Navigating a Pathway to Improve Treatment in Psoriasis

Steven R. Feldman, MD, PhD

Overview: Steven Feldman, MD, PhD, discusses some of the recent developments in the management of psoriasis, with a focus on the biologic therapies. He summarizes key points from the American Academy of Dermatology and National Psoriasis Foundation consensus guidelines for managing comorbid conditions, treatment targets, and the clinical application of biologics. Dr. Feldman adds his perspective on how to address patient concerns about the safety of biologic treatments and the increased risk of comorbidities patients with psoriasis may face.

Content Areas

- Comorbidities in patients with psoriasis
- Biologic treatments for psoriasis
- Safety of biologic treatments for psoriasis
- TNFα inhibitors
- IL-17 inhibitors
- IL-23 inhibitors

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Target Audience

The target learning audience is a national audience of dermatologists, dermatology physician assistants, nurse practitioners, and other clinicians who treat patients with moderate-to-severe psoriasis.

Learning Objectives

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

- Describe the most common adverse events associated with biologic treatments for psoriasis
- Select biologic treatments based on patient characteristics and comorbid conditions
- Apply the results of clinical trials, expert recommendations, and consensus guidelines to develop treatment plans

This activity is supported by an educational grant from Lilly. For further information concerning Lilly grant funding visit www.lillygrantoffice.com**.**

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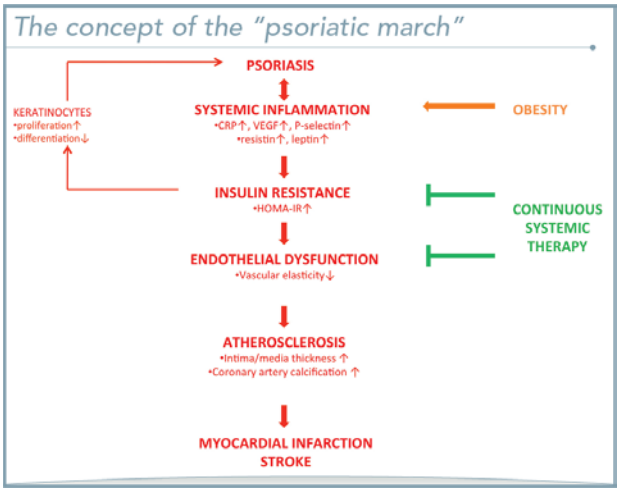
Pathophysiology and Comorbidities

Psoriatic march

The psoriatic march is the hypothesis that ties the inflammatory processes of psoriasis to cardiovascular morbidity.[1,2] Chronic, systemic elevation of inflammatory markers and adipokines (leptin and resistin) promote endothelial cell dysfunction and vascular stiffness. The cytokine and adipokine profile of patients with psoriasis resembles that seen in prediabetic patients, and patients with psoriasis exhibit insulin resistance.[3,4] Obesity also contributes to the proinflammatory state and the psoriatic march.

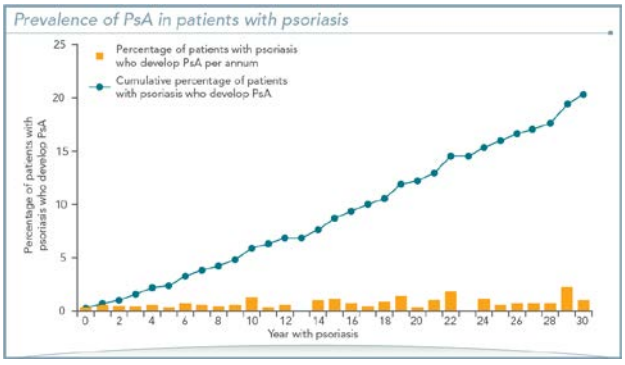


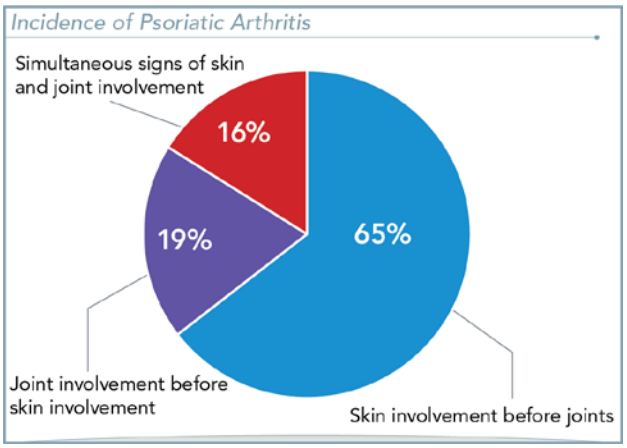
Common comorbidities: 2019 AAD-NPF guidelines

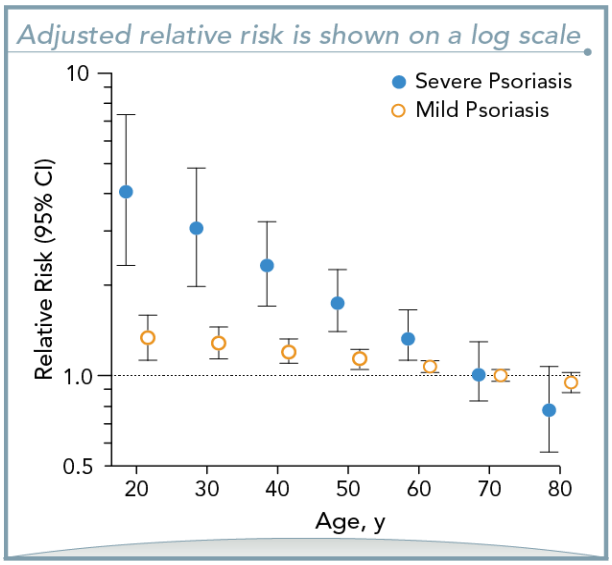
In February 2019, the American Academy of Dermatology and National Psoriasis Foundation published guidelines to address conditions that are associated with psoriasis.[5] The panel that developed these guidelines included not only dermatologists, but also other specialists, and addresses psoriatic arthritis, cardiovascular disease, metabolic syndrome, inflammatory bowel disease, mental health, and substance use. The guidelines can be found at [link], and in this activity we present the highlights of the guidelines for psoriatic arthritis, cardiovascular disease, and metabolic syndrome.

Incidence and timing of psoriatic arthritis

Inflammatory arthritis is a common comorbidity in patients with psoriasis—over the course of the disease, a third or more of patients will develop psoriatic arthritis (PsA), and PsA may go undiagnosed in as many as 15% (left).[6] Dermatologists should discuss the risk of PsA with their patients, and also consistently and regularly screen for signs and symptoms, since early diagnosis and treatment can reduce long-term morbidity.[5] In 73% of cases, cutaneous disease preceded PsA, often by >5 years (right).[7] Screening methods supported by the AAD-NPF include formal screening questionnaires and clinical examination, but both methods carry some caveats.[5] Validated screening tools (eg, the Early Arthritis for Psoriatic Patients questionnaire) are available, but individual tools may suffer from reduced reliability in routine clinical practice. Physical examination for signs of joint inflammation can be useful but can be time-consuming and is dependent on personal experience. Neither laboratory testing for systemic inflammation nor imaging (eg, plain X-rays) are sufficiently sensitive or specific for screening. Patients should report symptoms such as joint stiffness in the morning or swelling, and dermatologists should consider consulting with their rheumatologist colleagues to investigate signs and symptoms of PsA.







