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PRODUCT REVIEW

Monoclonal antibodies inhibiting IL-12, -23, and -17 for the treatment of psoriasis

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ABSTRACT

Psoriasis is a chronic, inflammatory, immune-mediated skin condition that affects 3 to 4% of the adult US population, characterized by well-demarcated, erythematous plaques with silver scale. Psoriasis is associated with many comorbidities including cardiometabolic disease and can have a negative impact on quality of life. The current armamentarium of psoriasis treatment includes topical therapies, phototherapy, oral immunosuppressive therapies, and biologic agents. Over the past 2 decades, there has been rapid development of novel biologic therapies for the treatment of moderate-to-severe plaque psoriasis. This article will review the role of IL-12, IL-23, and IL-17 in the pathogenesis of psoriasis and the monoclonal antibodies (ustekinumab, secukinumab, ixekizumab, brodalumab, guselkumab, tildrakizumab, and risankizumab) that target these cytokines in the treatment of this disease.

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Introduction

Psoriasis is a chronic, inflammatory, immune-mediated skin condition that affects 3 to 4% of the adult US population.[1] Psoriasis is characterized by well-demarcated, erythematous plaques with silver scale, which can be associated with potential symptoms of pruritus, pain, skin tightness, bleeding, and flaking. Psoriasis is increasingly believed to be a systemic inflammatory disease and is associated with comorbidities such as psoriatic arthritis, cardiovascular disease, metabolic syndrome, kidney disease, malignancy, infection, and mood disorders.[2] Psoriasis can also have a significant negative impact on quality of life, including impairment in physical and mental functioning, psychological well-being, and work productivity.[3-5]

Although our knowledge of psoriasis has greatly expanded, the exact etiology of psoriasis remains unknown. Psoriasis involves an extremely complex immunologic pathogenesis of both the innate and adaptive immune systems (Fig. 1). Impaired T-cell activity contributes to hyperproliferation and abnormal differentiation of keratinocytes.[6] The keratinocytes then recruit dendritic cells to release interleukin (IL)-12 and 23.[7] IL-22 and IL-23 then activate 2 types of T-cells: T helper 1 (Th1) and T helper 17 (Th17), which release the psoriatic cytokines IL-17, interferon (IFN)-γ, tumor necrosis factor (TNF)-α, and IL-22.[8]

The current armamentarium of psoriasis treatment includes topical therapies, phototherapy, oral immunosuppressive therapies, and biologic agents.[9] There has been rapid development of novel therapies over the past 2 decades, especially biologic agents for the treatment of moderate-to-severe plaque psoriasis. TNFα inhibitors, such as the fusion protein etanercept (Enbrel) and the monoclonal antibodies adalimumab (Humira) and infliximab (Remicade), make up the first class of biologic agents. The next class to be approved by the Food and Drug Administration (FDA) was the monoclonal antibody ustekinumab, an IL-12/23 inhibitor. A more recent class of monoclonal antibodies are IL-17 inhibitors including secukinumab and ixekizumab, which block IL-17A, as well as brodalumab, which blocks the IL-17 receptor (IL-17RA). Lastly, a new class of biologics currently undergoing clinical trials includes the monoclonal antibody IL-23 inhibitors guselkumab, tildrakizumab, and risankizumab. This article will review the role of IL-12, IL-23, and IL-17 in the pathogenesis of psoriasis and the monoclonal antibodies (ustekinumab, secukinumab, ixekizumab, brodalumab, guselkumab, tildrakizumab, and risankizumab) that target these cytokines in the treatment of this disease.

IL-12 and IL-23 inhibitors

The role of IL-12 and IL-23 in psoriasis

Pre-clinical studies highlight the role of IL-12 and IL-23 in the pathogenesis of psoriasis.[10,11] Binding of IL-12 to the IL-12R on CD4+ T cells results in differentiation to Th1 and subsequent increase in production of the pro-inflammatory cytokine IFN-γ.[12] IL-23 binds to the IL-23R on CD4+ T cells resulting in intracellular signaling for Th17 differentiation, which produce a multitude of cytokines including IL-17A, IL-17F, IL-22, IL-26, IFN-γ, CCL20, and TNF-α.[13,14] Both IL-12 and IL-23 are hetereodimers that share the same p40 subunit necessary for binding to their receptor.[12,13] The p40 subunit of IL-12 and IL-23 has been shown to be overexpressed in psoriasis plaques.[15] This commonality of the p40 subunit is a therapeutic target for psoriasis, whereby inhibiting the p40 subunit impedes the downstream effects of IL-12 and IL-23.

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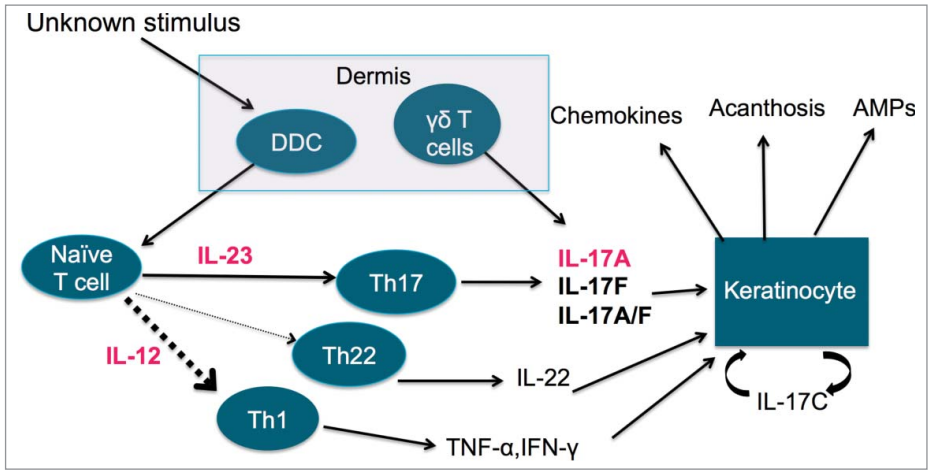

Figure 1. The pathogenesis of psoriasis. Abbreviations: DDC – dermal dendritic cells, AMP – anti-microbial peptides, IL – interleukin, Th1 – T-helper type 1, Th17 – T-helper type 17, Th22 – T-helper type 22, TNF-α – tumor necrosis factor – α, INF-γ – interferon-gamma.

Ustekinumab

Ustekinumab (CNTO1275; Stelara®, Janssen Biotech Inc., Horsham, PA, USA) is a fully human IgG1 monoclonal antibody that binds with high affinity to the p40 subunit of IL-12 and IL-23 cytokines, neutralizing their activity and consequently blocking their downstream effects.

