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Comparison of the Safety and Efficacy of Tumor Necrosis Factor Inhibitors and Interleukin-17 Inhibitors in Patients With Psoriasis

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ABSTRACT

Psoriasis (PsO) is a common, systemic, chronic inflammatory disease characterized by key clinical symptoms, including itching, pain, and scaling, and is associated with substantial physical, psychosocial, and economic health burdens. Currently, there is no cure for PsO; however, the introduction of biologic therapies has revolutionized the clinical management of patients with PsO by expanding treatment options to include multiple therapies with different mechanisms of action targeting cytokines, including tumor necrosis factor inhibitors (TNFis), interleukin (IL)-17A inhibitors, an IL-12/23 inhibitor, and IL-23 inhibitors. TNFis are historically considered the first-line biologic treatment and the first-generation biologics; however, increased understanding of TNF-α and IL-17 synergistic functions have recently led to evidence that specifically targeting IL-17 may be more likely to improve disease activity than a more general, nonspecific therapy target, such as TNF-α. This review highlights currently available evidence and demonstrates the differences between TNFis and IL-17A inhibitors in patients with PsO with regard to efficacy and safety.

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INTRODUCTION

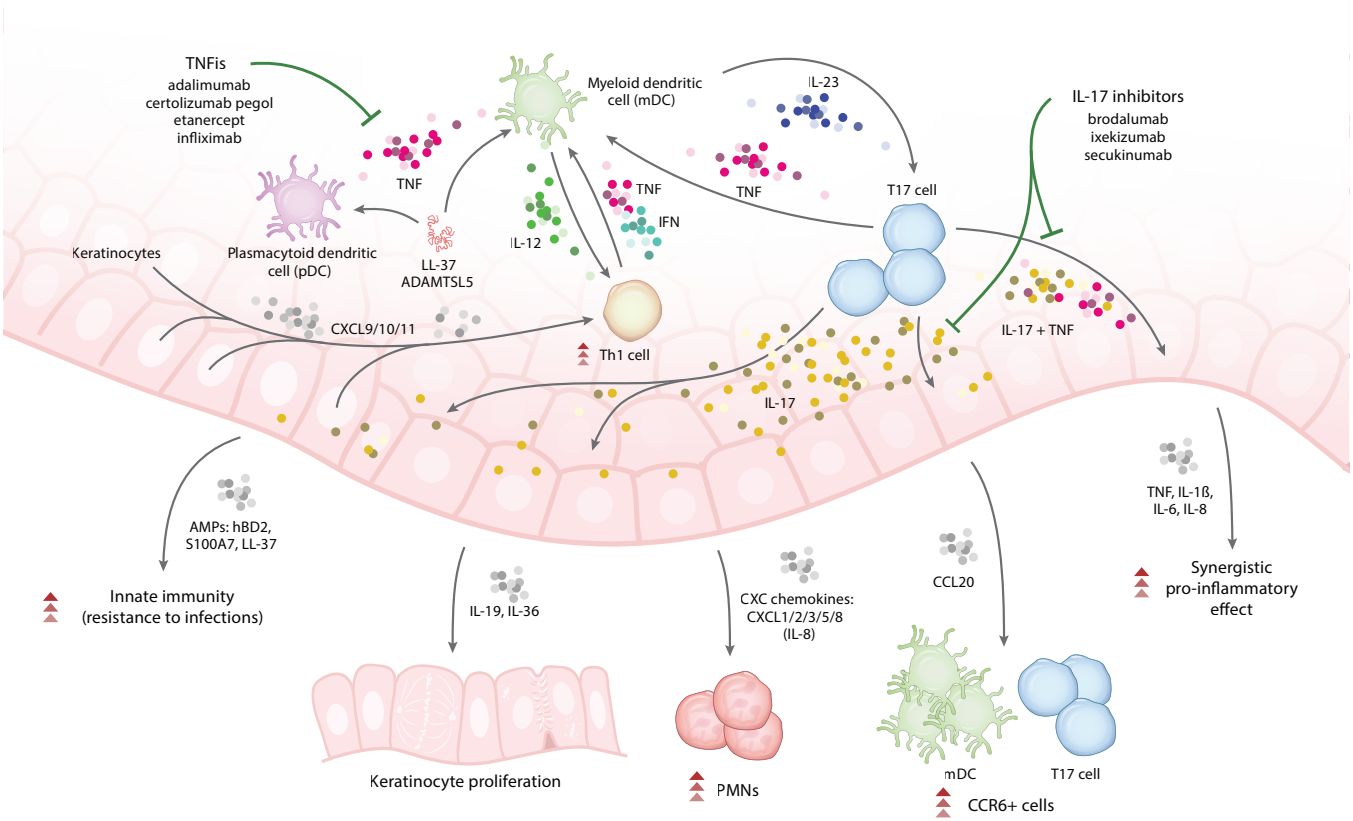
Overview of Psoriasis

Psoriasis (PsO) is systemic, chronic inflammatory disease that manifests mainly as plaque PsO, but other variants include guttate, flexural, erythrodermic, pustular, scalp, palmoplantar, and nail PsO.[1,2] Patients with PsO can experience substantial physical, psychosocial, and economic health burdens due to the signs and symptoms associated with the PsO skin lesions that negatively affect their overall quality of life.[3,4] Further, patients with PsO have a higher risk of developing comorbidities than the general population, which compounds the negative effects that PsO has on their quality of life.[5-7] PsO has been shown to be associated with a higher prevalence of cardiovascular disease, malignancy, metabolic syndrome, other autoimmune diseases, and psychiatric disorders, such as anxiety and depression.[8] Approximately 30% of patients with PsO develop psoriatic arthritis (PsA), which can lead to progressive joint damage and disability.[9,10]