Cardiovascular comorbidity

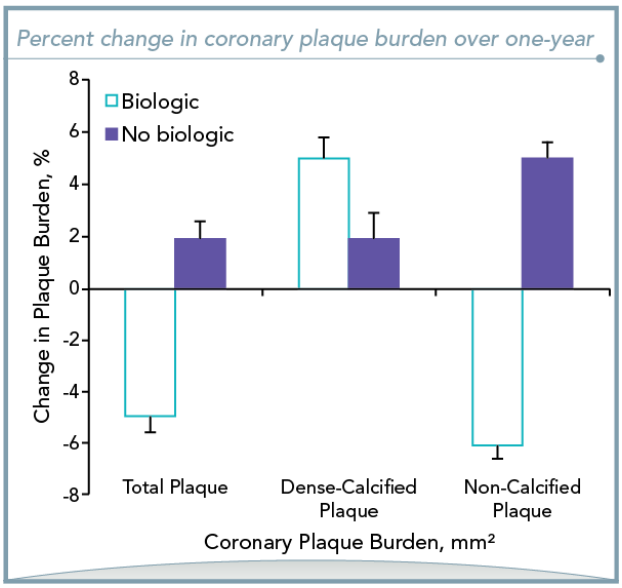
Psoriasis is associated with an increased risk of cardiovascular and cerebrovascular events, and the risk appears to be proportionate to psoriasis symptom severity (left).[8,9] While cardiovascular disease is an important cause of morbidity and mortality, several studies illustrating the relative and absolute risks help put this in perspective. Gelfand and colleagues showed an age- and disease severity-dependent increase in risk for myocardial infarction (left) and stroke. In a 50-60-year-old patient with severe psoriasis, a relative risk of 1.36 translates to 1 additional event per year in 430 patients (right).[10] The AAD-NPF guidelines emphasize patient education and engagement with primary care providers to ensure that the patient is receiving appropriate cardiovascular screening.[5] In addition, cardiovascular risk models have been developed that adjust risk for patients with chronic inflammatory disorders.[11,12]

Comorbidity	Psoriasis Severity	Relative Risk (95% CI)	NNTH
Ischemic Stroke	Mild	1.25 (1.17-1.34)	1320
	Severe	1.65 (1.33-2.05)	508
MI (Age 50-60)	Mild	1.08 (1.03-1.13)	2146
	Severe	1.36 (1.13-1.64)	430
MI (Age 30-40)	Mild	1.29 (1.14-1.46)	9346
	Severe	3.10 (1.98-4.86)	1385

Cardioprotective effect of psoriasis treatment

Biologic treatment may be protective against cardiovascular events. In a study by Wu et al, patients who only had received topical therapy had an incidence of myocardial infarction of 6.73 cases per 1000 patient years; those receiving either a TNFα inhibitor, an oral systemic therapy, or phototherapy had a risk of 3.05-3.85 cases per 1000 patient years.[13] In a follow-up study, the effect of TNFα inhibitors appeared to be greater than for methotrexate (left).[14] Patients treated with a biologic therapy had improvements in coronary artery disease processes associated with

inflammation (specifically the formation of lipid-rich, noncalcified plaque and plaque necrosis) when compared to patients who were treated with topical therapy or phototherapy (center, right). [15] When compared to baseline measurements, patients treated with a biologic had a 6% decrease (*P*=0.005) in noncalcified plaque, while patients who did not receive a biologic had a 5% increase (not significant); the necrotic burden was reduced by 57% (*P*=0.03) in the group treated with a biologic, compared to a 33% increase (not significant) in the reference group (not shown).



Metabolic syndrome

Metabolic syndrome and its constituent disorders (obesity, hypertension, hyperlipidemia, and diabetes) are associated with psoriasis, and should be of concern given its association with cardiovascular disease, fatty liver disease, and other causes of mortality.[5,16] The AAD-NPF recommends education, screening, and monitoring of comorbid metabolic disease, either by the patient's dermatologist or in coordination with their primary care provider.[5] National guidelines such as the NCEP ATP III criteria for monitoring blood pressure, waist circumference, fasting blood glucose and/or hemoglobin A1C, and fasting lipid levels should be used.[17]

Diabetes. Psoriasis and diabetes are linked, with risk being proportionate to psoriasis severity.[18] The AAD-NPF recommends that providers consider periodic laboratory testing and screening for insulin resistance and diabetes, using established national guidelines (eg, the American Diabetes Association), and that prediabetes or newly-diagnosed diabetes be managed by the patient's primary care provider or a specialist.[5,19]

Obesity. The basis for the association between obesity and psoriasis is not known, but may be linked to the increased expression of proinflammatory cytokines and adiponectin. In particular, adipose tissue is a source for TNFα. Screening for obesity in patients with moderate-to-severe psoriasis should be done annually, and include height, weight, waist circumference, and BMI.[5]

Hypertension. The relationship between psoriasis and hypertension or hyperlipidemia is less-well understood and has not been conclusively demonstrated in studies.[5,20] The AAD-NPF recognizes a possible link, and therefore does not recommend avoiding managing of hypertension with antihypertensive medications (eg, β-blockers or calcium channel blockers); they also caution against the use of immunomodulators such as cyclosporine that can worsen existing or induce hypertension. Likewise, serum lipid levels can be affected by acitretin and cyclosporine; in these cases, serum lipids should be monitored routinely during treatment with these agents, especially when initiating treatment or during dose increases.[5]

Treatment Strategies

Treating to target: Summary of National Psoriasis Foundation consensus targets for plaque psoriasis

The National Psoriasis Foundation has developed recommendations for treatment targets during the initiation and maintenance phases of treatment; in addition, they also defined an acceptable response during the initiation phase as "an adequate or sufficient level of response to treatment."[21] During the initiation phase, the NPF concluded that the initial assessment of a treatment's efficacy should be performed 3 months after treatment initiation, and then every 6 months thereafter. Although BSA is a clinically-practical measure, as the sole measure of a therapy's utility BSA falls short since it does not account for quality-of-life, cost, side effects, or the location of lesions, and even patients who are not meeting the targets can benefit from treatment.[22]

Initiation Phase	
Acceptable response*	BSA ≤3% OR BSA improvement ≥75% from baseline at 3 months after treatment initiation
Target response*	BSA ≤1% at 3 months after treatment initiation
Maintenance Phase	
Target response	BSA ≤1% at every 6-month assessment intervals during maintenance therapy

*An acceptable response is considered an adequate or sufficient level of response to treatment; a target response is defined as a goal toward which clinicians and patients could strive.

Monitoring for inflammatory bowel disease during IL-17 inhibitor treatment

Patients with a history of IBD treated with an IL-17 inhibitor for psoriasis have a risk for reactivation or worsening of inflammatory bowel disease (IBD).[23,24] The AAD-NPF recommends avoiding IL-17 inhibitors in these patients to reduce the risk of IBD flares, even though this was an uncommon occurrence in clinical trials.[23] In a review of 7 ixekizumab trials (N=4209) that enrolled patients with moderate-to-severe psoriasis, 10 cases of probable and 9 cases of definite IBD or Crohn's disease (CD) were reported.[24] Of the patients with a history of IBD, no treatment-emergent adverse events or serious adverse events related to IBD were reported by the majority of patients (12 of 16). We have to ask whether we think the glass is half full (12 out of 16 patients were fine …) or is it half empty (but 4 of them had an exacerbation)?

The authors conclude that new cases of IBD or CD during ixekizumab treatment occur in fewer than 1% of patients, and that flares during treatment are also uncommon. Similar conclusions were drawn after a retrospective analysis of the secukinumab trials.[25] Of note, secukinumab and brodalumab were tested as potential therapies for IBD, and in both cases there was either no observed treatment effect or disease worsening.[26,27]

Monitoring for gastrointestinal AEs during apremilast treatment

Diarrhea is the most commonly reported adverse event during treatment with apremilast. In a review, 1905 patients treated for psoriasis or psoriatic arthritis in phase 3 trials, the incidence of diarrhea was 9-10 per 100 person-years.

