

IL-17 and -23 Inhibitors for the Treatment of Psoriasis

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Abstract

Psoriasis is a chronic inflammatory skin condition with a significant global burden of disease and a wide array of potential treatment options, ranging from topical to systemic therapies. There are currently 11 biologic agents approved by the U.S. Food and Drug Administration (FDA) for the treatment of moderate-to-severe psoriasis. The emergence of IL-17 and IL-23 inhibitors has significantly improved the efficacy and safety of treatment options for patients with psoriasis. Given the number of potential therapies, a variety of factors may be considered in optimising a patient's regimen, including efficacy, safety, cost, persistence rate, and discontinuation rate. The aim of this narrative review is to provide a concise yet comprehensive review of the biologic agents that inhibit IL-17 or IL-23 available for patients 18 years of age or older with moderate-to-severe psoriasis.

Key Points

1. Psoriasis is a chronic and debilitating dermatologic condition with significant global burden of disease. Given the arsenal of newer biologics available for treatment of moderate-to-severe plaque psoriasis, there is a need for a condensed review of these medications that incorporates not only data on efficacy and side effects, but also elements of the patient experience.

2. This manuscript provides a comprehensive and holistic, yet concise, analysis of these biologics, and is designed to serve as a useful reference for clinicians when deciding how to best optimise the management of psoriasis for each patient.

3. The newer biologics available for treatment of moderate-to-severe plaque psoriasis in adults have shown clear superiority in many metrics to older treatment options. Determining the optimal biologic of choice for each patient requires consideration of factors such as patient preference and goals, safety, cost, long-term efficacy, rapidity of response, comorbidities, biologic naivety, and the unique features of each biologic.

INTRODUCTION

Psoriasis is a chronic inflammatory skin disorder affecting approximately 60 million people worldwide.¹ The condition presents with rapid hyperproliferation and dysregulated differentiation of epidermal keratinocytes, manifesting clinically as salmon pink plaques with overlying silvery-white scale.² Mild disease is often treated topically, while moderate-to-severe cases require systemic therapy. The advent of biologic agents has significantly improved treatment outcomes and provided more favourable safety profiles than traditional immunosuppressive therapies, such as methotrexate.³ Biologic agents modulate cytokine activity implicated in the pathogenesis of psoriasis.³ IL-23 is a cytokine involved in the immune response to bacterial and fungal infections.² Dysregulation of IL-23 production may result in autoimmune inflammation.² The IL-23 complex is also an upstream regulatory cytokine that impacts proliferation of T helper 17 cells, which secrete cytokines such as IL-17, IL-22, and TNF- α .^{2,3} These inflammatory mediators provide targets that can be intervened upon with biologic agents.

There are currently eleven biologic medications approved by the U.S. Food and Drug Administration (FDA) for treatment of moderate-to-severe psoriasis.³ Given the multitude of treatment options, a host of factors must be considered when choosing the best regimen.⁴⁻⁷ Of these, adherence, patient satisfaction, and preference are significant and heavily interlaced.^{6,8,9} Medication adherence is the degree to which a person's behaviour corresponds with the agreed recommendations from a healthcare provider.^{4,10} Patient preferences and satisfaction play a key role in medication adherence, and should be taken into account so the goals and perceptions of both the patient and physician are in alignment.^{6,8,11,12} These variables can be quantified using surrogate measures such as efficacy, safety, cost, persistence rate, and discontinuation rate.⁴ The Psoriasis Area and Severity Index (PASI) score is used to quantify the severity of psoriasis by rating three variables (erythema, induration, and scale of psoriatic plaques) to produce a score ranging from 0 to 72.¹³ Mild-to-moderate psoriasis has a PASI score of ≤ 10 , while severe psoriasis has a score of >10 .¹³ Nowadays, the

FDA and clinical trials use a reduction of $\geq 75\%$ of PASI, termed PASI75, as an endpoint to assess the efficacy of psoriasis therapies.¹⁴ However, the severity of psoriasis is not a reliable measure of the psychological impact of disease on health-related quality of life (QoL).¹⁵ Therefore, patient-reported outcomes are a critical component of treatment evaluation.¹⁵