Currently, there is no cure for PsO; however, the development of various treatment strategies has allowed for symptom control, the ability to lead a disease-free life while on therapy, and improved health-related quality of life. Phototherapy and traditional systemic therapies are often the mainstay treatment options for moderate to severe PsO[11]; however, patients may experience loss of efficacy, adverse events (AEs), or inadequate responses with these traditional treatments. Therefore, the introduction of biologic therapies has revolutionized the clinical management of patients with PsO by expanding treatment options to include multiple therapies with different mechanisms of action. Because of the proinflammatory response associated with PsO symptom manifestation, biologic therapies have been developed to specifically block cytokine signalling. Approved biologics for the treatment of PsO that block cytokine signaling include tumor necrosis factor inhibitors (TNFis; adalimumab, certolizumab pegol, etanercept, and infliximab),[12-20] IL-17A inhibitors (ixekizumab and secukinumab),[21-25] an IL-17 receptor A antagonist (brodalumab),[26,27] an IL-12/23 inhibitor (ustekinumab),[28-30] and the IL-23 inhibitors (guselkumab, tildrakizumab, and risankizumab).[31-34]

Historically, as there were no other therapeutic choices, switching to another second-line TNFi treatment after an inadequate response to a first-line TNFi has been common and recommended in routine clinical practice[35-37]; however, some patients may still not achieve optimal treatment responses due to the similar mechanism of action and may benefit from switching to a drug

FIGURE 1. Therapeutic targets in IL-17 and TNF-mediated pathways in the pathogenesis of psoriasis. AMP, antimicrobial peptide; CCL, chemokine (C-C motif) ligand; CCR, chemokine (C-C motif) receptor; CXC, chemokine (C-X-C motif); CXCL, chemokine (C-X-C motif) ligand; IFN, interferon; IL, interleukin; PMN, polymorphonuclear neutrophil; T17, T helper 17; Th1, T helper 1; TNF, tumor necrosis factor; TNFi, tumor necrosis factor inhibitor.



with a different mechanism of action. Both TNF-α and IL-17A levels are elevated in psoriatic skin lesions, and there is extensive interplay between the 2 proinflammatory cytokines.[38,39] Increased understanding of TNF-α and IL-17 synergistic functions has recently led to the development of an IL-17 inhibitor biologic drug class specifically targeting the IL-17–driven pathogenesis underlying the disease and allowed for a more targeted biologic drug class to be used in the treatment of psoriasis.[40] Several randomized controlled trials have demonstrated the efficacy and safety of the TNFi and IL-17A inhibitor treatments in patients with PsO compared with placebo.[12-17,20-27] However, there are differences in the efficacy and safety profiles of TNFis and IL-17A that healthcare professionals need to be aware of to make the proper treatment decision. This review aims to establish evidence and demonstrate the differences between TNFis and IL-17 in patients with PsO with regard to efficacy and safety.

Immunopathogenesis of PsO and the Role of TNF-α and IL-17A

The aberrant immune response that underlies the clinical manifestations of PsO includes increased activity of T cells, antigen-presenting cells, and T helper (Th) 17 cell–related cytokines to cause systematic inflammation.[1] Antigenic stimuli in psoriatic skin lesions induce plasmacytoid dendritic cell–mediated activation and maturation of myeloid dendritic cells by releasing interferon-α in the epidermis and dermis; these cells migrate to local lymph nodes, where they present antigens and release costimulatory signals and cytokines, including TNF-α, that induce differentiation of naive T cells into mature Th cells, including Th1 and Th17.[10] Th cells circulate back to the epidermis and dermis, facilitating complex interactions between cells and cytokines, including TNF-α and IL-17A, that stimulate continual proliferation of keratinocytes as well as ongoing recruitment of T cells, creating a cyclic pathology. This leads to the clinical features of growth and dilation of superficial blood vessels, hyperplasia of the epidermis, and skin scaling and flaking.[41]

Mechanism of action of TNFis and IL-17A Inhibitors

Although several cytokines have been identified as possible key players in the immunopathogenesis of PsO, growing evidence has implicated the proinflammatory cytokine TNF-α[39] and Th17-associated cytokine IL-17A,[42] which has been further supported by the efficacy of TNFis and IL-17A inhibitors, respectively, in the treatment of PsO (Figure 1).[12-17,20-27,43] Targeting the activation

and migration of T cells into the skin by TNF-α as a potentially successful drug mechanism of action for alleviating PsO symptoms, TNFis were the first biologics developed that were considered a viable treatment option for PsO.[37] TNF-α plays a central role in systemic amplification of both innate and adaptive immune responses by being the key regulator of immune cells and is produced by multiple cells involved in the pathogenesis of PsO, including activated dendritic cells, Th1 cells, Th17 cells, and keratinocytes.[44] Therefore, inhibiting TNF-α proinflammatory signaling is a widespread treatment approach by targeting multiple central steps within the pathogenesis of PsO to obtain disease control and prevent disease activity; however, because TNF-α is a key component of a myriad of inflammatory pathways, there is the possibility of AEs and contraindication.

IL-17 cytokines play a central role in immunopathogenesis and consist of 6 isoforms (IL-17A-IL17F)[45-47]; of these, IL-17A, IL-17C, and IL-17F are elevated in psoriatic skin lesions.[48,49] Furthermore, IL-17A circulates as homodimers and heterodimers with IL-17F,[50] implicating IL-17A and IL-17F as potential targets for the treatment of PsO. Emerging evidence has identified IL-17 and its isoforms as the main driver of the inflammatory response in PsO.[50-52] IL-17A, the main effector cytokine produced by Th17 cells in epithelial tissue, is involved in several downstream signaling functions that link the innate and adaptive immune responses in the skin manifested in the pathogenesis of PsO, including keratinocyte activation and growth; the promotion of the release of other proinflammatory cytokines (TNF-α, IL-1, and IL-6) and antimicrobial peptides; and the enhancement of angiogenesis.[53-55] In addition to Th17 cells, innate lymphoid cells, mast cells, γδT cells, and αβ T cells may be significant cellular sources of IL-17A in patients with PsO.[56] IL-17A activation of keratinocyte responses creates a positive feedback loop of cytokine production and cell recruitment; therefore, IL-17A has been considered a pivotal cytokine along with other isoforms of IL-17 and the Th17 cytokine IL-22 in driving the pathogenesis of PsO.[57,58] Because IL-17A is more downstream in the pathophysiological pathway inducing PsO symptoms, biologics with a mechanism of action that directly inhibits the IL-17A–mediated inflammatory response offer a more targeted therapeutic intervention than that of TNFis.