Rule Out Red Flags
- Fever (temperature ≥38°C)
- Blood or mucous in stool
- Moderate-severe dehydration
- Recent hospitalization, antibiotics, foreign travel

First-line Intervention (non-pharmacologic)
- Hydration
- Small, frequent meals
- Recommend avoiding dairy, caffeine, artificial sweeteners

Second-line Intervention (over-the-counter therapies)
- Fiber supplementation (ie, psyllium 10-20 g/d)* and/or
- Bismuth subsalicylate 525 mg QID** or
- Loperamide 2-4 mg QID (max 16 mg/d)†

Third-line Intervention (prescription therapies)
- Refer to gastroenterology for consideration of alternative approach to treatment

Fourth-line Intervention
- Adjust apremilast dose or discontinue

*Should not be taken within 2 hours of medication
** Should not be taken within 2 hours of medication; not to be taken with aspirin or other salicylates; exercise caution in patients with blood-clotting disorders, gout, or diabetes or those taking anticoagulants.
† Exercise caution in patients with liver disease

In general, symptoms were mild to moderate and began within the first 2 weeks of treatment; in most cases, diarrhea self-resolved within 1 month without a change in apremilast dose or other medical intervention. The table shows the recommendations for managing diarrhea. Initiating treatment with a slow ramp-up phase has been used to minimize GI tolerability issues.

Autoimmune conditions and infection during TNFα inhibitor treatment

What is the risk of multiple sclerosis during treatment with a TNFα inhibitor? Cases of central nervous system (CNS) demyelination have been reported in the post-marketing surveillance of the TNFα antagonists, leading to the concern that TNFα treatment can act as a trigger for multiple sclerosis (MS).[28-30] The clinical development of lenercept (a soluble TNF receptor 1 protein) to treat MS contributed to these concerns: there was a dose-related increase in annual MS relapse rate in patients treated with lenercept.[31] While the TNFα antagonists do appear to be associated with an increased risk for MS, this is such an uncommon event that it may be of little real concern.

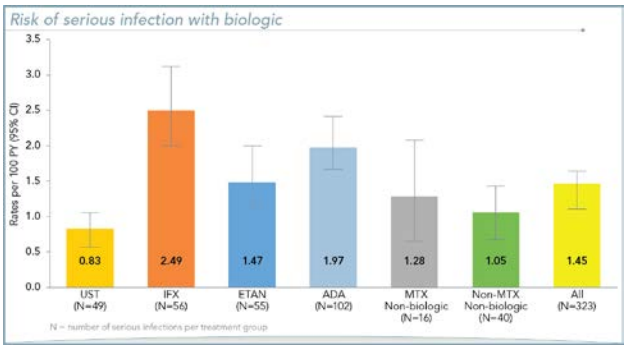
How common is drug-induced lupus erythematosus (DILE)? Antinuclear antibodies (ANA) and anti-double stranded DNA antibodies are a relatively common but typically clinically silent phenomenon during TNFα antagonist treatment.[32,33] Generally, the incidence of DILE with TNFα antagonists is considered low—approximately 2 per 1000 in one study—asymptomatic, and in most cases resolves after discontinuing treatment.[34,35]

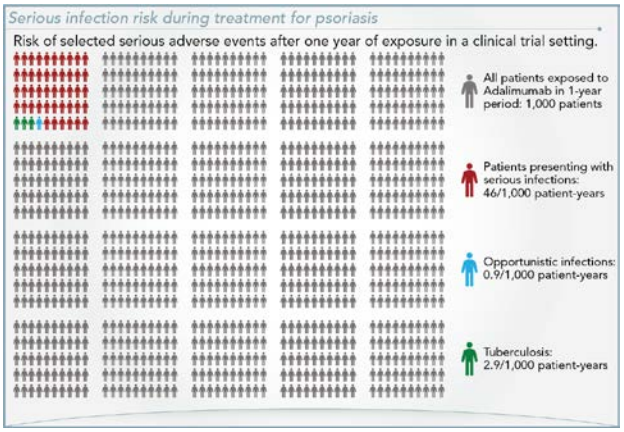
Does anti-TNFα treatment cause psoriasis in patients treated for inflammatory bowel disease (IBD), Crohn's disease (CD), or ulcerative colitis (UC)? There is an increased risk of psoriasis in patients with IBD treated with any of the TNFα antagonists (OR 1.8 compared to the general population).[36] The incidence of psoriasis during TNFα treatment to be about 1.6%.[37,38] This paradox poses a problem given the effectiveness of TNFα antagonists for IBD. If this side effect is encountered, topical treatment can be the first line for mild-to-moderate cases, and continued TNFα antagonist treatment is often possible.

Serious infection risk during treatment for psoriasis

What do I tell patients about the risk of infections with psoriasis? Some patients may be concerned about infection risk during treatment with biologics. Serious opportunistic infections are rarely seen with IL-12/IL-23 inhibitors, but IL-17 inhibitors may increase the risk of infection (particularly *Candida* infections).[23] Kalb et al also estimated the cumulative risk of serious infection for the TNFα antagonists to be between 1.47 and 2.49 per 100 patient-years (left).[39] In most cases, combination of a biologic with methotrexate can increase the risk of infection.[23] However, the

overall risk of infection with any of the treatments remains low, and when communicating this risk to patients, it may help to put this risk into perspective using a graphic representation or by relating the risk to benchmarks. Alternatively, present the chance of not getting an infection—99 out of a 100—rather than the 1 in 100 chance of getting an infection.



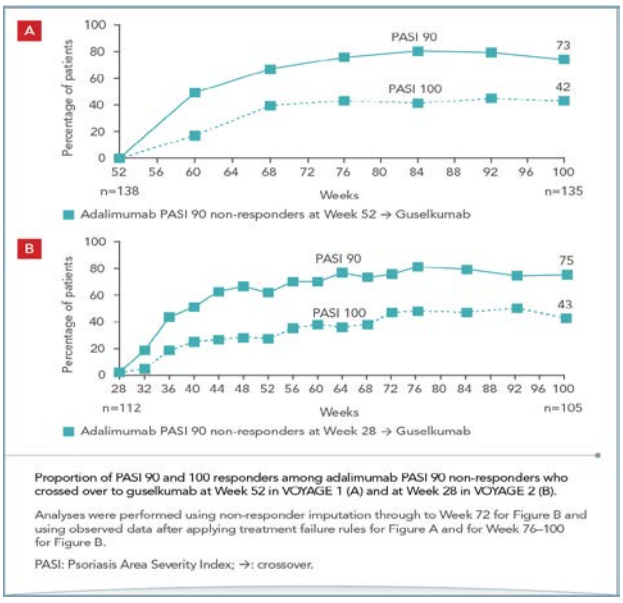


Switching to guselkumab after adalimumab treatment: VOYAGE trial pooled analysis

Little guidance is available for cases where a patient needs to be switched from one biologic treatment to another.[40,41] In the VOYAGE 1 and 2 trials, the response to guselkumab was evaluated in a subset of patients who had not responded to adalimumab.[42] These patients (n=138 in VOYAGE 1 and n=112 in VOYAGE 2) were initially randomized to adalimumab in one of the VOYAGE trials, but did not achieve a PASI 90 complete response at the conclusion of the initial treatment phase of the trial (either week 52 or week 28). Switching to guselkumab led to PASI 90 responses in over 70% of patients, and PASI 100 responses in over 40%, after 1-1.5 years of switching treatments.