Dosing

Ustekinumab is dosed based on weight in which patients weighing 100 kg (220 lbs) or less receive 45 mg and those weighing more than 100 kg (220 lbs) receive 90 mg. Each subcutaneous (SC) dose of 45 or 90 mg dose is given at week 0, 4, then every 12 weeks there after[16] (Table 1).

Phase I clinical trials

In a phase I, multi-center, double-blind, placebo-controlled, intra-cohort randomized, dose escalation study, a single subcutaneous dose of ustekinumab was administered to patients with moderate-to-severe plaque psoriasis.[17] Twenty-one subjects were randomly enrolled in a 1:4 ratio to receive placebo or ustekinumab 0.27 mg/kg, 0.675 mg/kg, 1.35 mg/kg, and 2.7 mg/kg. Patients receiving ustekinumab achieved rapid disease improvement with dose-dependent clinical response. At the higher dose of 2.7 mg/kg, all 4 subjects maintained an improvement of 67–89% in the Psoriasis Area and Severity Index (PASI) from baseline to week 12 and 24, which was the greatest and longest sustained response out of all groups. These findings were consistent with another Phase I open-label, sequential dose-escalation study examining ustekinumab IV administrations.[18]

Phase II clinical trials

A Phase II, double-blind, multi-center, placebo-controlled, parallel-group study evaluated the safety and efficacy of ustekinumab in 320 moderate-to-severe psoriasis patients assigned to receive ustekinumab at a single 45 mg dose, a single 90 mg dose, 4 weekly 45 mg doses, 4 weekly 90 mg doses, or placebo.[19] Improvement of 75% or greater in PASI from baseline (PASI 75) at week 12 were observed in 52%, 59%, 67%, 81% and 2%, of patients respectively ($P < 0.001$, all comparisons vs. placebo). Improvement of 90% or greater in PASI from baseline (PASI 90) at week 12 were 23%, 30%, 44%, 52%, and 1%, respectively ($P < 0.001$, all comparisons vs. placebo). In general, response was sustained up to 24 weeks.[20]

Phase III clinical trials

There were 2 pivotal Phase III studies, PHOENIX 1 and PHOENIX 2, investigating the safety and efficacy of ustekinumab for the treatment of moderate-to-severe psoriasis.[20-23] PHOENIX 1 is a parallel, double-blind, multi-center, placebo-controlled trial of 766 patients with moderate-to-severe psoriasis randomly assigned to either 45 or 90 mg ustekinumab administered at week 0 and 4 and every 12 weeks thereafter, or placebo at week 0 and 4 followed by ustekinumab starting at week 12.[21] PASI 75 rates at week 12 were 67.1% and 66.4% of patients receiving 45 mg and 90 mg ustekinumab, respectively, which were significantly higher than placebo (3.1%, $P < 0.0001$ for both comparisons). Similarly, a greater number of patients in the ustekinumab group achieved PASI 90 at week 12 compared with placebo (36.7–41.6% vs. 2%). By week 24, PASI 75 rates peaked and were generally maintained until week 40. Long-term ustekinumab responders (PASI 75 at week 40) were re-

Table 1. Dosing regimens of approved monoclonal antibodies targeting IL-12/23 and IL-17.

	Target	Loading dosing	Maintenance dosing
Ustekinumab (Stelara)	P40 subunit of IL12 and 23	Weight ≤100 kg: 45 mg SC at weeks 0 and 4 Weight > 100 kg: 90 mg SC at weeks 0 and 4	Weight ≤100 kg: 45 mg SC every 12 weeks starting at week 16 Weight > 100 kg: 90 mg SC every 12 weeks starting at week 16
Secukinumab (Cosentyx)	IL-17A	300 mg SC weekly at weeks 0, 1, 2, 3, and 4	300 mg SC every 4 weeks starting at week 8
Ixekixumab (Taltz)	IL-17A	160 mg SC at week 0, then 80 mg SC at weeks 2, 4, 6, 8,10, and 12	80 mg SC every 4 weeks starting at week 16
Brodalumab (Siliq)	IL-17RA	210 mg at Weeks 0, 1, and 2	210 mg every 2 weeks starting at week 4

randomized to continued maintenance dose or withdrawal. PASI 75 was maintained in a significantly greater number of patients continued on ustekinumab therapy compared with the withdrawal group ($p < 0.0001$). Initial clinical responses were generally maintained at week 76,[20] year 3,[21] and year 5.[22]

PHOENIX 1 allowed for minimal dosing flexibility, thus PHOENIX 2 was designed to assess the long-term efficacy of ustekinumab with greater dosing flexibility.[23] At week 12, 66.7% of patients receiving ustekinumab 45 mg, 75.7% receiving ustekinumab 90 mg, and 3.7% receiving placebo achieved PASI 75 ($p < 0.0001$, vs. placebo for both comparisons). PASI 90 in the 45 mg and 90 mg dosing groups at week 12 was 32.3% and 50.9%, respectively, which was maintained at week 24. Partial responders (patients achieving PASI $\geq$ 50% but <75%) at week 28 were randomized to continue ustekinumab every 12 weeks or escalate dosing to every 8 weeks. A significantly greater number of partial responder receiving a dose escalation of 90 mg every 8 weeks reached PASI 75 at 52 weeks compared with those continued at 90 mg every 12 weeks (68.8% vs. 33.3%, respectively, $P = 0.004$). No difference in improvement was observed with dosing escalation from 45 mg every 12 weeks to every 8 weeks. Other Phase III clinical trials have been performed in specific psoriasis subpopulations with similar tolerability, safety, and efficacy responses.[24-29]

Safety and tolerability

Both short-term and long-term reports from Phase II and III trials regarding the safety profile of ustekinumab are favorable without observable dose-dependent adverse events (AEs). In a pooled assessment of Phase 2 trials, PHOENIX 1, and PHOENIX 2, rates of AEs were comparable among patients treated with placebo (50.4%), ustekinumab 45 mg (57.6%), or ustekinumab 90 mg (51.6%).[30] Similar rates of AEs were also found among ustekinumab and etanercept groups during the ACCEPT trial (etanercept: 70.0%; ustekinumab 45 mg: 66.0%; and ustekinumab 90 mg: 69.2%).[28] The most common AEs reported were headache, nasopharyngitis, upper respiratory tract infections (URTI), fatigue, pruritus, back pain, injection site reactions (ISR) and arthralgia.[30] Ustekinumab and placebo groups also had comparable rates per 100 patient-years for infections, serious infections, malignancies, and serous adverse events (SAEs).[31] Data from the Psoriasis Longitudinal Assessment and Registry (PSOLAR) has shown that unadjusted rates of serious infection for infliximab (2.91/100PY) and other biologics (1.91/100PY) were numerically higher compared with ustekinumab (0.93/100PY).[32,33]