Safety Profile of TNFi Therapies

Because TNFis have a broader mechanism of action than IL-17A inhibitors—they target the main proinflammatory cytokine that mediates systemic inflammatory responses during the acute phase immune reaction—they have been associated with numerous warnings and precautions, including for tuberculosis, invasive fungal infections, heart failure, hypersensitivity reactions, hepatitis B virus reactivation, neurological reactions, hematologic reactions, use with other biologics, autoimmunity, and immunizations, with boxed warnings for serious infections and malignancies (Table 1).[59-62]

The most common AEs are injection site reactions and upper respiratory tract infections, while the most frequently reported serious AEs (SAEs) are serious infections (SIs).[37] For adalimumab and etanercept, the most frequently reported AEs are injection site reactions (adalimumab, 3.2%[12]; etanercept, 15.9%[16]) and upper respiratory infections (adalimumab, 7.2%12; etanercept, 12.2%[16]); for certolizumab pegol, they are nasopharyngitis (6.9%-20.5%) and upper respiratory infections (4.8%-9.1%)[14,15]; and for infliximab, infusion reactions (3%-23%).[37] Although infliximab seems to be superior in efficacy compared with adalimumab and etanercept, patients receiving infliximab have a greater risk of developing AEs.[63] Moreover, TNFis can cause paradoxical worsening of PsO and, in some cases, can lead to new onset of pustular-like PsO in regions such as the distal extremities.[64]

Due to the widespread modifications within both the innate and adaptive immune system, as well as disruption of tuberculosis granulomas, it has been proposed that TNFis increase the risk of tuberculosis and mycobacterial infections. TNFis have been associated with an elevated risk of causing reactivation of tuberculosis in patients with immune-mediated disease, such as rheumatoid arthritis and inflammatory bowel disease.[65] In a previous retrospective study, a small proportion of patients (n = 4; 1.08%) developed tuberculosis during treatment with TNFis, of whom 1 patient with gastrointestinal tuberculosis developed renal failure.[66] Because patients with PsO are at risk for reactivation of tuberculosis,[65] physicians should screen and tightly monitor patients for latent tuberculosis infection prior to and during TNFi treatment and astutely consider the risk of opportunistic infection when making their treatment decisions.

Certolizumab pegol has been considered safe for treating patients during pregnancy and breastfeeding due to its unique pegylated molecular structure lacking the Fc region, which limits its transfer across the placenta or from plasma to breast milk. In the CRIB and CRADLE pharmacokinetic studies of certolizumab pegol in women who were in the third trimester of their pregnancy or lactating mothers, respectively, there was no to minimal placental transfer of certolizumab pegol or transfer from plasma to breast milk, supporting the use of certolizumab pegol treatment during pregnancy and breast feeding.[67,68] Therefore, the label for certolizumab pegol indicates that it can be used for the treatment of pregnant and lactating patient populations, with tight monitoring by physicians.[60]

Safety Profile of IL-17A Inhibitors

Because the mechanism of action of IL-17A inhibitors is more targeted than that of TNFis, they generally have fewer warnings and precautions; these typically include infections, hypersensitivity reactions, inflammatory bowel disease, and use with immunizations (Table 1).[61,69,70] Overall, the most common AEs associated with IL-17A inhibitors are naso-

TABLE 1.

Overview of Safety of TNFis and IL-17A Inhibitors Currently Approved for the Treatment of Psoriasis Based on the US Package Inserts

Drug	Contraindications	Warnings and Precautions
TNFis		
Adalimumab[59]	None	**Risk of serious infections[a]** • Tuberculosis • Invasive fungal infections **Malignancies[a]** • Hypersensitivity reactions • Hepatitis B virus reactivation • Neurological reactions • Hematologic reactions • Use with anakinra • Heart failure • Autoimmunity • Immunizations • Use with abatacept
Certolizumab pegol[60]	Serious hypersensitivity reaction to certolizumab pegol or to any of the excipients	**Risk of serious infections[a]** • Tuberculosis • Invasive fungal infections **Malignancies[a]** • Heart failure; worsening or new onset may occur • Hypersensitivity reactions • Hepatitis B virus reactivation • Neurological reactions • Hematologic reactions • Use in combination with other biologic DMARDs • Autoimmunity • Immunizations • Immunosuppression
Etanercept[61]	Sepsis	**Risk of serious infections[a]** • Tuberculosis • Invasive fungal infections • Neurological reactions **Malignancies[a]** • Heart failure • Hematologic reactions • Hepatitis B reactivation • Allergic reactions • Immunizations • Autoimmunity • Immunosuppression • Use in Wegener granulomatosis • Use with anakinra or abatacept • Use in patients with moderate to severe alcoholic hepatitis
Infliximab[62]	Doses > 5 mg/kg in moderate to severe heart failure Previous severe hypersensitivity reaction to infliximab or known hypersensitivity to inactive components of infliximab or to any murine proteins	**Risk of serious infections[a]** • Tuberculosis • Invasive fungal infections **Malignancies[a]** • Hepatitis B virus reactivation • Hepatotoxicity • Heart failure • Hematologic reactions • Hypersensitivity • Cardiovascular and cerebrovascular reactions during and after infusion

TABLE 1. (CONTINUED)