Switching to guselkumab after ustekinumab treatment: results from the NAVIGATE study

An analysis similar to that done in the VOYAGE trial was done for patients who did not have an adequate response (in this case, improvement in the Investigator's Global Assessment) after 16 weeks of treatment with ustekinumab.[43] This subset of patients (n=268) was randomized to continued ustekinumab treatment or crossover to guselkumab. Although patients who remained on ustekinumab continued to improve, patients who were switched to guselkumab had better outcomes during weeks 28 through 52 of the study, including a greater proportion of patients who achieved PASI 90 or PASI 100. These studies provide a model for dermatologists to consider when faced with a patient who has not achieved an acceptable response to one biologic and is considering whether to switch treatments, and emphasize that an unacceptable response to one treatment does not necessarily predict the response to subsequent treatments.

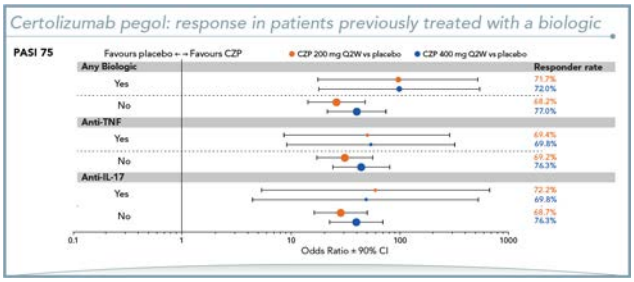


Advances in Treatment—Current and Emerging Disease Pathway Targets

TNFα Inhibitors

Certolizumab pegol: response in patients previously treated with a biologic

Certolizumab pegol is an anti-TNFα Fab monoclonal antibody fragment attached to polyethylene glycol approved for treating moderate-to-severe plaque psoriasis and psoriatic arthritis. The structure of certolizumab pegol is thought to offer reduced immunogenicity, increased half-life, and a more favorable safety profile for pregnant women (since it is not transferred across the placental boundary) than monoclonal antibodies.[44,45] A pooled analysis of ongoing phase 3 trials demonstrated that certolizumab pegol at a dose of 200 mg or 400 mg every 2 weeks induced PASI 75 responses in 75%-80% of patients (compared to 7.5 in patients who received placebo; *P*<0.0001).[46] Responses also appeared to be independent of prior biologic therapy, suggesting that certolizumab pegol may be an option for patients who have not responded to other treatments.



Apremilast: Efficacy in scalp psoriasis

Scalp psoriasis is a common and bothersome complication for many patients, and although scalp psoriasis can respond well to topical treatments, adherence and access to the affected sites can limit their efficacy.[47] Improving adherence to a super-potent topical can be a highly effective way to treat "resistant" scalp psoriasis The biologics are another effective way for treating scalp psoriasis, but few studies have prospectively considered patients in which scalp psoriasis is their primary complaint.[47-51]

In October 2018, results from the STYLE study assessed how often apremilast treatment led to complete or almost-complete resolution with 16 weeks of treatment.[52] Apremilast is a phosphodiesterase 4 inhibitor that acts as an immunomodulator by suppressing production of TNFα and other inflammatory cytokines.[53,54] The STYLE study randomized 303 patients with moderate-to-severe psoriasis of the scalp to either placebo or treatment with apremilast for 16 weeks, after which all patients were treated with apremilast for a total of 32 weeks. Patients responding to treatment achieved either clear or almost clear skin on the scalp, and had at least a 2-point reduction from baseline on the scalp Physician Global Assessment (ScPGA). Compared to placebo, significantly more patients treated with apremilast responded to treatment (43% vs 14%). Patients treated with apremilast also saw improvements in scalp and whole-body itch, and began experiencing improvements in symptoms within 2-4 weeks of starting treatment.

IL-17 Pathway Inhibitors

Secukinumab: Label update to include scalp psoriasis

Secukinumab has been studied specifically in patients with scalp psoriasis, and the label was updated in February 2018 to expand its approved uses to include moderate-to-severe scalp psoriasis, in addition to plaque psoriasis and psoriatic arthritis.[55] This difficult-to-treat manifestation of psoriasis has not been as well studied as plaque psoriasis, and treatment with topical agents or phototherapy can be difficult.[47]

Secukinumab is a human monoclonal antibody to IL-17A and was the first approved treatment to target this pathway. The most recent approval was based on a randomized, double-blind study of patients (N=102) with moderate-to-severe scalp psoriasis (involvement of ≥30% of the scalp surface area), with or without concurrent plaque psoriasis on the rest of the body.[48,55] Patients received either placebo or treatment with secukinumab for 12

weeks; at the conclusion of this first randomized period, patients in the placebo group who did not have ≥90% clearing of scalp symptoms (assessed on the Psoriasis Scalp Severity Index, PSSI) entered a second randomization for an additional 12-week period. At the end of the 12-week initial treatment period, 53% of patients in the secukinumab group had a PSSI 90 response, compared to 2% in the placebo group (*P*<0.001); in addition, 35% had complete clearing (PSSI 100) when treated with secukinumab, while none of the patients in the placebo group achieved this response (*P*<0.001). Responses occurred as early as 3 weeks after treatment, and by the end of the 24-week period, 59% of patients had a PSSI 90 response.

Ixekizumab: Genital psoriasis indication approval

Genital psoriasis is experienced by a third or more patients with psoriasis, and more commonly affects men.[56] However, genital psoriasis often goes untreated for a number of reasons—in some cases simply because no treatment is offered when patients do discuss their symptoms with their doctor.[47,57] As with scalp psoriasis, there are few studies that would provide an evidence-based approach, and literature reports focus on topical steroids, vitamin D analogs, calcineurin inhibitors, and retinoids or retinoid analogs.[47,58]

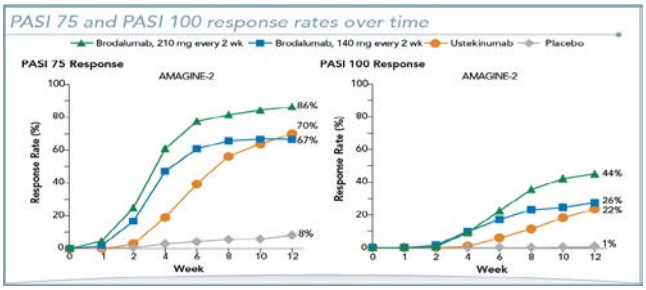
In June 2018, the FDA expanded the label for ixekizumab to include genital psoriasis, in addition to the previously-approved indications for plaque psoriasis and psoriatic arthritis.[59,60] Patients in this trial (N=149) had already failed to respond or did not tolerate at least one prior topical treatment for genital psoriasis. After 12 weeks, patients treated with ixekizumab had a significant improvement in their symptoms (using the static Physician Global Assessment genital symptom scale) compared to patients in the placebo group: 73% had clear or almost-clear skin in the ixekizumab group, compared to 8% of those who received a placebo (*P*<0.001). Responses were evident within a week of starting treatment.

Recent head-to-head trials

Head-to-head trials offer some insight to differences in the time-to-onset and long-term efficacy for the different treatment classes. In August of 2019, the initial results of a head-to-head study were released that suggest a difference in treatment effect for ixekizumab compared to guselkumab.[61] Although the full data release is not expected until 2020, the preliminary report was that more patients attained a PASI 100 response after 12 weeks of treatment with ixekizumab than with guselkumab. In a 48-week study that compared guselkumab and secukinumab about 80% of patients had at least a PASI 75 response after 12 or 48 weeks of treatment; by the end of the study more patients treated with guselkumab had a PASI 90 response (84%, vs 70% for secukinumab, *P*<0.0001).[62]

Brodalumab: Efficacy compared to ustekinumab and placebo

With its approval in February 2017, brodalumab became the third treatment to target the IL-17 pathway; rather than binding IL-17 directly, brodalumab binds the IL-17 receptor thereby interfering with the receptor-ligand interaction.[63] In addition to a phase 3 placebo-controlled trial, brodalumab was compared to ustekinumab in 2 placebo-controlled, randomized trials which also assessed 2 brodalumab doses. The PASI 75 and PASI 100 results are shown above for the AMAGINE-2 trial, but the results were similar for the second of these studies (AMAGINE-3).