Immunogenicity

In PHOENIX 1, of the 746 patients with available data at 76 weeks, 38 (5.1%) subjects developed antibodies to ustekinumab, predominantly with low titers (< 1/320).[20]

IL-17 inhibitors

The role of IL-17 in psoriasis

IL-17 is a key player in the pathogenesis of psoriasis. IL-17 acts as a driver of inflammation and induces production of cytokines such as TNF-α, which recruit neutrophils and monocytes at the site of T-cell activation and leads to a self-sustaining keratinocyte hyperproliferation.[33] Among the many subtypes, IL-17A levels, in particular, are elevated in psoriatic lesions and can act directly on keratinocytes to induce expression of other pro-inflammatory molecules involved in psoriasis.[34,35] IL-17A, IL-17F, and the IL-17A/F heterodimer stimulate a receptor complex consisting of IL-17RA and IL-17RC subunits. The 3 anti-IL-17 agents currently available for treatment of moderate-to-severe plaque psoriasis are ixekizumab, secukinumab, and brodalumab.

Secukinumab

Secukinumab (AIN475, Cosentyx®, Novartis Pharma AG, Basel, Switzerland) is a human IgG1κ monoclonal antibody that selectively targets and neutralizes IL-17A.

Dosing

Secukinumab is available as 150 mg/mL prefilled syringes (PFS) or auto-injector pens (AI). Secukinumab is usually given at a dose of 300 mg SC at weeks 0, 1, 2, 3, and 4, then every 4 weeks thereafter (Table 1). For some patients, 150 mg may be acceptable.[36]

Phase I clinical trials

In a randomized, placebo-controlled, proof-of-concept Phase I clinical trial to demonstrate the safety and efficacy of secukinumab, 36 chronic plaque psoriasis patients were randomized to receive either a single intravenous 3 mg/kg dose of secukinumab or placebo.[37] Patients in the secukinumab group experienced relatively quick reduction in disease symptoms as early as 2 weeks after infusion. At week 12, the mean decrease in PASI score from baseline was 63% in the secukinumab group compared with 9% in the placebo group ($P = 0.0005$). Immunostains of patient skin biopsies revealed that the area occupied by dermal IL-17A+ CD3+ T cells was significantly smaller in secukinumab treated patients compared with placebo ($P = 0.042$). Analysis of skin samples using reverse transcription polymerase chain reaction (RT-PCR) showed significant down-regulation of a variety of pro-inflammatory cytokines and chemokines including IL-17A, IL-21, CCL20, IL-12B, and INF-γ.[37]

Phase II clinical trials

Four phase II studies with a total of 665 patients were conducted to determine the optimal dosing regimen, as well as efficacy and safety of secukinumab. In a study conducted by Papp et al., 4 subcutaneous doses of secukinumab (25 mg, 3 × 25 mg, 3 × 75 mg, and 3 × 150 mg) at 0, 4, and 8 weeks were compared with placebo over 36 weeks in 125 patients.[38] At week 12, the 3 × 150 mg and 3 × 75 mg dose groups resulted in significantly higher PASI 75 rates relative to placebo (82% and 57% vs. 9%; $P < 0.001$ and $P = 0.002$, respectively), which were maintained throughout the 36 weeks. Another phase II study by Rich et al. used 3 different induction regimens of secukinumab 150 mg (a single dose at week 0, early weekly regimen at weeks 0, 1, 2, 4, and monthly regimen at 0, 4, 8 weeks) compared with placebo in 404 psoriasis patients.[39] Following completion of the induction regimen, PASI 75 responders were re-randomized to a fixed interval maintenance regimen

(secukinumab 150 mg at weeks 12 and 24) or treated at the start of relapse with 150 mg secukinumab. The early weekly and monthly regimens were associated with higher PASI 75 response rates compared with placebo. Maintenance of PASI 75 and 90 from weeks 20 to 28 were higher in the fixed interval regimen.[39]

Phase III clinical trials

Two 52-week randomized, double-blinded, placebo-controlled Phase III clinical trials ERASURE (n = 738) and FIXTURE (n = 1306) investigated the efficacy of secukinumab in lyophilized powder formulation (LYO) at 300 mg and 150 mg doses administered once weekly for 5 weeks, then every 4 weeks.[40] In ERASURE, both doses of secukinumab showed significantly higher proportions of patients achieving PASI 75 at week 12 vs. placebo (300 mg: 81.6% and 150 mg: 71.6% vs. placebo: 4.5% $P < 0.001$).[40] In addition to a placebo group, FIXTURE used an active-control arm, comparing secukinumab to etanercept.[40] At week 12, a significantly greater proportion of patients achieved PASI 75 in the secukinumab group compared with etanercept and placebo (300 mg: 77.1%, 150 mg: 67.0%, etanercept: 44.0%, placebo: 4.9%; $P < 0.001$for all comparisons). PASI 75 was maintained through 52 weeks in 84.3% patients receiving secukinumab 150 mg ($P < 0.001$ vs. etanercept), 82.2% receiving secukinumab 300 mg ($P = 0.009$ vs. etanercept), 72.5% receiving etanercept, and 0% in placebo group.[40] Similar rates of PASI 75 were reached in other Phase III trials, JUNCTURE using secukinumab AI[41] and FEATURE using secukinumab in PFS.[42]

Two other phase III clinical trials studied alternative dose regimens of secukinumab. In the SCULPTURE study, the fixed dose regimen achieved consistently higher PASI 75, 90, and 100 and IGA 0/1 responses vs. the retreatment as needed regimen.[43] In the STATURE study, partial responders in SCULPTURE (defined as $\geq$ 50% but $<$ 75% improvement from baseline) showed improved treatment response with increased dosing regimen of both 300 mg and 10 mg/kg IV.[44]

Safety and tolerability

The rate of AEs did not differ significantly between groups treated with 300 mg and 150 mg doses of secukinumab, placebo, and etanercept in all phase I, II, and III clinical trials. The most common AEs associated with secukinumab were nasopharyngitis, diarrhea, and URTI.[45] A pooled analysis of 10 phase II and III clinical studies of secukinumab showed that nasopharyngitis and URI's were significantly more common in patients who received long-term treatment with secukinumab compared with those who had placebo.[46] In addition, there was a dose-dependent increase in non-serious Candida and herpes virus infections in secukinumab-treated patients.[47] Rates of SAEs were comparable between patients who received secukinumab 300 mg and 150 mg and placebo (2%, 2%, 1.7%).