In the past decade, with the advent of IL-17 and IL-23 inhibitors, the improvement in efficacy and safety have provided an unprecedented change in the management of psoriasis. Indeed, although several clinical trials have demonstrated the improved profiles of these biologics, real-life data are important because these refer to patients who are typically excluded by clinical trials.¹⁶ Rigid inclusion and exclusion criteria of clinical trials frequently exclude patients with several comorbidities, with other forms than plaque psoriasis, and with ongoing concomitant medications such as elderly patients.^{17,18} This review provides a concise yet thorough reference of the biologic agents that inhibit IL-17 or IL-23 available for patients aged 18 years or older with moderate-to-severe psoriasis. Additionally, while there are further biologic and non-biologic treatment options for psoriatic arthritis, the authors only discuss psoriatic arthritis therapy in the context of agents appropriate for treatment of plaque psoriasis.

REVIEW

IL-17 Inhibitors

Secukinumab

Secukinumab is a fully humanised IgG1 κ monoclonal antibody that selectively inhibits IL-17A.³ Initial dosing is 300 mg, administered subcutaneously (SQ) at Weeks 0, 1, 2, 3, and 4, followed by 300 mg SQ maintenance dosing every 4 weeks.³ For those patients with a lower total body weight and/or decreased severity of psoriasis, 150 mg every 4 weeks may be a suitable alternative maintenance dose.³ Conversely, patients with a more resistant form of disease and/or a higher total body weight may benefit from a more aggressive maintenance regimen of 300 mg SQ every 2 weeks.³

In terms of efficacy, in the ERASURE and FIXTURE randomised controlled trials (RCT), secukinumab had a PASI75 rate of 82% and PASI90 of 59%.¹⁹ It is effective in treatment of plaque psoriasis and difficult to treat clinical manifestations such as scalp psoriasis, nail psoriasis, and palmoplantar psoriasis.³ In a recent real-life monocentric cohort study, secukinumab showed considerable efficacy in treatment of erythrodermic psoriasis and sustained drug survival through Week 48 of treatment.²⁰ Secukinumab has also demonstrated high satisfaction and perceived improvement by users.¹²

Additionally, it is effective in the treatment of psoriatic arthritis.^{3,5}

Secukinumab has a very high recapture rate; after cessation of treatment and subsequent exacerbation of psoriasis, resuming secukinumab led to 95% of patients reaching PASI75 by Week 12 of treatment.³ This quality suggests utility for patients under circumstances where injections have been missed.

Secukinumab has the highest adherence rate out of all the IL-17 inhibitors, ranging from 46–52% at 9 months of treatment.²¹ This may be because it is one of the best-tolerated biologics in terms of injection site reactions.³ Compared to all the other IL-17 inhibitors, secukinumab had the most extensive safety record in terms of patient data, and no black box warnings currently exist.³ Only a very mild increase in superficial fungal and yeast infections has been observed.³ The incidence of new-onset inflammatory bowel disease (IBD) is less than 1 out of 1,000 patients on secukinumab, but increased side effects have been documented among patients with IBD taking secukinumab for other conditions.^{3,22} Therefore, it should be used with caution in these patients.⁵

Ixekizumab

Ixekizumab is a humanised IgG4 monoclonal antibody with high affinity against IL-17A.³ The regimen requires an initial loading dose of 160 mg SQ at Week 0, followed by 80 mg SQ at Weeks 2, 4, 6, 8, 10, and 12.³ Maintenance dosing is 80 mg SQ every 4 weeks.³

In terms of efficacy, in the UNCOVER-1, -2, and -3 RCTs, ixekizumab showed a PASI75

of 83% and PASI90 of 67%.¹⁹ It is also the fastest-acting biologic.³ Ixekizumab is FDA-approved for plaque psoriasis, psoriatic arthritis, ankylosing spondylitis, and non-radiographic axial spondyloarthritis.³ It is also the only biologic with FDA approval for the treatment of genital psoriasis.³ In a real-life case series of adult patients affected by genital psoriasis, ixekizumab significantly improved disease severity, itch, and QoL.²³