Brodalumab: REMS program for suicidal ideation and behavior

The clinical development of brodalumab was initially halted due to several patient suicides during trials for psoriasis, rheumatoid arthritis, and psoriatic arthritis.[63,64] This led the FDA to later add a black box warning and implement a Risk Evaluation and Mitigation Strategy (REMS) after the approval of brodalumab.

Prescribers must be certified with the program and counsel patients about this risk. Patients with new or worsening symptoms of depression or suicidality should be referred to a mental health professional, as appropriate.

Patients must sign a Patient-Prescriber Agreement Form and be made aware of the need to seek medical attention should they experience new or worsening suicidal thoughts or behavior, feelings of depression, anxiety or other mood changes.

Pharmacies must be certified with the program and must only dispense to patients who are authorized to receive brodalumab.

In the psoriasis trials, the patients who completed a suicide attempt were treated with brodalumab during the long-term follow-up phase of the study, and an analysis of their histories suggested that their deaths may not have been related to brodalumab treatment.[63,65]

L-23 Pathway Inhibitors
Guselkumab: 3-year follow-up from VOYAGE-1

Guselkumab was approved in July 2017 for moderate-to-severe plaque psoriasis and is the first of this class to be approved. This agent is a human IgG to IL-23, and has been evaluated in 3 phase 3 trials that included placebo and active-comparator arms.[43,66,67] In the VOYAGE-1 trial, patients were randomized to placebo or treatment with guselkumab or adalimumab; patients in the placebo group crossed over to guselkumab by week 16 of the study, and patients receiving adalimumab switched to guselkumab by week 52. In an open-label long-term follow-up (week 156) of VOYAGE-1, the PASI 75 for patients initially randomized to guselkumab or placebo was 96%, with 83% achieving a PASI 90.[68,69]

Tildrakizumab: ReSURFACE pivotal trials

Tildrakizumab is a humanized anti-IL-23 monoclonal antibody that was approved for plaque psoriasis in March 2018.[70] The reSURFACE 1 (N=772) and reSURFACE 2 (N=1090) trials evaluated tildrakizumab at one of 2 doses vs either placebo and/or etanercept (reSURFACE 2).[71] In the active comparator trial, patients were initially randomized to 12 weeks of either treatment with tildrakizumab (100 mg or 200 mg) or etanercept, or placebo. After this period, patients in the placebo group were re-randomized to treatment with one of the 2 doses of tildrakizumab. Finally, after 28 weeks, patients responding to tildrakizumab were re-randomized to tildrakizumab treatment or placebo, and patients who did not have a complete response to etanercept were crossed-over to the highest dose of tildrakizumab (200 mg). Significantly more patients in either tildrakizumab group achieved the co-primary endpoints of PASI 75 or “clear” or “minimal” symptoms (on the Physician Global Assessment) compared to placebo or etanercept during the 12-week treatment phase (Table). In a recently published study, patients who were responders to tildrakizumab at week 28 continued treatment or were switched from etanercept to tildrakizumab continued treatment for 148 weeks.[72] Tildrakizumab responders continued to benefit, and 67% of patients switched from etanercept achieved a PASI 75 response. When considering PASI 90 responses, tildrakizumab may not be as effective as other IL-23 inhibitors, but patients still see quality of life improvements.

Risankizumab: Pivotal trials key findings

Risankizumab, which is also a humanized IgG monoclonal antibody to IL-23, was approved in April 2019. Approval was based on the results after 16 weeks of treatment, in which PASI 90 responses were significantly greater with risankizumab compared to placebo (75%, vs ≤5%, P<0.001). [73,74]

At one year, >80% of patients treated with risankizumab had a PASI 90 response. In addition, phase 3 trials compared risankizumab to ustekinumab and adalimumab.[74] When compared to ustekinumab, risankizumab-treated patients were more likely to attain a PASI 90 response (75%, compared to ≤48%, *P*<0.001) after 16 weeks of treatment. Likewise, 72% of patients treated with risankizumab and 47% of patients who received adalimumab in the IMMvent trial attained a PASI 90 response (*P*<0.0001).[75] Intermediate responders to adalimumab who switched to risankizumab were also more likely to meet the PASI 90 endpoint after 44 weeks of treatment than patients who continued adalimumab (66%, vs 21%, *P*<0.0001).

Tildrakizumab	100 mg	200 mg	Etanercept	Placebo
PASI 75 in reSURFACE 2	66%**,†	61%**,†	48%	6.0%

**P<0.001 vs both tildrakizumab groups vs placebo; †P<0.05 for both tildrakizumab groups vs etanercept

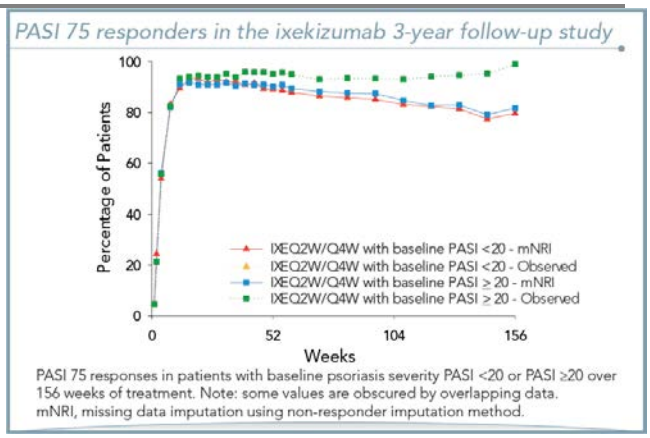
	Tildrakizumab 100 mg	Tildrakizumab 200 mg
PASI 75 in reSURFACE 1	62%*	64%*

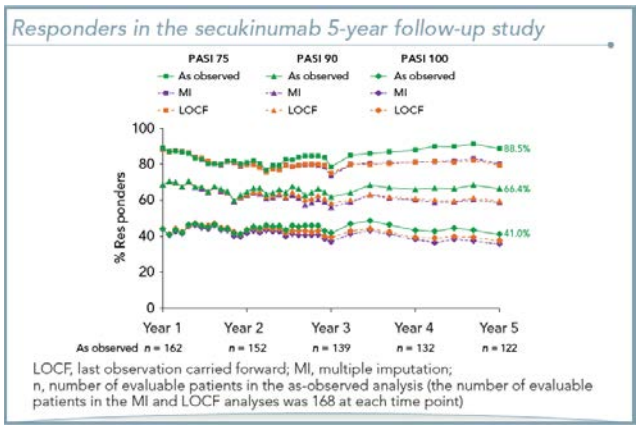
*P<0.001 vs either tildrakizumab group vs placebo

Implications for Patient Care

IL-17 inhibitor long-term efficacy data

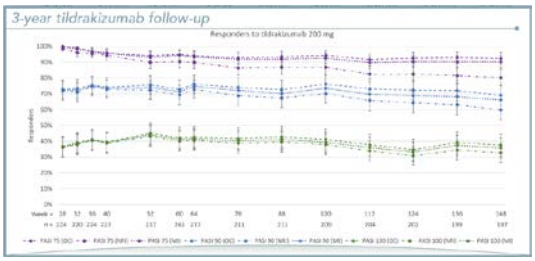
In an abstract from the 2019 American Academy of Dermatology Annual Meeting, 4-year follow-up data for the ixekizumab open-label follow-up study were presented.[76] These findings support previously-published data from the analysis of the 3-year follow-up data (left): 83% of patients attained a PASI 75 response during the study, and 69% and 49% achieved PASI 90 and PASI 100 responses, respectively. Similar data has been published for another IL-17 inhibitor, secukinumab (right).[77] Another way of assessing a treatment's long-term effectiveness is by considering how many patients continue treatment—the "happy drug" survival.[78] In the ixekizumab study, 986 of 1346 patients (73%) completed 4 years of follow-up, and in the secukinumab study, 126 of the 168 patients (75%) enrolled to the follow-up study completed 5 years of treatment.[76,77]





3-year tildrakizumab follow-up

A 148-week follow-up study for tildrakizumab suggested that responses were maintained during this period at both 100 mg and 200 mg (shown) doses, and for patients who were partial responders to tildrakizumab or nonresponders to etanercept.[72] In this study, 197 patients of the 224 (88%) who entered the follow-up phase completed the 148-week study.



