1):31 e31-15. doi:10.1016/j.jaad.2006.07.017
43. Blauvelt A, Papp KA, Sofen H, et al. Continuous dosing versus interrupted therapy with ixekizumab: an integrated analysis of two phase 3 trials in psoriasis. *J Eur Acad Dermatol Venereol*. 2017;31(6):1004-1013. doi:10.1111/jdv.14163
44. Secukinumab retreatment shows rapid recapture of treatment response: An analysis of a phase 3 extension trial in psoriasis. *J Am Acad Dermatol*. 2017;76(6):AB232. doi:10.1016/j.jaad.2017.04.900
45. Ortonne JP, Taieb A, Ormerod AD, et al. Patients with moderate-to-severe psoriasis recapture clinical response during re-treatment with etanercept. *Br J Dermatol*. 2009;161(5):1190-1195. doi:10.1111/j.1365-2133.2009.09238.x
46. Leonardi CL, Kimball AB, Papp KA, et al. Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 76-week results from a randomised, double-blind, placebo-controlled trial (PHOENIX 1). *Lancet*. 2008;371(9625):1665-1674. doi:10.1016/S0140-6736(08)60725-4
47. Blauvelt A, Reich K, Tsai TF, et al. Secukinumab is superior to ustekinumab in clearing skin of subjects with moderate-to-severe plaque psoriasis up to 1 year: Results from the CLEAR study. *J Am Acad Dermatol*. 2017;76(1):60-69 e69. doi:10.1016/j.jaad.2016.08.008
48. Puig L, Augustin M, Blauvelt A, et al. Effect of secukinumab on quality of life and psoriasis-related symptoms: A comparative analysis versus ustekinumab from the CLEAR 52-week study. *J Am Acad Dermatol*. 2018;78(4):741-748. doi:10.1016/j.jaad.2017.10.025
49. Warren RB, Hansen JB, Reich K, Paul C, Puig L. Complete clearance and psoriasis area and severity index response for brodalumab and ustekinumab in AMAGINE-2 and -3. *J Eur Acad Dermatol Venereol*. 2021;35(2):450-457. doi:10.1111/jdv.16816
50. Griffiths CE, Reich K, Lebwohl M, et al. Comparison of ixekizumab with etanercept or placebo in moderate-to-severe psoriasis (UNCOVER-2 and UNCOVER-3): results from two phase 3 randomised trials. *Lancet*. 2015;386(9993):541-551. doi:10.1016/S0140-6736(15)60125-8
51. Yamazaki F. Psoriasis: Comorbidities. *J Dermatol*. 2021;48(6):732-740. doi:10.1111/1346-8138.15840
52. Armstrong AW, Schupp C, Bebo B. Psoriasis comorbidities: results from the National Psoriasis Foundation surveys 2003 to 2011. *Dermatology*. 2012;225(2):121-126. doi:10.1159/000342180
53. Gelfand JM, Neimann AL, Shin DB, Wang X, Margolis DJ, Troxel AB. Risk of myocardial infarction in patients with psoriasis. *JAMA*. 2006;296(14):1735-1741. doi:10.1001/jama.296.14.1735
54. Gelfand JM, Dommasch ED, Shin DB, et al. The risk of stroke in patients with psoriasis. *J Invest Dermatol*. 2009;129(10):2411-2418. doi:10.1038/jid.2009.112
55. Grundy SM, Stone NJ, Bailey AL, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol*. 2019;73(24):3168-3209.
56. Elmets CA, Leonardi CL, Davis DMR, et al. Joint AAD-NPF guidelines of care for the management and treatment of psoriasis with awareness and attention to comorbidities. *J Am Acad Dermatol*. 2019;80(4):1073-1113. doi:10.1016/j.jaad.2018.11.058
57. Wu JJ, Poon KY, Channual JC, Shen AY. Association between tumor necrosis factor inhibitor therapy and myocardial infarction risk in patients with psoriasis. *Arch Dermatol*. 2012;148(11):1244-1250. doi:10.1001/archdermatol.2012.2502
58. Christophers E, Barker JN, Griffiths CE, et al. The risk of psoriatic arthritis remains constant following initial diagnosis of psoriasis among patients seen in European dermatology clinics. *J Eur Acad Dermatol Venereol*. 2010;24(5):548-554. doi:10.1111/j.1468-3083.2009.03463.x
59. Ritchlin CT, Colbert RA, Gladman DD. Psoriatic Arthritis. *N Engl J Med*. 2017;376(21):2095-2096. doi:10.1056/NEJMc1704342
60. Sobolewski P, Walecka I, Dopytalska K. Nail involvement in psoriatic arthritis. *Reumatologia*. 2017;55(3):131-135. doi:10.5114/reum.2017.68912
61. Singh JA, Guyatt G, Ogdie A, et al. Special Article: 2018 American College of Rheumatology/National Psoriasis Foundation Guideline for the Treatment of Psoriatic Arthritis. *Arthritis Care Res (Hoboken)*. 2019;71(1):2-29. doi:10.1002/acr.23789
62. Ibrahim GH, Buch MH, Lawson C, Waxman R, Helliwell PS. Evaluation of an existing screening tool for psoriatic arthritis in people with psoriasis and the development of a new instrument: the Psoriasis Epidemiology Screening Tool (PEST) questionnaire. *Clin Exp Rheumatol*. 2009;27(3):469-474.
63. Coates LC, Aslam T, Al Balushi F, et al. Comparison of three screening tools to detect psoriatic arthritis in patients with psoriasis (CONTEST study). *Br J Dermatol*. 2013;168(4):802-807. doi:10.1111/bjd.12190
64. Johansen CB, Jimenez-Solem E, Haerskjold A, Sand FL, Thomsen SF. The use and safety of TNF inhibitors during pregnancy in women with psoriasis: A review. *Int J Mol Sci*. 2018;19(5):1349. doi:10.3390/ijms19051349
65. Methotrexate [package insert]. Accessed July 30, 2021. https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/008085s066lbl.pdf