An AE of special interest with secukinumab is inflammatory bowel disease (IBD). A pooled analysis of all psoriasis patients who had been exposed to at least one dose of secukinumab showed that the exposure-adjusted incidence of IBD per 100 patient-years was comparable between patients receiving the 300 mg and 150 mg dose of secukinumab and etanercept (0.26, 0.35 and 0.34, respectively). However, a previous randomized, double-blind, placebo-controlled clinical trial of secukinumab for Crohn's disease revealed a significantly higher Crohn's Disease Activity Index (CDAI) and rate of AEs in the secukinumab treatment group relative to placebo.[48] Thus, there is concern for worsening or new onset Crohn's disease in patients with personal or family history of IBD.

Immunogenicity

Secukinumab has demonstrated low immunogenicity in both in vitro experiments and clinical trials.[49] Across the phase 3 clinical trials, 10 out of 2842 subjects (0.4%) treated with secukinumab developed anti-drug antibodies (ADA), most of which were non-neutralizing.[45,47] There was no evidence of altered pharmacokinetics, safety, and efficacy with presence of ADA, although the small number of patients who developed ADA limited the power of such analyses.

Ixekizumab

Ixekizumab (LY2439821, Taltz®, Eli-Lilly and company, Indianapolis, IN, USA) is a humanized IgG subclass 4-kappa (IgG4-κ) anti-IL-17A monoclonal antibody.

Dosing

Ixekizumab comes as an 80 mg/mL PFS or AI. It is given as one 160 mg SC injection at week 0, then 80 mg every 2 weeks until week 12. Starting at week 16, 80 mg is administered every 4 weeks for maintenance[50] (Table 1).

Phase I clinical trials

In a 20-week, randomized, double-blind, placebo-controlled study, 40 patients with psoriasis received placebo or 5, 15, 50, or 150 mg of ixekizumab at weeks 0, 2, and 4[51]. At week 6, PASI 75 was achieved by 0% (5 mg), 25% (15 mg), 71.4% (50 mg), and 100% (150 mg) of patients, while PASI 90 was achieved by 0% (5 mg), 12.5% (15 mg), 43% (50 mg), and 62.5% (150 mg) of patients. Sixteen weeks after the third dose, 74.1% of the patients treated with 150 mg of ixekizumab maintained PASI 90. Skin biopsies performed at week 2 and 6, when compared with baseline, showed significant and dose-dependent improvement of keratinocyte proliferation, epidermal hyperplasia, and number of inflammatory cells in the epidermis and dermis, with near normalization of skin by week 6 in patients treated with 50 mg and 150 mg of ixekizumab.[51]

Phase II clinical trials

A total of 142 patients participated in the randomized, double-blind, placebo-controlled Phase II trial and received placebo or 10, 25, 75, or 150 mg of ixekizumab at weeks 0, 2, 4, 8, 12, and 16.[52] At week 12, PASI 75 was achieved by 29% (10 mg), 77% (25 mg), 83% (75 mg), and 82% (150 mg) of patients, while PASI 90 was achieved by 18% (10 mg), 50% (25 mg), 59% (75 mg), and 71% (150 mg) of patients. Of these, all except the 10 mg dose achieved significantly greater PASI 75 rates compared with placebo. In the open-label extension (OLE) study, patients who had not achieved PASI 75 were administered 120 mg of ixekizumab every 4 weeks, while patients who had achieved PASI 75 were withdrawn from treatment until loss of PASI 75 or until week 32, when they were treated with

ixekizumab 120 mg every 4 weeks. At week 52, 77% of patients achieved PASI 75.[53]

Phase III clinical trials

The pivotal clinical trials for ixekizumab were UNCOVER- 1, -2, and -3.[54-56] These were large, randomized, double-blind, placebo-controlled trials. UNCOVER-1 evaluated ixekizumab dosed 160 mg at week 0 followed by 80 mg every 2 or 4 weeks compared with placebo, while UNCOVER-2 and -3 involved the additional etanercept treated arm.. In UNCOVER-1 and -2, patients achieving static physician global assessment (sPGA) 0/1 at week 12 were re-randomized to receive placebo or ixekizumab 80 mg every 4 or 12 weeks. Patients with relapse after re-randomization, defined as sPGA score of 3 or greater, were then treated with ixekizumab 80 mg every 4 weeks. Any patients with sPGA scores greater than 1 at week 12 were treated with 80 mg of ixekizumab administered every 4 weeks. At week 12 in UNCOVER-1, -2, and -3, patients treated with ixekizumab every 2 weeks had a PASI 75 between 87.3–89.7% and a PASI 90 of 68.1–70.9%, which were better than PASI 75 (77.5%-84.2%) and PASI 90 (59.7%-65.3%) of patients treated every 4 weeks.[54] Rapid treatment response was observed in UNCOVER-2 and -3; about 50% of patients achieved PASI 75 by week 4 in both ixekizumab treated groups.[55,56]

Safety and tolerability

Ixekizumab is generally well tolerated, with the most commonly reported AEs being nasopharyngitis, URTI, ISR/erythema/pain, pruritus, headache, and arthralgia. Overall frequency of serious infections was not increased in patients on ixekizumab during the first 12 weeks of therapy.[57] No cases of active or reactivated tuberculosis have been observed in the clinical trials involving ixekizumab. The rate of oral candidiasis was significantly greater in patients treated every 2 weeks compared with placebo, with most of these infections resolving with antifungal treatment. Rates of non-melanoma skin cancer (NMSC) and other malignancies were not significantly different than expected in the psoriasis population.[58] Major adverse cardiovascular events (MACE) were rare, with only one patient receiving ixekizumab every 4 weeks experiencing a stroke. The rate of MACE was less than 0.2% in the induction period with incidence rate less than 0.7 per 100 patient-years during the long-term component of the clinical trials.

Among 4209 clinical trials patients with a combined 6480 patient-exposure years, there were 29 patients with suspected IBD. Nineteen of these 29 were determined to be definite or probable, with incidence rates of 1.1/1000 and 1.9/1000 patient-exposure years for Crohn's disease and ulcerative colitis, respectively. Of these 19 patients, 15 patients had new onset of IBD, while 4 patients experienced flare up of their pre-existing IBD. Overall, at baseline, there were 16 patients who had a history of IBD, 4 of whom experienced flare up during clinical trials with ixekizumab.[59]

Immunogenicity

Twenty-two percent of patients developed anti-ixekizumab antibodies. The presence of anti-ixekizumab antibodies did not affect response to ixekizumab through week 60 of treatment.[60]

Brodalumab

Brodalumab (AMG 827, Siliq®, Valeant Pharmaceuticals, Bridgewater Township, NJ) is a fully human IgG2 anti-IL-17RA monoclonal antibody. It binds with high affinity to human IL-17RA, which leads to a disruption in the IL-17 pathway by blocking the activity of IL-17A, IL-17F, IL-17A/F heterodimer, IL-17C, and IL-25 molcules.[61]

Dosing

Brodalumab is available as 210 mg/1.5 mL solution in a PFS. It is given at a dose of 210 mg at Weeks 0, 1, and 2 followed by 210 mg every 2 weeks[61] (Table 1).