Optimizing treatment: managing comorbid psoriatic arthritis

The AAD-NPF guidelines recommend a TNFα inhibitor for patients with concomitant psoriasis and psoriatic arthritis.[23] Both ixekizumab and secukinumab also can be considered as monotherapies for these patients.[23] Although ustekinumab can be considered as a monotherapy in patients with comorbid psoriatic arthritis, it is not approved for the prevention of joint destruction and is considered less effective than the TNFα inhibitors.[23] However, ustekinumab did prevent joint progression in one study and part of the perception of lower efficacy may be due to having been tested in patients who had failed TNFα inhibitors. Newer IL-23 blocking agents are likely to also improve psoriatic arthritis. As far as guideline recommendations for dermatologists, the AAD-NPF considers dermatologists to have a crucial role in early recognition of psoriatic arthritis through screening and patient education.[5] It may be prudent to consult a rheumatologist for patients who have signs or symptoms of psoriatic arthritis.

Approved Psoriasis Treatment	ACR20 in PsA	Approved for Psoriatic Arthritis
TNFα inhibitors		
Adalimumab[1]	57%[a]	Yes
Apremilast	38%[a]	Yes
Certolizumab[1]	64%[a]	Yes
Etanercept[1]	59%[b]	Yes
Infliximab[1]	54%[a]	Yes
IL-17 inhibitors		
Ixekizumab[3]	58-62%[a]	Yes
Secukinumab[1]	51%[a]	Yes
Brodalumab[4]	37-39%[b]	No
IL-23 inhibitors		
Ustekinumab[1]	42%[a]	Yes
Guselkumab[5]	58%[a]	No
Tildrakizumab	N/A	No
Risankizumab	N/A	No
[a]ACR20 at week 24; [b]ACR20 at week 12		
[1]Reviewed in D'Angelo et al, 2017; [2]Kavanaugh et al, 2015; [3]Mease et al, 2017; [4]Mease et al, 2014; [5]Deodhar et al, 2018		

[references for table][79-82]

Optimizing treatment: dose modification in obese patients

Patients who are overweight or obese may not respond to standard doses or dosing regimens.[23] Patients treated with a TNFα inhibitor may require either a shorter dose interval or dosing above the approved dose, and infliximab dosing is weight-based.[23] Ustekinumab is also used with weight

based dosing; patients >100kg do better on the 90 mg dose.[23,83] In one trial, higher body weight patients (≥90 kg) had a higher PASI 90 response when treated with every-other-week secukinumab than with an every-4-weeks regimen, although the difference was not significant.[84] While the possibility for dose modification is considered in the AAD-NPF guidelines, the authors also emphasize that lower doses may be equally effective and better tolerated.[23]

Concluding thoughts on the biologics for treating psoriasis

Offer a biologic treatment to patients who you think need them. In addition to discussing the options, give patients written information—the National Psoriasis Foundation publishes a patient-information overview of the biologics and oral treatments [link] https://www.psoriasis.org/sites/default/files/systemic_treatments_-_biologics_and_oral_tx.pdf[link], fact sheets on the biologics [link] https://www.psoriasis.org/about-psoriasis/treatments/biologics/resources[link], and a comparison chart [link] https://www.psoriasis.org/sites/default/files/treatment_comparison_chart_2018.pdf[link]. When it comes to addressing patient concerns about safety and comorbidities, put these risks in perspective by discussing not only the relative risk but the absolute risk. Likewise, when it comes to relative efficacy of the treatments, while there may be statistically-significant differences, in some cases the differences might have little clinical impact.

References

1. Boehncke WH. Systemic inflammation and cardiovascular comorbidity in psoriasis patients: Causes and consequences. *Front Immunol.* 2018;9:579.
2. Reich K. The concept of psoriasis as a systemic inflammation: implications for disease management. *J Eur Acad Dermatol Venereol.* 2012;26 Suppl 2:3-11.
3. Boehncke S, Thaci D, Beschmann H, et al. Psoriasis patients show signs of insulin resistance. *Br J Dermatol.* 2007;157(6):1249-1251.
4. Ucak S, Ekmekci TR, Basat O, Koslu A, Altuntas Y. Comparison of various insulin sensitivity indices in psoriatic patients and their relationship with type of psoriasis. *J Eur Acad Dermatol Venereol.* 2006;20(5):517-522.
5. 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.
6. 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.
7. Torre Alonso JC, Rodriguez Perez A, Arribas Castrillo JM, Ballina Garcia J, Riestra Noriega JL, Lopez Larrea C. Psoriatic arthritis (PA): a clinical, immunological and radiological study of 180 patients. *Br J Rheumatol.* 1991;30(4):245-250.
8. 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.
9. Gelfand JM, Dommasch ED, Shin DB, et al. The risk of stroke in patients with psoriasis. *J Invest Dermatol.* 2009;129(10):2411-2418.
10. Saleem MD, Kesty C, Feldman SR. Relative versus absolute risk of comorbidities in patients with psoriasis. *J Am Acad Dermatol.* 2017;76(3):531-537.
11. Mehta NN, Yu Y, Pinnelas R, et al. Attributable risk estimate of severe psoriasis on major cardiovascular events. *Am J Med.* 2011;124(8):775 e771-776.
12. Ogdie A, Yu Y, Haynes K, et al. Risk of major cardiovascular events in patients with psoriatic arthritis, psoriasis and rheumatoid arthritis: a population-based cohort study. *Ann Rheum Dis.* 2015;74(2):326-332.
13. Wu JJ, Poon KY. Tumor necrosis factor inhibitor therapy and myocardial infarction risk in patients with psoriasis, psoriatic arthritis, or both. *J Drugs Dermatol.* 2014;13(8):932-934.
14. Wu JJ, Guerin A, Sundaram M, Dea K, Cloutier M, Mulani P. Cardiovascular event risk assessment in psoriasis patients treated with tumor necrosis factor-alpha inhibitors versus methotrexate. *J Am Acad Dermatol.* 2017;76(1):81-90.
15. Elnabawi YA, Dey AK, Goyal A, et al. Coronary artery plaque characteristics and treatment with biologic therapy in severe psoriasis: results from a prospective observational study. *Cardiovasc Res.* 2019;115(4):721-728.
16. Gami AS, Witt BJ, Howard DE, et al. Metabolic syndrome and risk of incident cardiovascular events and death: a systematic review and meta-analysis of longitudinal studies. *J Am Coll Cardiol.* 2007;49(4):403-414.
17. Grundy SM, Cleeman JI, Daniels SR, et al. Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement: Executive Summary. *Crit Pathw Cardiol.* 2005;4(4):198-203.
18. Armstrong AW, Harskamp CT, Armstrong EJ. Psoriasis and the risk of diabetes mellitus: a systematic review and meta-analysis. *JAMA Dermatol.* 2013;149(1):84-91.