Overview of Safety of TNFis and IL-17A Inhibitors Currently Approved for the Treatment of Psoriasis Based on the US Package Inserts		
Drug	**Contraindications**	**Warnings and Precautions**
Infliximab[62]		• Neurological reactions • Use with anakinra • Use with abatacept • Concurrent administration with other biological therapies • Switching between biological DMARDs • Autoimmunity • Live vaccines/therapeutic infectious agents
IL-17A inhibitors		
Brodalumab[61]	Crohn disease; brodalumab may cause worsening of disease	**Suicidal ideation and behavior**[a] • Infections • Tuberculosis • Crohn disease • Immunizations; avoid use of live vaccines in patients treated with brodalumab
Ixekizumab[69]	Serious hypersensitivity reaction to ixekizumab or to any of the excipients	• Infections • Tuberculosis • Hypersensitivity • Inflammatory bowel disease • Immunizations
Secukinumab[70]	Serious hypersensitivity reaction to secukinumab or to any of the excipients	• Infections • Tuberculosis • Inflammatory bowel disease • Hypersensitivity reactions and risk of hypersensitivity in latex-sensitive individuals • Vaccinations

DMARD, disease-modifying antirheumatic drug; IL, interleukin;TNFi, tumor necrosis factor inhibitor.
[a]Boxed warning.

pharyngitis (secukinumab, 12.6%-33.7%; ixekizumab, 19.6%; brodalumab, 9.3%), headache (secukinumab, 4.9%-21.4%; ixekizumab, 6.5%, brodalumab, 5.2%), and upper respiratory tract infection (secukinumab, 4.2%; ixekizumab, 10.0%; brodalumab, 8.2%).[22,26,47,71,72] Additionally, injection site reactions were a common AE associated with ixekizumab, but were less common with the other IL-17A inhibitors (ixekizumab, 10.4%; brodalumab, 0.9%; secukinumab, 0.7%).[22,23,26] Other potential AEs with IL-17A inhibitors are neutropenia, *Candida* infections, and inflammatory bowel disease; there is a warning for exacerbation of inflammatory bowel disease with secukinumab and ixekizumab, while brodalumab is contraindicated in patients with Crohn disease because IL-17 plays a key role in the pathophysiology of these various diseases.[71,73,74] However, these IL-17A inhibitor–associated AEs have been reported as manageable.[37] In a pooled analysis of 10 phase 2 and 3 secukinumab clinical studies, the incidence of neutropenia was 1.3%, *Candida* infections was 2.6%, and Crohn disease, 0.03%.[75] Furthermore, an exploratory clinical study evaluating secukinumab treatment in patients with Crohn disease demonstrated that blocking IL-17A was ineffective and led to higher rates of adverse events than placebo.[76] In a pooled analysis that integrated safety data from the UNCOVER ixekizumab trials, the incidence of neutropenia was 11.5%; the incidence rate (IR)/100 patient-years (PY) of *Candida* infections was 3.7, with no *Candida* infection meeting the criteria for a SAE; and the IR/100 PY of Crohn disease was 0.1.[22] In the brodalumab AMAGINE-1 study, the exposure-adjusted events rates/100 PY were 0.4 for neutropenia and 3.5 for suspected *Candida* infections.[26] All infections, such as upper respiratory tract infection and *Candida* infections, that occurred during IL-17A inhibitor treatment were mild to moderate and did not result in discontinuation of therapy.[21,23] Overall, because TNFis have a broader spectrum mechanism of action, theoretically these drugs would be associated with a higher risk of infections, specifically latent tuberculosis, than IL-17A inhibitors; therefore, latent tuberculosis confers a warning/precaution for TNFis. To date, no cases of latent tuberculosis have been reported with IL-17A inhibitors. Although IL-17A inhibitors may be preferred for the treatment of these patients, the risk of new onset of tuberculosis may be the same irrespective of biologic therapy. However, only TNFis have been reported to be associated with a risk of reactivating tuberculosis, possibly indicating that IL-17A inhibitors have a better safety profile with regard to tuberculosis reactivation.

Of 4464 patients receiving brodalumab in phase 2 and 3 (AMAGINE-1, AMAGINE-2, and AMAGINE-3) clinical trials, 3 completed suicides were reported, with a fourth that was later judged as

indeterminate.[61,74,77] All suicides occurred after patients had already stopped using brodalumab therapy, and investigators felt that the suicides were unrelated to the study medication. The brodalumab package insert states that there is "no causal relationship" found between brodalumab and suicide ideation or completion.[61] The US Food and Drug Administration has noted that patients with PsO have a higher prevalence of depression, anxiety, and suicidality compared with the general population, and this was not controlled for in the clinical trial exclusion criteria.[78] However, due to the increased risk of psychiatric disorder comorbidities in patients with PsO, physicians need to tightly monitor patients receiving brodalumab for signs of psychiatric disorders and carefully consider the use of brodalumab in patients already experiencing symptoms of depression and suicidal ideation.

Efficacy of TNFi Therapies

TNFis have demonstrated significant efficacy in patients with moderate to severe plaque PsO (Table 2) and are often used as a first-line biologic treatment. TNFi's onset of action, defined as achieving ≥ 75% improvement in Psoriasis Area and Severity Index (PASI) score from baseline (PASI 75), varies by drug from approximately 3.5 to 10 weeks; infliximab has the fastest onset of action (3.5 weeks), followed by adalimumab (4.6 weeks) and etanercept (high dose [50 mg], 6.6 weeks; low dose [25 mg], 9.5 weeks).[79]