Phase I clinical trials

In a phase I, randomized, double-blind, placebo-controlled, dose-ranging trial, 25 patients with moderate-to-severe plaque psoriasis were randomized to receive a single dose of placebo or 140 or 350 mg SC or 700 mg IV of brodalumab.[62] In the 350 mg SC arm, 62.5% patients achieved PASI 75 during the study. In the 700 mg IV arm, 88% reached PASI 75 and 38% reached PASI 90 by week 6. Skin biopsy results showed significant reductions in epidermal thickening, keratin 16 (KRT16) levels, and Ki67-expressing cells in patients receiving 350 mg SC and 700 mg IV on day 8 (350 mg SC arm) or day 15 (140 mg SC and 700 mg IV arms). In the 700 mg IV arm, KRT16 protein expression in suprabasal keratinocytes was reduced to the range seen in nonlesional skin by day 43 in 7 of 8 subjects.[62] Similar results were seen in another phase I randomized, placebo-controlled trial of 6 patients.[63]

Phase II clinical trials

In a 16-week dose-ranging, randomized, double-blind, placebo-controlled trial, 188 patients with moderate-to-severe plaque psoriasis were randomized to receive placebo or brodalumab at a dose of 70, 140, or 210 mg SC on day 1 and at weeks 1, 2, 4, 6, 8, and 10, or a dose of 280 mg SC on day 1 and at weeks 4 and 8.[64,65] At week 12, mean improvements in the PASI score were significantly greater in the 140, 210, and 280 mg brodalumab-treated groups than in the 70 mg brodalumab-treated group (85.9%, 86.3%, and 76.0%, respectively, vs. 45.0%; $p < 0.001$) and placebo (16.0%; $p < 0.001$). In the OLE study, a total of 181 patients continued to receive brodalumab at a dose of 210 or 140 mg.[66] sPGA 0/1 was achieved by 90% of patients at week 12 and 72% at week 120. PASI and sPGA improvements were similar for patients who received 210 and 140 mg. Another phase II trial with the same study designed showed similar results.[67,68] At week 52, PASI 75 was maintained in 94.4% and 78.1%, and PASI 90 in 87.5% and 71.2% of patients receiving brodalumab 210 and 140 mg, respectively.[69]

Phase III clinical trials

AMAGINE-1 was a Phase III, randomized, double-blind, placebo-controlled trial. This trial consisted for a 12-week induction phase followed by a withdrawal-retreatment period up to 52 weeks.[70,71,72] A total of 661 patients were randomized in 1:1:1 ratio to biweekly injections of 210 mg, 140 mg, or placebo for 12 weeks. Re-randomization occurred at week 12 for

patients with sPGA 0/1 in the 210 and 140 mg treated groups to either continue their current dose or switch to placebo. Those re-randomized to placebo and subsequently lost disease control were restarted on the original dose. At week 12, PASI 75 was achieved by 83.3%, 60.3%, and 2.7%, of patients in the 210 mg, 140 mg, and placebo groups, respectively. Efficacy was maintained through week 52. The majority of patients re-randomized to placebo during the withdrawal-retreatment phase lost disease control, but the majority of those patients recaptured their response, most within 12 weeks of retreatment.[70,71,72]

AMAGINE-2 and AMAGINE-3 were 2 large double-blind, placebo-controlled, active comparator-controlled Phase III clinical trials.[73] During the 12-week induction phase, patients were randomized in 2:2:1:1 ratio to receive placebo, brodalumab 210 or 140 mg biweekly, or ustekinumab. In the 40-week maintenance phase, patients who received brodalumab during the induction phase underwent a repeat randomization in 2:2:2:1 ratio to receive brodalumab 210 mg biweekly, 140 mg biweekly, 140 mg every 4 weeks, or 140 mg every 8 weeks. Patients receiving placebo during the induction phase were started on brodalumab 210 mg biweekly. Patients in the ustekinumab group continued to receive ustekinumab every 12 weeks until week 52. At week 12, brodalumab 210 mg was superior to ustekinumab (PASI 90, AMAGINE-2: 69.9% vs. 47%; AMAGINE-3:68.9% vs 49%; PASI 75, AMAGINE-2: 86.3% vs .70%; AMAGINE-3: 85.1% vs. 69.3%, $p < 0.001$ for all). However, brodalumab 140 mg was superior to ustekinumab only in AMAGINE-3 ($p < 0.007$). The median time to PASI 75 of brodalumab 210 mg was 4 weeks vs. 8 weeks for ustekinumab. After re-randomization at week 12, patients on 210 mg or 140 mg of brodalumab biweekly maintained or achieved a sPGA 0/1 at a higher rate than 140 mg every 4 or 8 weeks ($p < 0.001$).[73]

Safety and tolerability

The most common AEs included nasopharyngitis, headache, URTI, and arthralgia, which were all mild to moderate in severity.[72,73,74] Cases of transient, self-resolving neutropenia without associated infection were also reported. Psychiatric AEs including depression and suicide ideation and behavior (SIB) were also reported.[75] Three patients out of 4,464 completed suicide. While there is currently no evidence that suggests a causal association between brodalumab and depression or SIB, there is a warning label and Risk Evaluation and Mitigation Strategy (REMS) for SIB per the US FDA.[61]

Immunogenicity

Approximately 3% of patients treated with brodalumab developed antibodies to the drug through the 52-week treatment period. None of the antibodies to brodalumab were classified as neutralizing.[61]

IL-23 inhibitors

The role of IL-23 in psoriasis

IL-23 is upregulated in psoriatic lesions and is though to be the major regulator of the Th17 pathway involved in the pathogenesis of psoriasis.[76] IL-23 is primarily produced by antigen-presenting cells and induces and maintains differentiation of Th17 and Th22 cells, which produce proinflammatory cytokines such as IL-17 and IL-22 that mediate the inflammation and epidermal hyperplasia of psoriasis.[77] IL-23 is composed of p19 and p40 subunits that bind to the IL-23 receptor (IL-23R) and IL-12 receptor b1 (IL-12Rb1), which results in activation of pro-inflammatory Janus kinase 2 (JAK2), tyrosine kinase 2 (TYK2), and signal transducer and activator of transcription (STAT) signaling molecules.[78] IL-23 antagonism blocks downstream effector cytokines observed in psoriasis such as IL-17A, IL-17F, IL-22 and TNF secreted by T cells, natural killer cells, type 3 innate lymphoid cells, neutrophils, and mast cells.[79,80,81]

Guselkumab

Guselkumab (CNTO1959; Janssen Research & Development LLC, Spring House, PA) is a fully human IgG1 lambda monoclonal antibody that binds to the p19 subunit of IL-23 and inhibits the IL-23-specific intracellular and downstream signaling.