A relatively higher rate of injection site reactions and pain has been reported with ixekizumab; however, during Phase III trials, 97% of patients did not consider this significant enough to stop treatment, and the reactions improved over the treatment course.^{3,24} Ixekizumab is now formulated without citrate to reduce injection site complaints.²⁵ Concern regarding the risk of IBD exists and warrants caution when using ixekizumab in these patients. However, the incidence of new-onset IBD in patients on ixekizumab is less than one out of 1,000.³ Additionally, data from an integrated database of seven ixekizumab trials found the prevalence of IBD cases to be less than 1%.⁵ Lastly, there is a slight increase in superficial yeast and fungal infections in patients on ixekizumab.³

Ixekizumab has shown the highest cumulative clinical benefits for complete skin clearance and the highest cumulative days at PASI100 (23 weeks of the year) relative to guselkumab, secukinumab, and TNF- α inhibitors.⁶ Ixekizumab also has the best patient satisfaction, attitude, and self-reported improvement scores compared to secukinumab and ustekinumab.¹² In a real-life retrospective observational study, ixekizumab led to a rapid and progressive improvement in average PASI and patient satisfaction, and the clinical results were maintained for up to 4 years of continuous treatment.²⁶ These results were not influenced by specific factors such as gender, previous biologic therapies, and average BMI.²⁶

In another study population of patients with difficult-to-treat psoriasis and a poor response to TNF- α inhibitors, ixekizumab was significantly better than placebo in improving symptoms of disease, and this further correlated with improved mental symptoms, such as better mood and self-esteem.²² In another study of patients with psoriasis with moderately severe depressive symptoms, a 12-week course of ixekizumab

showed improved remission rates of depression for 40% of patients, along with decreased parameters of systemic inflammation.²² Ixekizumab has the second-highest adherence rates out of the IL-17 inhibitors, following secukinumab, at 46% after 9 months of treatment.²¹

Brodalumab

Brodalumab is a humanised monoclonal antibody that binds the IL-17A receptor subunit, and blocks the activities of not only IL-17A but also IL-17F, IL-17A/F, and IL-17E.³ The initial loading dose for brodalumab is 210 mg SQ at Weeks 0, 1, and 2, followed by a maintenance dose of 210 mg SQ every 2 weeks.³

In terms of efficacy, in the AMAGINE-2 and -3 RCTs, brodalumab showed a PASI75 of 85% and PASI90 rate of 70%.¹⁹ Brodalumab has a strong efficacy and rapid onset of action.³ In a single-centre, real-life, retrospective study, brodalumab showed a significant reduction in mean PASI and body surface area, and was comparable to ixekizumab in terms of efficacy and safety.²⁷

Brodalumab has a black box warning for suicide and suicidal ideation. While clinical trials did note the presence of suicidal ideation and behaviours in patients, subsequent detailed analysis of these trials failed to identify a causal association between the drug and these events.⁵ Furthermore, it was found that patients were not excluded for history of suicidal ideation/behaviour or illicit drug/alcohol history, suggesting a potential confounding effect.³ Currently, the USA is the only country with this black box warning.^{3,28} There have also been higher rates of superficial skin infections seen with brodalumab, which may be attributed to the more extensive blockade on multiple aspects of the IL-17 receptor.²⁴ Lastly, caution should still be taken when considering brodalumab for patients with existing IBD. In a study on patients with moderate-to-severe Crohn's disease, brodalumab was ineffective and caused increased exacerbations in those patients with active disease.²² This finding was also observed in a Phase II RCT evaluating the efficacy of brodalumab in treatment of Crohn's disease.⁵

An advantage of brodalumab is its significantly lower cost of treatment combined with high PASI rates, rendering it the most cost-effective choice

for treatment of moderate-to-severe psoriasis.³ In comparison to other biologics, brodalumab was shown to have the third-highest cumulative clinical benefit for skin clearance, along with the third-highest cumulative days at PASI100.⁶ Lastly, brodalumab was found to have the highest efficacy in complete skin clearance as early as Weeks 4 and 8 of treatment.¹¹