19. American Diabetes Association. Standards of medical care in diabetes--2013. *Diabetes Care.* 2013;36 Suppl 1:S11-66.
20. Armstrong AW, Harskamp CT, Armstrong EJ. The association between psoriasis and hypertension: a systematic review and meta-analysis of observational studies. *J Hypertens.* 2013;31(3):433-442; discussion 442-433.
21. 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.
22. Gordon KB, Armstrong AW, Menter MA, Wu JJ. Treating to target-A realistic goal in psoriasis? *Semin Cutan Med Surg.* 2018;37(2S):S44-S47.
23. 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.
24. Reich K, Leonardi C, Langley RG, et al. Inflammatory bowel disease among patients with psoriasis treated with ixekizumab: A presentation of adjudicated data from an integrated database of 7 randomized controlled and uncontrolled trials. *J Am Acad Dermatol.* 2017;76(3):441-448 e442.
25. Schreiber S, Colombel JF, Feagan BG, et al. Incidence rates of inflammatory bowel disease in patients with psoriasis, psoriatic arthritis and ankylosing spondylitis treated with secukinumab: a retrospective analysis of pooled data from 21 clinical trials. *Ann Rheum Dis.* 2019;78(4):473-479.
26. Targan SR, Feagan B, Vermeire S, et al. A randomized, double-blind, placebo-controlled phase 2 study of brodalumab in patients with moderate-to-severe Crohn's disease. *Am J Gastroenterol.* 2016;111(11):1599-1607.
27. Hueber W, Sands BE, Lewitzky S, et al. Secukinumab, a human anti-IL-17A monoclonal antibody, for moderate to severe Crohn's disease: unexpected results of a randomised, double-blind placebo-controlled trial. *Gut.* 2012;61(12):1693-1700.
28. Papp KA. The safety of etanercept for the treatment of plaque psoriasis. *Ther Clin Risk Manag.* 2007;3(2):245-258.
29. Magnano MD, Robinson WH, Genovese MC. Demyelination and inhibition of tumor necrosis factor (TNF). *Clin Exp Rheumatol.* 2004;22(5 Suppl 35):S134-140.
30. Mohan N, Edwards ET, Cupps TR, et al. Demyelination occurring during anti-tumor necrosis factor alpha therapy for inflammatory arthritides. *Arthritis Rheum.* 2001;44(12):2862-2869.
31. TNF neutralization in MS: results of a randomized, placebo-controlled multicenter study. The Lenercept Multiple Sclerosis Study Group and The University of British Columbia MS/MRI Analysis Group. *Neurology.* 1999;53(3):457-465.
32. Vannucchi V, Grazzini M, Pieralli F, Giannotta M, Biagioni C, Nozzoli C. Adalimumab-induced lupus erythematosus with central nervous system involvement in a patient with Crohn's disease. *J Gastrointestin Liver Dis.* 2011;20(2):201-203.
33. Charles PJ, Smeenk RJ, De Jong J, Feldmann M, Maini RN. Assessment of antibodies to double-stranded DNA induced in rheumatoid arthritis patients following treatment with infliximab, a monoclonal antibody to tumor necrosis factor alpha: findings in open-label and randomized placebo-controlled trials. *Arthritis Rheum.* 2000;43(11):2383-2390.
34. Ramos-Casals M, Roberto Perez A, Diaz-Lagares C, Cuadrado MJ, Khamashta MA, Group BS. Autoimmune diseases induced by biological agents: a double-edged sword? *Autoimmun Rev.* 2010;9(3):188-193.
35. De Bandt M, Sibilia J, Le Loet X, et al. Systemic lupus erythematosus induced by anti-tumour necrosis factor alpha therapy: a French national survey. *Arthritis Res Ther.* 2005;7(3):R545-551.

36. Guerra I, Algaba A, Perez-Calle JL, et al. Induction of psoriasis with anti-TNF agents in patients with inflammatory bowel disease: a report of 21 cases. *J Crohns Colitis.* 2012;6(5):518-523.
37. Rahier JF, Buche S, Peyrin-Biroulet L, et al. Severe skin lesions cause patients with inflammatory bowel disease to discontinue anti-tumor necrosis factor therapy. *Clin Gastroenterol Hepatol.* 2010;8(12):1048-1055.
38. Bernstein CN, Wajda A, Blanchard JF. The clustering of other chronic inflammatory diseases in inflammatory bowel disease: a population-based study. *Gastroenterology.* 2005;129(3):827-836.
39. Kalb RE, Fiorentino DF, Lebwohl MG, et al. Risk of serious infection with biologic and systemic treatment of psoriasis: Results from the Psoriasis Longitudinal Assessment and Registry (PSOLAR). *JAMA Dermatol.* 2015;151(9):961-969.
40. 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.
41. Mrowietz U, de Jong EM, Kragballe K, et al. A consensus report on appropriate treatment optimization and transitioning in the management of moderate-to-severe plaque psoriasis. *J Eur Acad Dermatol Venereol.* 2014;28(4):438-453.
42. Griffiths CE. Clinical response after guselkumab treatment among adalimumab PASI 90 non-responders: Results from the VOYAGE 1 and 2 trials. *EMJ Dermatol.* 2018;6:79-87.
43. Langley RG, Tsai TF, Flavin S, et al. Efficacy and safety of guselkumab in patients with psoriasis who have an inadequate response to ustekinumab: results of the randomized, double-blind, phase III NAVIGATE trial. *Br J Dermatol.* 2018;178(1):114-123.
44. Mariette X, Forger F, Abraham B, et al. Lack of placental transfer of certolizumab pegol during pregnancy: results from CRIB, a prospective, postmarketing, pharmacokinetic study. *Ann Rheum Dis.* 2018;77(2):228-233.
45. Pasut G. Pegylation of biological molecules and potential benefits: pharmacological properties of certolizumab pegol. *BioDrugs.* 2014;28 Suppl 1:S15-23.
46. Blauvelt A, Reich K, Lebwohl M, et al. Certolizumab pegol for the treatment of patients with moderate-to-severe chronic plaque psoriasis: pooled analysis of week 16 data from three randomized controlled trials. *J Eur Acad Dermatol Venereol.* 2019;33(3):546-552.
47. Merola JF, Qureshi A, Husni ME. Underdiagnosed and undertreated psoriasis: Nuances of treating psoriasis affecting the scalp, face, intertriginous areas, genitals, hands, feet, and nails. *Dermatol Ther.* 2018;31(3):e12589.
48. Bagel J, Duffin KC, Moore A, et al. The effect of secukinumab on moderate-to-severe scalp psoriasis: Results of a 24-week, randomized, double-blind, placebo-controlled phase 3b study. *J Am Acad Dermatol.* 2017;77(4):667-674.
49. Feldman SR, Green L, Kimball AB, et al. Secukinumab improves scalp pain, itching, scaling and quality of life in patients with moderate-to-severe scalp psoriasis. *J Dermatolog Treat.* 2017;28(8):716-721.
50. Reich K, Leonardi C, Lebwohl M, et al. Sustained response with ixekizumab treatment of moderate-to-severe psoriasis with scalp involvement: results from three phase 3 trials (UNCOVER-1, UNCOVER-2, UNCOVER-3). *J Dermatolog Treat.* 2017;28(4):282-287.
51. Nguyen CM, Leon A, Danesh M, Beroukhim K, Wu JJ, Koo J. Improvement of nail and scalp psoriasis using apremilast in patients with chronic psoriasis: Phase 2b and 3, 52-week randomized, placebo-controlled trial results. *J Drugs Dermatol.* 2016;15(3):272-276.
52. Voorhees A, Gold L, Lebwohl M, et al. Efficacy and safety of apremilast in patients with moderate to severe plaque psoriasis of the scalp: Results of a phase 3, multicenter, randomized, placebo-controlled, double-blind study. Paper presented at: Maui Derm for Dermatologists 2019 Meeting; January 26-30, 2019; Maui, HI.