Phase I clinical trials

In a randomized, double-blind, placebo-controlled, proof-of-concept study, 24 patients with moderate-to-severe plaque psoriasis were randomized to receive a single dose of placebo or 10, 30, 100, or 300 mg of guselkumab. At week 12, 50% (10 mg), 60% (30 and 100 mg), and 100% (300 mg) of guselkumab-treated patients achieved PASI 75.[82] Improvements in PASI scores were generally maintained through week 24 in guselkumab-treated patients. Analysis of lesional and nonlesional skin biopsy specimens demonstrated decreases in epidermal thickness and T-cell and dendritic cell expression in guselkumab-treated patients compared with placebo-treated patients. At week 12, significant reductions in psoriasis gene expression and serum IL-17A levels were observed in guselkumab-treated patients.[82]

Phase II clinical trials

In a 52-week, dose-ranging, randomized, double-blind, placebo-controlled, active-comparator trial, guselkumab was compared with adalimumab in patients with moderate-to-severe plaque psoriasis.[83] A total of 293 patients were randomized to receive guselkumab, placebo, or adalimumab. Guselkumab was given at a dose of 5 mg at weeks 0 and 4 and every 12 weeks thereafter, 15 mg every 8 weeks, 50 mg at weeks 0 and 4 and every 12 weeks thereafter, 100 mg every 8 weeks, or 200 mg at weeks 0 and 4 and every 12 weeks thereafter through week 40. At week 16, patients in the placebo group crossed over to receive guselkumab at a dose of 100 mg every 8 weeks. At week 16, the rate of patients achieving PASI 75 was higher in each guselkumab group than in the placebo group ($P < 0.001$ for all comparisons). At week 40, the proportion of patients with a PGA 0/1 remained significantly higher in the guselkumab 50 mg, 100 mg, and 200 mg groups than in the adalimumab group (71%, 77%, and 81% vs. 49%, $P < 0.05$ for all comparisons).[84]

Phase III clinical trials

Data from 2 Phase III, multicenter, randomized, double blind, placebo- and comparator- controlled clinical trials, VOYAGE 1 and VOYAGE 2, evaluated efficacy and safety of guselkumab compared with placebo and adalimumab in patients with moderate-to-severe psoriasis over 48 weeks.[84,85] VOYAGE 2 included a randomized withdrawal and retreatment period to evaluate the effect of interrupted treatment on the safety and efficacy of guselkumab.

In VOYAGE 1, a significantly higher proportion of patient receiving guselkumab achieved PASI 90 (2.9% vs. 73.3%) compared with placebo at week 16. Similarly, significantly higher proportion of subjects in the guselkumab vs. adalimumab group achieved PASI 90 (73.3% vs 49.7%) and PASI 75 (91.2% vs 73.1%) at week 16. These findings were maintained through weeks 24 and 48. In VOYAGE 2, a significantly higher proportion of subjects taking guselkumab achieved PASI 90 (2.4% vs. 70.0%) compared with placebo at week 16. Similarly, significantly higher proportion of subjects in the guselkumab vs. adalimumab group achieved PASI 90 (70.0% vs. 46.8%) and PASI 75 (86.3% vs. 68.5%) at week 16. In the randomized withdrawal and re-treatment phase, the median time to loss of PASI 90 response for patients in the withdrawal group was 15.2 weeks (23 weeks after last guselkumab dose). Through week 48, PASI 90 was maintained in 88.6% of patients in the maintenance group vs. 36.8% of those in the withdrawal group ($P < .001$). In the 112 adalimumab non-responders who initiated guselkumab at week 28 (5 weeks after the last adalimumab dose), PASI 90 and PASI 100 rates increased from baseline after switching, reaching 66.1% and 28.6%, respectively, at week 48.[85]

Safety and tolerability

In the Phase I, II, and III clinical trials for guselkumab, the rates of AEs were comparable between guselkumab, placebo, and adalimumab (phase II and III only) groups throughout the durations of the trials.[82,83,84,85] There was no evidence of a relationship between guselkumab dose and the rate of AEs.[83] In Phase III trials, the most common AEs in patients treated with guselkumab were nasopharyngitis, headache, and URTI.[84,85] Serious infection, malignancy, and MACE did not appear to be increased in patients treated with guselkumab compared with placebo and adalimumab. ISR were more common in patients treated with adalimumab compared with guselkumab. There were 5 cases of NMSC, 4 of which were in the guselkumab group (2 BCCs and 3 SCCs) and the other in the adalimumab group.

Immunogenicity

Antibodies to guselkumab were detected in 5.3% (VOYAGE 1) and 6.6% (VOYAGE 2) of patients through week 48. Titers were generally low (81% $\leq$ 1:320) and no association was observed between antibody development and reduced efficacy or ISR occurrence.[84,85]

Tildrakizumab

Tildrakizumab (MK-3222 or SCH 900222; MERCK/Sun Pharma, Kenilworth, NJ) is a high-affinity humanized IgG1/κ monoclonal antibody that binds to the p19 subunit of human IL-23.

Phase I clinical trials

A randomized, placebo-controlled, sequential, rising multiple-dose, proof-of-concept phase I study was conducted to evaluate tildrakizumab for the treatment of moderate-to-severe psoriasis.[86] Seventy-seven patients underwent a 3-part study. In part 1, patients were randomized to intravenous injections of placebo (n = 6) or 0.1 mg/kg (n = 3), 0.5 mg/kg (n = 3), 3 mg/kg (n = 6) or 10 mg/kg (n = 6) of tildrakizumab on days 0, 56 and 84. In part 2, patients were randomized to placebo (n = 11) or 3 mg/kg (n = 15) or 10 mg/kg (n = 14) of tildrakizumab on days 1, 28 and 56. In part 3, patients received placebo (n = 3) or 0.05 mg/kg (n = 6) or 0.1 mg/kg (n = 3) of tildrakizumab on days 1, 56 and 84. Tildrakizumab at a dose of 0.05 to10 mg/kg resulted in a mean reduction in PASI score of 50–80% on day 112 with a sustained response at day 196. In part 2, mean decrease in PASI score of 50% was observed on study day 308, which was 36 weeks after the last administered dose. All patients who received 3 and 10 mg/kg of tildrakizumab achieved PASI 75 in part 1 by day 196 and a majority achieved PASI 75 in part 2 by day 112.[86]