In phase 3 studies, a higher proportion of patients receiving adalimumab 40 mg achieved PASI 75 responses within 12 to 16 weeks than those receiving placebo (week 12, 80% vs 4%, respectively; week 16, 71% vs 7%, respectively)[12,13]; furthermore, approximately 75% of patients who achieved PASI 75 responses maintained the response up to 60 weeks.[13] At week 24 of a retrospective study, patients who received adalimumab reported significant improvements in their quality of life as assessed by Dermatology Life Quality Index (DLQI; $P = 0.001$), with significant decreases from baseline in Nail Psoriasis Severity Index, palmoplantar PsO, and scalp involvement.[80] Pooled data from the phase 3 CIMPASI-1, CIMPASI-2,[14] and CIMPACT[15] studies showed that a higher proportion of patients receiving certolizumab pegol 400 mg achieved PASI 75 responses (80.1% vs 7.5%; $P < 0.0001$) and 5-point Physician's Global Assessment (PGA) scores of 0 (clear) or 1 (almost clear) (63.7% vs 2.8%; $P < 0.0001$) at week 16 than did patients who received placebo[81]; at the highest dose of 400 mg, certolizumab pegol was superior to etanercept at week 12, as measured by PASI 75 responder rate (66.7% vs 53.3%; $P = 0.0152$).[15] In a pooled population of patients from CIMPASI-1 and CIMPASI-2, change from baseline to week 16 in DLQI was significantly greater in certolizumab pegol–treated patients than in placebo-treated patients.[14] In phase 3 studies, approximately 50% of patients receiving etanercept 50 mg had achieved PASI 75 responses and approximately 60% reported improvement in DLQI at 12 weeks.[16,17] Patients receiving etanercept in a phase 3 clinical trial have reported clinically meaningful improvement in DLQI (≥ 5-point improvement or score of 0) as well as significant improvements in Short Form-36 Health Survey and Patient Global Assessment.[82] In phase 3 studies, > 70% of patients receiving infliximab 5 mg/kg achieved PASI 75 responses at week[10,19,20,83] which were maintained up to 24 weeks[83]; infliximab significantly improved health-related quality of life, measured by percentage improvement in DLQI scores, at week 10 compared with placebo (91% vs 0%; $P < 0.001$).[84] A meta-analysis study of randomized controlled trials measuring health-related quality of life showed significant improvements in DLQI with infliximab and etanercept therapy compared with placebo.[85] Another meta-analysis study revealed that infliximab (risk difference [95% CI], 78% [72%-83%]) was the most effective approved TNFi for PsO; however, after 24 weeks, there was an observed decrease in efficacy with infliximab, adalimumab, and etanercept.[86]

Efficacy of IL-17A Inhibitors

Recent data have demonstrated that biologics that neutralize IL-17A (ixekizumab, secukinumab) or target the IL-17A receptor (brodalumab) are highly effective and have a favorable safety profile in the treatment of moderate to severe PsO (Table 2), thereby offering new treatment options, especially to patients who have an inadequate response with TNFi therapies. IL-17A inhibitors have a rapid onset of action, defined as achieving PASI 75 responses in approximately 2 to 3 weeks (ranging from 2.1 weeks with brodalumab[87] to 2.4 weeks and 3.0 weeks with ixekizumab[21] and secukinumab,[23] respectively). Earlier onset of responses with secukinumab were again shown in the CLARITY study[88]; compared with patients treated with ustekinumab, a higher proportion of patients treated with secukinumab achieved PASI 75 (40.2% vs 16.3%) and PASI 90 (16.7% vs 4.0%) responses at week 4.[88]

In the phase 3 UNCOVER-1, UNCOVER-2, and UNCOVER-3 studies, a significantly higher proportion of patients receiving ixekizumab 80 mg achieved PASI 75 responses and static Physician's Global Assessment (sPGA) score of 0 (clear) or 1 (almost clear) at week 12 compared with those receiving placebo ($P <$ 0.001 for all comparisons) or etanercept 50 mg (UNCOVER-2 and UNCOVER-3: $P < 0.001$ for all comparisons).[21,22] In the phase 3 ERASURE,[23] FEATURE,[24] JUNCTURE,[25] and FIXTURE[23] studies, a higher proportion of patients with moderate to severe PsO receiving secukinumab 300 mg achieved PASI 75 responses (≈ 80%) and 5-point Investigator's Global Assessment (IGA) score of 0 (clear) or 1 (almost clear) (≈ 60%) compared with those receiving placebo (PASI 75, ≈ 5%; IGA 0/1, ≈ 2%) or etanercept 50 mg (FIXTURE study: PASI 75, 44%; IGA 0/1, 27%). Pooled analysis of ERASURE, FEATURE, JUNCTURE, and FIXTURE demonstrated that a majority of patients with moderate to severe PsO receiving secukinumab 300 mg achieved PASI 75 responses by 12 weeks and sustained responses over

TABLE 2.

Overview of the Efficacy of TNFis and IL-17A Inhibitors Currently Approved for the Treatment of Psoriasis from Clinical Trials

Drug	Clinical Trial	Primary Endpoint(s)	Outcomes
TNFis			
Adalimumab	Phase 3[12]	• PASI 75 at week 16	• Adalimumab 40 mg q2w: 71% • Placebo: 7%
	Phase 3[13]	• PASI 75 at week 12	• Adalimumab 40 mg qw: 80% • Adalimumab 40 mg q2w: 53% • Placebo: 4%
Certolizumab pegol	CIMPASI-1 and CIMPASI-2[14]	• PASI 75 at week 16 • PGA 0/1 at week 16	• Certolizumab pegol 400 mg q2w: PASI 75, 82.0%; PGA 0/1, 65.3% • Certolizumab pegol 200 mg q2w: PASI 75, 76.7%; PGA 0/1, 56.8% • Placebo: PASI 75, 9.9%; PGA 0/1, 2.7%
	CIMPACT[15]	• PASI 75 at week 12	• Certolizumab pegol 400 mg q2w: 66.7% • Certolizumab pegol 200 mg q2w: 61.3% • Placebo: 5.0%
Etanercept	Phase 3[16,17]	• PASI 75 at week 12	• Etanercept 25 mg qw: 14% • Etanercept 25 mg biw: 34% • Etanercept 50 mg biw: 49% • Placebo: 4%
	Phase 3[17]	• PASI 75 at week 12	• Etanercept 25 mg biw: 34% • Etanercept 50 mg biw: 49% • Placebo: 3%
Infliximab	Phase 3[19,20,83]	• PASI 75 at week 10	• Infliximab 5 mg/kg: 80% • Placebo: 3%
	Phase 3[20]	• PASI 75 at week 10	• Infliximab 3 mg/kg: 72% • Infliximab 5 mg/kg: 75% • Placebo: 6%
	Phase 3[81]	• PASI 75 at week 10	• Infliximab 3 mg/kg: 70.3% • Infliximab 5 mg/kg: 75.5% • Placebo: 1.9%
IL-17A inhibitors			
Brodalumab	AMAGINE-1[26,27]	• PASI 75 at week 12	• Brodalumab 140 mg q2w: 60% • Brodalumab 210 mg q2w: 83% • Placebo: 3%
	AMAGINE-2[22]	• PASI 75 at week 12 vs placebo • sPGA 0/1 at week 12 vs placebo • PASI 100 at week 12 vs ustekinumab	• Brodalumab 140 mg q2w: PASI 75, 67%; sPGA 0/1, 58% • Brodalumab 210 mg q2w: PASI 75, 86%; sPGA 0/1, 79%; PASI 100, 44% • Placebo: PASI 75, 8%; sPGA 0/1, 4% • Ustekinumab 45 mg q12w: PASI 100, 22%
	AMAGINE-3[22]	• PASI 75 at week 12 vs placebo • sPGA 0/1 at week 12 vs placebo • PASI 100 at week 12 vs ustekinumab	• Brodalumab 140 mg q2w: PASI 75, 69%; sPGA 0/1, 60% • Brodalumab 210 mg q2w: PASI 75, 85%; sPGA 0/1, 80%; PASI 100, 34% • Placebo: PASI 75, 6%; sPGA 0/1, 4% • Ustekinumab 45 mg q12w: PASI 100, 19%