Bimekizumab

Bimekizumab is a humanised IgG1κ monoclonal antibody that selectively inhibits the IL-17A and IL-17F cytokines.²⁹ While it is still pending FDA approval, bimekizumab has shown a high degree of skin clearance with rapid onset of action and persistent results over time.^{29,30} Phase III trials have demonstrated superior efficacy and clinical results compared to placebo, adalimumab, ustekinumab, and secukinumab.³¹ In a recent network meta-analysis, bimekizumab was statistically superior to all other biologics in attaining PASI90 and PASI100 levels.³² The most commonly reported safety concern is oral candidiasis, but most cases have been mild-to-moderate and do not necessitate cessation of treatment.³¹ The IL-17 pathway is involved in inhibiting fungal infections, and while this is an adverse effect known in all IL-17 inhibitors, it is more common with bimekizumab.³¹

In the BE READY Phase III RCT, bimekizumab's clinical efficacy was sustained for 8 months after discontinuation, indicating its high clinical durability.³¹ Additionally, given adherence to medical treatment may be improved with a regimen of less-frequent dosing, bimekizumab's maintenance regimen offers an advantage, as the schedule may be every 4 weeks or every 8 weeks, versus the every-4-week regimen of secukinumab and ixekizumab and the every-2-week regimen of brodalumab.³¹

IL-23 Inhibitors

Guselkumab

Guselkumab is a completely human IgG1γ monoclonal antibody that blocks the p19 subunit of IL-23.^{33,34} The dosing regimen for this biologic agent is an initial loading dose of 100 mg SQ at Weeks 0 and 4, followed by 100 mg SQ as maintenance dosing every 8 weeks.³ Guselkumab is FDA-approved for psoriatic arthritis.

In terms of efficacy, in the VOYAGE-1 RCT, guselkumab showed a PASI75 of 91% and PASI90 of 73%.¹⁹ The ECLIPSE study found guselkumab to have superior long-term efficacy based on PASI90 at Week 48 compared to secukinumab.³⁴ In real-life studies, guselkumab has shown considerable efficacy and safety in real-world clinical practice for up to 3 years of treatment.³⁵⁻³⁷ It is also a valuable option for patients with psoriasis who have previously failed anti-IL17 treatments.³⁵ Guselkumab has also shown the highest overall drug survival associated with effectiveness and safety compared to other biologics.³⁸

Results from VOYAGE 2 found guselkumab to be associated with greater improvements in symptoms of anxiety and depression in patients with psoriasis when compared to a placebo and adalimumab.⁵

Guselkumab has no FDA warnings for an increased risk of infections from superficial tinea or candidiasis.³ There also have been no reports of an increased risk of IBD.³ In a comparison to adherence rates among adalimumab, certolizumab, etanercept, guselkumab, ixekizumab, secukinumab, and ustekinumab, guselkumab had an adherence rate of 56.9% at 9-month follow-up, which was second-highest after ustekinumab.²¹

Risankizumab

Risankizumab is a fully humanised IgG1 monoclonal antibody that selectively targets the p19 subunit of IL-23.³⁹ The dosing regimen begins with 150 mg SQ injections given at Weeks 0 and 4 for initiation.³ The maintenance dose is 150 mg every 12 weeks for a total of 4 injections annually.³ Risankizumab is FDA-approved for psoriasis and psoriatic arthritis.

In terms of efficacy, risankizumab achieved a PASI90 rate of 75.3% in the UltIMMa-1 Phase III trial.⁴⁰ The UltIMMa-1 and -2 clinical trials showed that risankizumab has superior efficacy to both placebo and ustekinumab.^{40,41} This agent has a quick onset of action and high durability of 295 days for recurrence after discontinuing treatment.^{3,42,43}

Risankizumab has the second-highest cumulative clinical benefits in regards to total skin clearance.⁶ Compared to other psoriasis

treatments, risankizumab has the most favourable long-term benefit-risk profile due to its excellent PASI response rate and lowest rate of adverse events (AE).⁴⁴ Available data demonstrates that risankizumab is safe and well-tolerated at 58 months.³ Serious AEs in the NCT02054481 trial⁴⁵ included two patients with basal cell carcinoma, one patient with a myocardial infarction, and one patient with a cerebrovascular accident;⁴⁰ however, there was no significant difference in rates of AEs across all the groups in the Gordon et al. trial.⁴¹ In real-life studies, risankizumab has shown high efficacy in treatment of difficult-to-treat areas (scalp, nails, genitalia, lower limbs, and palmo-plantar area) and in patients with psoriasis who have previously failed anti-IL17 treatments.^{46,47}