53. McCann FE, Palfreeman AC, Andrews M, et al. Apremilast, a novel PDE4 inhibitor, inhibits spontaneous production of tumour necrosis factor-alpha from human rheumatoid synovial cells and ameliorates experimental arthritis. *Arthritis Res Ther.* 2010;12(3):R107.
54. Perez-Aso M, Montesinos MC, Mediero A, Wilder T, Schafer PH, Cronstein B. Apremilast, a novel phosphodiesterase 4 (PDE4) inhibitor, regulates inflammation through multiple cAMP downstream effectors. *Arthritis Res Ther.* 2015;17:249.
55. N. Novartis receives FDA approval for Cosentyx® label update to include moderate-to-severe scalp psoriasis.
56. Rachakonda TD, Schupp CW, Armstrong AW. Psoriasis prevalence among adults in the United States. *J Am Acad Dermatol.* 2014;70(3):512-516.
57. Meeuwis KA, van de Kerkhof PC, Massuger LF, de Hullu JA, van Rossum MM. Patients' experience of psoriasis in the genital area. *Dermatology.* 2012;224(3):271-276.
58. Meeuwis KA, de Hullu JA, Massuger LF, van de Kerkhof PC, van Rossum MM. Genital psoriasis: A systematic literature review on this hidden skin disease. *Acta Derm Venereol.* 2011;91(1):5-11.
59. Yosipovitch G, Foley P, Ryan C, et al. Ixekizumab improved patient-reported genital psoriasis symptoms and impact of symptoms on sexual activity vs placebo in a randomized, double-blind study. *J Sex Med.* 2018;15(11):1645-1652.
60. Ryan C, Menter A, Guenther L, et al. Efficacy and safety of ixekizumab in a randomized, double-blinded, placebo-controlled phase IIIb study of patients with moderate-to-severe genital psoriasis. *Br J Dermatol.* 2018;179(4):844-852.
61. Lilly announces superiority of Taltz® (ixekizumab) versus TREMFYA® (guselkumab) in delivering total skin clearance at week 12 in topline results from head-to-head (IXORA-R) trial in people living with moderate to severe plaque psoriasis [press release]. August 13, 2019.
62. Reich K, Armstrong AW, Langley RG, et al. Guselkumab versus secukinumab for the treatment of moderate-to-severe psoriasis (ECLIPSE): results from a phase 3, randomised controlled trial. *Lancet.* 2019;394(10201):831-839.
63. Foulkes AC, Warren RB. Brodalumab in psoriasis: evidence to date and clinical potential. *Drugs Context.* 2019;8:212570.
64. Beck KM, Koo J. Brodalumab for the treatment of plaque psoriasis: up-to-date. *Expert Opin Biol Ther.* 2019;19(4):287-292.
65. Lebwohl MG, Papp KA, Marangell LB, et al. Psychiatric adverse events during treatment with brodalumab: Analysis of psoriasis clinical trials. *J Am Acad Dermatol.* 2018;78(1):81-89 e85.
66. Reich K, Armstrong AW, Foley P, et al. Efficacy and safety of guselkumab, an anti-interleukin-23 monoclonal antibody, compared with adalimumab for the treatment of patients with moderate to severe psoriasis with randomized withdrawal and retreatment: Results from the phase III, double-blind, placebo- and active comparator-controlled VOYAGE 2 trial. *J Am Acad Dermatol.* 2017;76(3):418-431.
67. Blauvelt A, Papp KA, Griffiths CE, et al. Efficacy and safety of guselkumab, an anti-interleukin-23 monoclonal antibody, compared with adalimumab for the continuous treatment of patients with moderate to severe psoriasis: Results from the phase III, double-blinded, placebo- and active comparator-controlled VOYAGE 1 trial. *J Am Acad Dermatol.* 2017;76(3):405-417.
68. Janssen announces new three-year TREMFYA® (Guselkumab) data demonstrates stably maintained rates of skin clearance in patients with moderate to severe plaque ssoriasis [press release]. October 19, 2018.

69. Griffiths CEM, Papp KA, Kimball AB, et al. Long-term efficacy of guselkumab for the treatment of moderate-to-severe psoriasis: Results from the phase 3 VOYAGE 1 trial through two years. *J Drugs Dermatol.* 2018;17(8):826-832.
70. Sun Pharma Announces U.S. FDA approval of ILUMYA™ (tildrakizumab-asmn) for the treatment of moderate-to-severe plaque psoriasis [press release]. March 21, 2018.
71. Reich K, Papp KA, Blauvelt A, et al. Tildrakizumab versus placebo or etanercept for chronic plaque psoriasis (reSURFACE 1 and reSURFACE 2): results from two randomised controlled, phase 3 trials. *Lancet.* 2017;390(10091):276-288.
72. Reich K, Warren RB, Iversen L, et al. Long-term efficacy and safety of tildrakizumab for moderate-to-severe psoriasis: pooled analyses of two randomised phase III clinical trials (reSURFACE 1 and reSURFACE 2) through 148 weeks. *Br J Dermatol.* 2019.
73. FaDA. FDA approves new therapy for moderate to severe plaque psoriasis. 2019. https://www.pharmacytimes.com/news/fda-approves-new-therapy-for-moderate-to-severe-plaque-psoriasis. Accessed June 29, 2019.
74. Gordon KB, Strober B, Lebwohl M, et al. Efficacy and safety of risankizumab in moderate-to-severe plaque psoriasis (UltIMMa-1 and UltIMMa-2): results from two double-blind, randomised, placebo-controlled and ustekinumab-controlled phase 3 trials. *Lancet.* 2018;392(10148):650-661.
75. Reich K, Gooderham M, Thaci D, et al. Risankizumab compared with adalimumab in patients with moderate-to-severe plaque psoriasis (IMMvent): a randomised, double-blind, active-comparator-controlled phase 3 trial. *Lancet.* 2019;394(10198):576-586.
76. A. Sustained high level of efficacy and favorable safety of ixekizumab in psoriasis: 4 years of follow-up from UNCOVER-3. 2019.
77. Bissonnette R, Luger T, Thaci D, et al. Secukinumab demonstrates high sustained efficacy and a favourable safety profile in patients with moderate-to-severe psoriasis through 5 years of treatment (SCULPTURE Extension Study). *J Eur Acad Dermatol Venereol.* 2018;32(9):1507-1514.
78. van den Reek JM, Zweegers J, Kievit W, et al. 'Happy' drug survival of adalimumab, etanercept and ustekinumab in psoriasis in daily practice care: results from the BioCAPTURE network. *Br J Dermatol.* 2014;171(5):1189-1196.
79. Kavanaugh A, Mease PJ, Gomez-Reino JJ, et al. Longterm (52-week) results of a phase III randomized, controlled trial of apremilast in patients with psoriatic arthritis. *J Rheumatol.* 2015;42(3):479-488.
80. D'Angelo S, Tramontano G, Gilio M, Leccese P, Olivieri I. Review of the treatment of psoriatic arthritis with biological agents: choice of drug for initial therapy and switch therapy for non-responders. *Open Access Rheumatol.* 2017;9:21-28.
81. Deodhar A, Gottlieb AB, Boehncke WH, et al. Efficacy and safety of guselkumab in patients with active psoriatic arthritis: a randomised, double-blind, placebo-controlled, phase 2 study. *Lancet.* 2018;391(10136):2213-2224.
82. Mease PJ, Genovese MC, Greenwald MW, et al. Brodalumab, an anti-IL17RA monoclonal antibody, in psoriatic arthritis. *N Engl J Med.* 2014;370(24):2295-2306.
83. 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.
84. Reich K, Puig L, Szepietowski JC, et al. Secukinumab dosing optimization in patients with moderate to severe plaque psoriasis: Results from the randomised, open-label OPTIMISE study. *Br J Dermatol.* 2019.