TABLE 2. (CONTINUED)

Overview of the Efficacy of TNFis and IL-17A Inhibitors Currently Approved for the Treatment of Psoriasis from Clinical Trials			
Drug	**Clinical Trial**	**Primary Endpoint(s)**	**Outcomes**
TNFis			
Ixekizumab	UNCOVER-1[21,22]	• PASI 75 at week 12 • sPGA 0/1 at week 12	• Ixekizumab 160 mg q2w: PASI 75, 89.1%; sPGA 0/1, 81.8% • Ixekizumab 160 mg q4w: PASI 75, 82.6%; sPGA 0/1, 76.4% • Placebo: PASI 75, 3.9%; sPGA 0/1, 3.2%
	UNCOVER-2[23]	• PASI 75 at week 12 • sPGA 0/1 at week 12	• Ixekizumab 160 mg q2w: PASI 75, 89.7%; sPGA 0/1, 83.2% • Ixekizumab 160 mg q4w: PASI 75, 77.5%; sPGA 0/1, 72.9% • Placebo: PASI 75, 2.4%; sPGA 0/1, 2.4% • Etanercept 50 mg biw: PASI 75, 41.6%; sPGA 0/1, 36.0%
	UNCOVER-3[23]	• PASI 75 at week 12 • sPGA 0/1 at week 12	• Ixekizumab 160 mg q2w: PASI 75, 87.3%; sPGA 0/1, 80.5% • Ixekizumab 160 mg q4w: PASI 75, 84.2%; sPGA 0/1, 75.4% • Placebo: PASI 75, 7.3%; sPGA 0/1, 6.7% • Etanercept 50 mg biw: PASI 75, 53.4%; sPGA 0/1, 41.6%
Secukinumab	ERASURE[23]	• PASI 75 at week 12 • IGA 0/1 at week 12	• Secukinumab 150 mg q4w: PASI 75, 71.6%; IGA 0/1, 51.2% • Secukinumab 300 mg q4w: PASI 75, 81.6%, IGA 0/1, 65.3% • Placebo: PASI 75, 4.5%; IGA 0/1, 2.4%
	FEATURE[26]	• PASI 75 at week 12 • IGA 0/1 at week 12	• Secukinumab 150 mg q4w: PASI 75, 69.5%; IGA 0/1, 52.5% • Secukinumab 300 mg q4w: PASI 75, 75.9%, IGA 0/1, 69.0% • Placebo: PASI 75, 0%; IGA 0/1, 0%
	FIXTURE[25]	• PASI 75 at week 12 • IGA 0/1 at week 12	• Secukinumab 150 mg q4w: PASI 75, 67.0%; IGA 0/1, 51.1% • Secukinumab 300 mg q4w: PASI 75, 77.1%, IGA 0/1, 2.5% • Placebo: PASI 75, 4.9%; IGA 0/1, 2.8% • Etanercept 50 mg biw: PASI 75, 44.0%; IGA 0/1, 27.2%
	JUNCTURE27	• PASI 75 at week 12 • IGA 0/1 at week 12	• Secukinumab 150 mg q4w: PASI 75, 71.7%; IGA 0/1, 53.3% • Secukinumab 300 mg q4w: PASI 75, 86.7%, IGA 0/1, 73.3% • Placebo: PASI 75, 3.3%; IGA 0/1, 0%

biw, biweekly; IGA, Investigator's Global Assessment; IL, interleukin; PASI, Psoriasis Area and Severity Index; PGA, Physician's Global Assessment; q2w, every 2 weeks; q4w, every 4 weeks; q12w, every 12 weeks; sPGA, static Physician's Global Assessment; TNFi, tumor necrosis factor inhibitor.

52 weeks in the trunk (66.3%), upper limbs (50.3%), and lower limbs (45.1%), indicating that secukinumab has rapid and sustained efficacy.[89] Additionally, pooled analysis of the ERASURE and FIXTURE studies demonstrated that secukinumab significantly improved patient-reported itching, pain, and scaling, as reported using the Psoriasis Symptom Diary, in patients with moderate to severe PsO at week 12 compared with placebo.[90] In the phase 3 CLEAR study,[91,92] secukinumab demonstrated superiority to ustekinumab because at week 52 a significantly higher proportion of patients receiving secukinumab 300 mg achieved PASI 90 (76% vs 61%; $P < 0.0001$) and IGA 0/1 (60% vs 65%; $P < 0.0001$) compared with those who received ustekinumab 45/90 mg.[92]

Approximately 80% of patients reported reduced pain, itching, and scaling with secukinumab treatment, and these patient-reported PsO symptoms remained low through 52 weeks; furthermore, almost 75% of patients receiving secukinumab achieved DLQI 0/1 by week 16.[93] In addition, secukinumab significantly improved EQ-5D-3L and all domains of Work Productivity and Activity Impairment, indicating an increased health-related quality of life.