Phase II clinical trials

A 3-part, randomized, double-blind, Phase IIb dose-finding trial was conducted in 355 adults with moderate-to-severe chronic plaque psoriasis. Patients were randomized to receive subcutaneous tildrakizumab (5, 25, 100, 200 mg) or placebo at weeks 0 and 4 (part 1) and every 12 weeks thereafter until week 52 (part 2). Study drug was discontinued at week 52 and participants were followed through week 72 (part 3).[88] At week 16, PASI 75 was achieved in 33.3%, 64.4%, 66.3%, 74.4% and 4.4% in the 5, 25, 100, and 200 mg tildrakizumab and placebo groups, respectively ($P \leq 0.001$ for all comparisons to placebo). PASI 75 was generally maintained through week 52. During part 2, more than 90% of PASI 75 responders at week 16 who continued to receive doses of 100 or 200 mg tildrakizumab maintained PASI 75 at week 52 vs. 70% of those who received a reduction in dose from 100 to 25 mg. For PASI 75 non-responders at week 16 who received an escalated dose of tildrakizumab (from 100 to 200 mg), PASI 75 tended to increase over time. Relapse was seen in only 8 of 222 participants up to week 72 who achieved PASI 75 at week 52 and continued to part 3.[87]

Phase III clinical trials

Phase III trials for Tildrakizumab are currently underway. NCT01722331 (reSURFACE 1) is a 64-week, randomized, placebo-controlled, parallel-design study to evaluate the efficacy and safety/tolerability of subcutaneous tildrakizumab, followed by an optional long-term safety extension study.[88] Patients are randomized to tildrakizumab 100 or 200 mg SC at week 0, 4, and then every 12 weeks or placebo at week 0 and 4, followed by tildrakizumab starting at week 12. The study completion date is August 2019.[89] NCT01729754 (reSURFACE 2) is a 52-week, randomized, active (tildrakizumab)-comparator (etanercept) and placebo-controlled study.[89,90]

Preliminary results for reSURFACE 1 and reSURFACE 2 are available.[91] At weeks 12 and 28, 63% and 77% of patients receiving tildrakizumab achieved PASI 75, respectively. IGA 0/1 was achieved in 57% and 66% of patients with the 100 mg dose at weeks 12 and 28, respectively. Of those receiving the

200 mg dose, IGA 0/1 was attained in 59% and 69% at weeks 12 and 28, respectively. PASI 90 and PASI 100 were observed in 37% (100 mg dose) and 36% (200 mg dose) of patients at week 12, and 54% (100 mg dose) and 59% (200 mg dose) at week 28, respectively. A higher proportion of patients on tildrakizumab achieved PASI 90 and 100 compared with placebo and etanercept.[91,92]

Safety and tolerability

Safety data are available from Phase I and II studies. The overall incidence of AEs was generally similar for all treatment arms and did not differ from placebo.[86,87] No dose-related increase in AEs was observed with tildrakizumab. In the Phase I trial, the most common AEs included headache, nasopharyngitis, URTI, and cough.[86] In Phase II trial, the most frequent AEs were nasopharyngitis and headache, which occurred with similar frequency in all treatment groups.[87]

Immunogenicity

In the Phase I trial, of the 56 tildrakizumab-treated subjects, 51 were pre-treatment negative for ADA.[86] Nine of these (18%) developed ADA and 5 of these 9 showed lower tildrakizumab exposure than ADA negative patients. ADA-positive patients did not differ in their PASI response or adverse effect profile compared with ADA-negative patients. In the Phase II trial, 46 of the 355 participants developed ADAs.[87] There was no apparent correlation between development of ADAs and AEs.

Risankizumab

Risankizumab (BI 655066, Abbvie, North Chicago, IL) is another fully human fully human IgG1 monoclonal antibody specific for the IL-23 p19 subunit.

Phase I clinical trials

A single-rising-dose, multicenter, randomized, double-blind, placebo-controlled, within-dose cohort phase I trial has been conducted to assess safety of risankizumab.[93] Thirty nine patients received risankizumab at a dose of 0.01, 0.05, 0.25, 1, 3, or 5 mg/kg intravenously (n = 18), 0.25 (n = 13) or 1 mg/kg (n = 8) subcutaneously, or matched placebo. At week 12, PASI 75, PASI 90, and PASI 100 were observed in 87% (27/31, $P < .001$ vs. placebo), 58% (18/31, $P = .007$ vs. placebo), and 16% (5/31, $P = .590$ vs. placebo) of patients receiving a single dose of risankizumab at any dose, respectively, and improvement was observed as early as week 2. Risankizumab treatment resulted in reduced expression of lesional skin genes associated with IL-23/IL-17 signaling pathways and normalization of psoriatic lesion gene expression profiles to a profile approaching that of nonlesional skin. Significant correlation between treatment-associated molecular changes and PASI scores was observed.[93]

Phase II clinical trials

In a 48-week, multicenter, randomized, dose-ranging, head-to-head Phase II trial, a total of 166 patients received subcutaneous injections of risankizumab (a single 18 mg dose at week 0 or 90 or 180 mg doses at weeks 0, 4, and 16) or ustekinumab (45 or 90 mg, according to body weight, at weeks 0,4, and 16).[94] At week 12, PASI 90 was achieved in 77% (64/83) of patients receiving risankizumab (90 and 180 mg groups, pooled) as compared with 40% (16/40) of patients receiving ustekinumab ($P < 0.001$). PASI 100 was observed in 45% in the risankizumab group (pooled 90 and 180 mg) compared with 18% in the ustekinumab group. Efficacy was generally maintained up to 20 weeks after the final dose of 90 mg or 180 mg of risankizumab. Complete clearing was maintained in 29% and 26% of the patients 32 weeks following the last dose of risankizumab in the 90 and 180 mg groups, respectively.

Safety and tolerability

Over the 24 weeks after treatment in the single-dose Phase I trial, 65% (20/31) of patients receiving risankizumab administered intravenously or subcutaneously experienced an AE compared with 88% (7/8) of patients receiving placebo.[93] The most frequently reported AEs were URTI, nasopharyngitis, and headache. The severity of the AEs did not appear related to the dose of drug. There were no SAEs considered related to

Table 2. PASI 75 and PASI 90 rates from Phase III trials of TNFα inhibitors vs. newer agents targeting IL-12, -23, and -17 for the treatment of psoriasis.