In the phase 3 AMAGINE-1,[26] AMAGINE-2, and AMAGINE-3[27] studies, a higher proportion of patients with moderate to severe PsO receiving brodalumab 210 mg achieved PASI 75 responses (83%-86% vs 1%-7%; $P < 0.001$) and sPGA scores of 0 or 1 (76%-79% vs 1%-4%; $P < 0.001$) at week 12 compared with those receiving placebo; brodalumab demonstrated superiority to ustekinumab because a higher proportion of patients receiving it achieved PASI 100 than did those receiving ustekinumab 45/90 mg (AMAGINE-2, 44% vs 22%; AMAGINE-3, 37% vs 19%; all $P < 0.001$).[27] A significantly higher proportion of patients who received brodalumab achieved a total score of ≤ 8 on the Psoriasis Symptom Inventory (PSI)—an 8-item measure to assess the severity of PsO symptoms, including itch, redness, scaling, burning, cracking, stinging, flaking, and pain—than did patients who received placebo (61% vs 4%; $P < 0.001$).[26] Furthermore, secondary analysis of the phase 2 study demonstrated that patients receiving brodalumab reported significant improvements in DLQI and patient-reported outcomes (PROs) assessed by the PSI than did those receiving placebo.[94]

Other studies have demonstrated that IL-17A inhibitors are an effective treatment for challenging-to-treat scalp, palmoplantar, nail, and genital PsO. In the phase 3b SCALP study, compared with those receiving placebo at week 12, a significantly higher proportion of patients with moderate to severe scalp PsO receiving secukinumab 300 mg achieved 90% improvement in Psoriasis Scalp Severity Index (PSSI 90) score (52.9% vs 2.0%; $P < 0.001$) and IGA modified 2011 scalp responses of 0 or 1 (56.9% vs 5.9%; $P < 0.001$).[95] Furthermore, at week 12 patients treated with secukinumab reported greater reduction in scalp pain (–1.98 vs 0.61), itching (–4.07 vs –0.04), and scaling (–5.76 vs –0.95), as well as greater improvements in scalp dermatitis-related quality of life measured by Scalpdex total scores (–39.62 vs –7.91) compared with patients who received placebo (all $P<0.001$).[96] In the phase 3 GESTURE study, the percentage of patients with palmoplantar PsO who achieved Palmoplantar Investigator's Global Assessment 0 (clear) or 1 (almost clear/minimal) palms and soles was significantly greater with secukinumab 300 mg 33.3% than with placebo (33.3% vs 1.5%; $P < 0.001$), while Palmoplantar Psoriasis Area and Severity Index was significantly reduced with secukinumab compared with placebo (–54.5% vs –4.0%; $P < 0.001$); DLQI 0/1 responses from patients receiving secukinumab were also significantly higher compared with placebo at week 16 ($P < 0.01$), and secukinumab improved pain and function of palms and soles, as measured by the palmoplantar Quality-of-Life Instrument.[97] In the phase 3b TRANSFIGURE study, patients with moderate to severe PsO with nail involvement receiving secukinumab 300 mg demonstrated a significantly higher percent change in the total fingernail Nail Psoriasis Severity Index than those receiving placebo (–45.4% vs –11.2%; $P < 0.0001$).[98] In the phase 3b IXORA-Q study,[99] a higher proportion of patients with moderate to severe genital PsO receiving ixekizumab 80 mg achieved a static Physician's Global Assessment of Genitalia score of 0 or 1 ($P < 0.001$) and a Genital Psoriasis Sexual Frequency Questionnaire item 2 score of 0 or 1 ($P < 0.001$) than those receiving placebo; additionally, patients reported greater improvement in genital itch ($P < 0.001$) and a significant decrease in sexual difficulties caused by skin (DLQI item 9 score 0 or 1) by week 2 ($P < 0.001$).[100]

A limited number of clinical studies have directly compared the efficacy and safety of IL-17A inhibitors with those of TNFis; however, the head-to-head studies that have been conducted demonstrated that IL-17A inhibitors are more efficacious than TNFis. With regard to patients with PsA, IL-17A inhibitors are as effective as TNFis, with ongoing studies comparing ixekizumab vs adalimumab (SPIRIT-H2H; NCT03151551) and secukinumab vs adalimumab (EXCEED 1; NCT02745080). Based on top-line results made available from the SPIRIT-H2H study, ixekizumab demonstrated superiority to adalimumab in achievement of the primary outcome; a significantly higher proportion of patients receiving ixekizumab simultaneously achieved ≥ 50% improvement in American Rheumatology College response criteria (ACR50) and PASI 100 responses at week 24 compared with those receiving adalimumab (36.0% vs 27.9%; $P = 0.036$).[101] In the phase 3 FIXTURE study, secukinumab demonstrated superiority to etanercept in patients with PsO; the safety profiles were similar, with comparable incidences of AEs.[23] Post hoc analyses of the FIXTURE study showed that a higher proportion of patients receiving secukinumab achieved a DLQI score of 0/1 at week 24 and sustained a DLQI 0/1 response rate up to week 52 compared with those receiving etanercept; furthermore, the

time to achieving a DLQI score of 0/1 was significantly shorter with secukinumab than with etanercept (12 weeks vs 24 weeks; $P < 0.01$).[102] In the phase 3 UNCOVER-2 and UNCOVER-3 studies, ixekizumab demonstrated superiority to etanercept in patients with PsO because a significantly higher proportion of patients receiving ixekizumab 80 mg achieved PASI 75 responses at week 12 than those receiving placebo.[21]

Treatment Implications for Psoriatic Arthritis

Because PsO and many PsO-associated comorbidities share common underlying inflammatory mechanisms, therapies that target the inflammation may treat both PsO and comorbidities. In particular, the high prevalence of PsA—a chronic, immune-mediated disorder characterized by nail and skin changes, peripheral joint inflammation, enthesitis, dactylitis, and/or axial disorders[9]—in patients with PsO has led to the overlapping therapeutic approach of using biologics, including TNFis and IL-17A inhibitors, to treat both the skin and musculoskeletal manifestations of PsA in patients PsO.[103] In the phase 3 FUTURE 1[104] and FUTURE 2[105] studies, a higher proportion of patients with PsA receiving secukinumab achieved ≥ 20% improvement in American Rheumatology College (ACR20) response criteria from baseline to week 24 compared with those receiving placebo (FUTURE 1, 50% vs 17%; FUTURE 2, 54% vs 15%, respectively); secukinumab-treated patients in the FUTURE 1 study showed no radiographic disease progression at week 104.[106] The FUTURE 5 study of patients with PsA who had inadequate response to TNFis had a key secondary endpoint evaluating radiographic structural progression, measured by van der Heijde modified total Sharp score (vdH-mTSS) at week 24; mean changes from baseline in vdH-mTSS demonstrated significant inhibition of radiographic structural progression in patients treated with secukinumab compared with placebo (0.08 vs 0.50; $P < 0.01$).[107] In the phase 3 SPIRIT-P1, among biologic-naive patients with PsO and PsA who at baseline had an affected body surface area ≥ 3%, a significantly higher proportion of patients receiving ixekizumab 80 mg or adalimumab 40 mg achieved PASI 75 at week 12 compared with those receiving placebo (75.3% [ixekizumab every 4 weeks {q4w}] to 69.5% [ixekizumab every 2 weeks {q2w}] and 33.8% [adalimumab] vs 7.5%; $P < 0.001$); progression of structural damage, measured by vdH-mTSS at week 24, was significantly less in patients treated with ixekizumab q4w (0.17), ixekizumab q2w (0.08), and adalimumab (0.10) than in those who received placebo (0.49; all $P < 0.01$).[108] In the phase 3 SPIRIT-P2, among patients with PsA who had a prior inadequate response to TNFis, a higher proportion of patients attained ACR20 with ixekizumab 80 mg q4w and q2w compared with placebo (53% and 48% vs 20%, respectively; $P < 0.0001$).[109] However, the loss of efficacy and AEs observed with TNFi treatment of PsA in patients with PsO indicates that patients may achieve optimal treatment responses using drugs with different mechanisms of action, such as IL-17A inhibitors.[103]

CONCLUSIONS

With any newly developed drug therapy, particularly one specifically targeting the immune system, rigorous attainment of efficacy and safety data has been crucial in providing appropriate guidelines for the treatment of PsO. Although TNFis are effective for many patients with PsO and PsA, IL-17A inhibitors have demonstrated better efficacy—including a more rapid onset of action and a more durable response—than the TNFi etanercept. In conjunction with higher efficacy, IL-17A inhibitors may also be safer than TNFis with regard to the risk of tuberculosis reactivation and have led to improved patient-reported outcomes, suggesting that IL-17A inhibitors should be the preferred first-line biologic treatment choice that is safe and highly effective in patients with PsO. Future long-term studies comparing the safety of TNFis and IL-17A inhibitors in patients with PsO are warranted to provide clinicians with additional information to help them choose the best treatment strategies for each of their patients.

DISCLOSURES

L. J. Green is an investigator, consultant, and/or speaker for Amgen, AbbVie, Celgene, LEO Pharma, Eli Lilly, Novartis, Ortho-Derm, Sienna, and Sun-Pharma. P. S. Yamauchi has served as an investigator for Amgen, Celgene, Dermira, Galderma, Janssen, LEO Pharma, Eli Lilly, Novartis, Pfizer, Regeneron, Sandoz, Valeant, and UCB; and has served as an advisor and/or speaker for AbbVie, Amgen, Celgene, Dermira, Janssen, LEO Pharma, Eli Lilly, Novartis, Ortho-Dermatologics, Pfizer, Regeneron, Sun, and UCB. L. H. Kircik is a consultant and/or speaker for and received honoraria from 3M, Abbott, Aclaris, Allergan, Amgen, Anacor Pharmaceuticals, Assos, Astellas, Biogen-Idec, Colbar, Celgene, Colla Genex, Connetics Corporation, Dermik Laboratories, Embil Pharmaceuticals, EOS, Ferndale Laboratories, Galderma, Genentech, Intendis, Innocutis, Innovail, Johnson & Johnson, Laboratory Skin Care, Leo, L'Oreal, Medical International Technologies, Merck, Merz, Nano Bio, Novartis, Onset, OrthoNeutrogena, Promius, PediaPharma, PharmaDerm, PuraCap, Quinnova, Serono, SkinMedica, Stiefel Laboratories, Taro, Triax, UCB, Valeant Pharmaceuticals, Warner-Chilcott, and ZAGE; has received research grants from Acambis, Allergan, Amgen, Anacor Pharmaceuticals, Astellas, Asubio, Berlex Laboratories, Biolife, Biopelle, Boehringer-Ingelheim, Breckinridge Pharma, Celgene, Centocor, CollaGenex, Combinatrix, Connetics Corporation, Coria, Dermira, Dow Pharmaceutical Sciences, Dusa, Eli Lilly, Ferndale Laboratories, Galderma, Genentech, GlaxoSmithKline, Health Point, Idera, Intendis, Johnson & Johnson, Leo, L'Oreal, 3M, Maruho, Medicis Pharmaceuticas Corp, Nano Bio, Novartis, Noven Pharmaceuticals, Nucryst Pharmaceuticals Corp, Obagi, Onset, OrthoNeutrogena, Promius, QLT, PharmaDerm, Pfizer, Quinnova, Quatrix, SkinMedica, Stiefel Laboratories, Toler Rx, UCB, Valeant Pharmaceuticals, Warner-Chilcott, and XenoPort; and owns stock in Johnson & Johnson.

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