		PASI 75			PASI 90		
	Maintenance dosing	Week 10	Week 12	Week 16	Week 10	Week 12	Week 16
TNFα inhibitors							
Etanercept (Enbrel)[95]	50 mg BIW		47			19	
Adalimumab (Humira)[96]	40 mg Q2W		68	71		37	45
Infliximab (Remicade)[97]	5 mg/kg Q8W	80–85			57–60		
Newer Agents							
Ustekinumab (Stelara)[21,22]	45 mg Q12W		66.7–67.1			41.6–42.3	
	90 mg Q12W		66.4–75.7			36.7–50.9	
Secukinumab (Cosentyx)[40–43]	300 mg Q4W		77.1–30.1			54.2–59.2	
	150 mg Q4W		67.0–84.4			39.1–41.9	
Ixekixumab (Taltz)[54–56]	80 mg Q2W		87.3–89.7			68.1–70.9	
	80 mg Q4W		77.5–84.2			59.7–65.3	
Brodalumab (Siliq)[70–73]	210 mg Q2W		83.3–86.3			68.9–70.3	
	140 mg Q2W		60.3–69.2			42.5–52.0	
Guselkumab [84,85]	100 mg Q8W			86.3–91.2			70.0–73.3
Tildrakizumab[91]	100 or 200 mg Q12W		63.0			36.0–37.0	

Abbreviations: BIW-twice weekly, NA-not available, PASI-Psoriasis Area and Severity Index, Q2W-every 2 weeks, Q4W-every 4 weeks, Q8W-every 8 weeks, Q12W-every 12 weeks, TNF-tumor necrosis factor

Table 3. The most common side effects of TNFα inhibitors vs. newer agents targeting IL-12, -23, and -17 for the treatment of psoriasis.

	Most common side effects	Boxed warnings
TNFα inhibitors		
Etanercept (Enbrel)[98]	>5%: infections and injection site reactions	Serious infections, malignancies
Adalimumab (Humira)[99]	>10%: infections (e.g. upper respiratory, sinusitis), injection site reactions, headache and rash	Serious infection, malignancy
Infliximab (Remicade)[100]	>10%: infections (e.g., upper respiratory, sinusitis, and pharyngitis), infusion-related reactions, headache, and abdominal pain	Serious infection, malignancy
Newer Agents		
Ustekinumab (Stelara)[16]	≥3%: nasopharyngitis, URTI, headache, and fatigue	None
Secukinumab (Cosentyx)[37]	≥1%: nasopharyngitis, diarrhea, URTI	None
Ixekixumab (Taltz)[51]	≥1%: injection site reactions, URTI, nausea, and tinea infections	None
Brodalumab (Siliq)[62]	≥1%: arthralgia, headache, fatigue, diarrhea, oropharyngeal pain, nausea, myalgia, injection site reactions, influenza, neutropenia, tinea infections	Suicidal ideation and behavior
Guselkumab[84,85]	nasopharyngitis, headache, URTI	Not Applicable
Tildrakizumab[86,87]	headache, nasopharyngitis, URTI, cough	Not Applicable
Risankizumab[93]	URTI, nasopharyngitis, and headache	Not Applicable

Abbreviations: URTI-upper respiratory tract infection

risankizumab. In the Phase II trial, the most common AE (< 10% of patients) was nasopharyngitis.[94] BCC developed in 2 patients who were treated with risankizumab and one patient had a major adverse cardiac event.

Discussion

Recent developments in monoclonal antibodies blocking IL-12, -23, and -17 for the treatment of moderate-to-severe psoriasis show promising efficacy in clinical trials. Compared to traditional TNFα inhibitors such as etanercept,[95] adalimumab,[96] and infliximab,[97] Phase III trials of newer biologic agents, specifically secukinumab, ixekizumab, brodalumab, and guselkumab show higher rates of PASI 75 and PASI 90 (Table 2). These monoclonal antibodies also have favorable side effect profiles. Compared to TNFα inhibitors, which carry US FDA boxed warnings for serious infection (including tuberculosis activation) and malignancy,[98,99,100] ustekinumab, secukinumab, and ixekizumab have no such boxed warnings.[16,37,51] Patients should still be screened for TB before starting any biologic agent. In addition, brodalumab carries a boxed warning for suicidal ideation and behavior[62] and all 3 IL-17 agents carry a unique concern for activation or exacerbation of IBD.[37,52,62] Summary of safety profiles of the TNFα inhibitors compared with the newer monoclonal antibody agents are shown in Table 3. Lastly, the rates of ADA formation vary greatly among agents (< 1% in secukinumab to 22% in ixekizumab) but appear not to be neutralizing and did not affect safety or efficacy of the drug in Phase III trials. On the other hand, studies have shown that ADA to TNFα inhibitors appear to be neutralizing and may be related to reduced drug plasma levels and efficacy.[101]

Expert opinion

Given the widely available options for biologic agents for the treatment of moderate-to-severe psoriasis today, it can be a difficult task for the clinician to choose "the best" agent. The authors feel that there is no "one right answer" when choosing a treatment of a particular patient but several considerations unique to each individual patient should be considered:

1. Efficacy: infliximab and the IL-17 agents appear to have the highest PASI 75 and 90 rates in clinical trials.
2. Speed of onset: patients who are erythrodermic or have other urgent circumstances may also consider infliximab or IL-17 agents which have rapid onset of action.
3. Safety: Although there are warnings regarding serious infection and malignancy, the traditional TNFα inhibitors have close to 20 y of long-term safety data vs. newer agents.
4. Past medical history: some medical problems may preclude the patient from certain agents (i.e. heart failure and TNFα inhibitors, demyelinating diseases and TNFα inhibitors, IBD and IL-17 agents, active depression and brodalumab, etc.).
5. Presence or absence of psoriatic arthritis: some biologic agents are more effective for psoriatic arthritis than others.
6. Patient convenience and compliance: i.e., infliximab requires infusion vs. subcutaneous self-administration of all other agents; needle-phobic patients or those who travel frequently may benefit from less frequent dosing schedules, etc.
7. Insurance or cost issues
8. The authors recommend that for each patient, a fine balance all of the above relevant factors can help to reach a decision that is agreeable to both the clinician and the patient.

Conclusion

Although long-term data and real-world experiences of these biologic agents are needed to further assess their therapeutic implications, the available data to date show an extremely promising future for deepening our knowledge of psoriasis immunopathogenesis and treatment.

Disclosure of potential conflicts of interest

Dr. Bhutani conducts research for AbbVie, Janssen, Merck/Sun Pharmaceutical Industries, Mela, and Novartis. Mr. Jeon, Dr. Sekhon, Ms. Yan, Ms. Afifi, and Dr. Nakamura have no conflicts of interest to disclose.

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