Tildrakizumab

Tildrakizumab is a humanised IgG1 monoclonal antibody designed to target the p19 subunit of IL-23.^{2,3} The initial loading dose is 100 mg SQ at Weeks 0 and 4, followed by a maintenance dose of 100 mg every 12 weeks.³ Tildrakizumab is readily covered by Medicare Part B.³ Thus, it cannot be self-administered; patients must receive their injections at injection or infusion centres, including their provider's office. Since there are only four maintenance injections per year, given its long half-life, this is a favourable regimen for long-term management and adherence.^{3,48}

In terms of efficacy, in the reSURFACE-1 and -2 RCTs, tildrakizumab had a PASI75 of 61–64% and PASI90 of 35–39%.¹⁹ Real-life studies have shown similar reported efficacy and safety, without significant risk of AEs even in more fragile patients (such as the elderly population) and in other forms of psoriasis such as erythrodermic psoriasis.^{49,50} In a real-world observational study, tildrakizumab also provided considerable efficacy in treatment of difficult-to-treat areas.⁴⁶

Tildrakizumab had the least number of AEs occurring in at least 1% in Phase II trials of all biologics for psoriasis, which may be an important consideration for clinicians interested in safety, especially in elderly patients.³ The long-term incidence of AEs of special interest was comparable with results from the psoriasis reference population captured in the Psoriasis Longitudinal Assessment and Registry.⁵¹

There was no specific association with or worsening of IBD and only one suspected case of new-onset Crohn's disease over the course of 5 years of treatment.^{48,51} Thaci et al.⁵¹ reported no severe cases of candidiasis in a pooled analysis of two randomised Phase III clinical trials over a 5-year period. Studies have reported improved Dermatology Life Quality Index (DLQI) metrics with tildrakizumab that correlated with Week 28 PASI improvement.^{48,49} Patients that failed to achieve a minimum of 50% PASI improvement at Week 28 could be differentiated as early as Week 8 from their PASI score.^{48,49} This suggests that an informed decision about whether or not to continue tildrakizumab therapy can be made before the third dose, around Week 12 or 16.⁵²

IL-12/23 Inhibitor

Ustekinumab

Ustekinumab is a biologic agent that inhibits the p40 subunit of both IL-12 and the IL-23.⁵³ The dosing for this biologic is weight-dependent.³ For patients who weigh less than 100 kg, there is an initial loading dose of 45 mg SQ at Weeks 0 and 4, followed by 45 mg maintenance injections every 12 weeks.³ For patients who weigh more than 100 kg, the initial loading dose is 90 mg SQ at Weeks 0 and 4, followed by maintenance doses of 90 mg every 12 weeks.³

Ustekinumab has shown high efficacy and a favourable safety profile.⁵⁴ In patients who had a response to this biologic at Week 40 and continued maintenance treatment, 80.9% of the patients who were taking 45 mg and 82.7% taking 90 mg achieved a PASI75 response at Year 3 of treatment.⁵⁵ Ustekinumab is FDA-approved for treatment of psoriatic arthritis and IBD.³ Although it has lower efficacy values than newer biologics, ustekinumab is the biologic that is least frequently discontinued due to loss of efficacy.^{3,54,56}

Ustekinumab is one of the most expensive biologics, but its sporadic dosing regimen gives it a favourable cost-efficacy profile.⁵⁴ Many patients favour the every 12 weeks maintenance schedule.⁵³ For up to 3 years of follow-up, ustekinumab was generally well tolerated, and none of the reported AEs necessitated treatment discontinuation.⁵⁵ Ustekinumab has a satisfaction rating of 77%, which is the highest rating for

biologics.^{54,55} Patients using ustekinumab have reported significantly higher perceived improvement of disease compared to those using other biologics.¹²

DISCUSSION

Overall, patients tend to view systemic psoriasis treatments positively and report high treatment satisfaction scores.¹² Patients with psoriasis using biologics specifically have shown higher rates of satisfaction with improved skin clearance, long-term efficacy, rapidity of response, and significantly lower risk of AEs as compared to those using non-biologics.⁵⁷ While users may initially express hesitation or concern due to the mode of administration, these feelings tend to dissipate with appropriate counselling, education, and familiarity over time.⁵⁷ Good communication between the clinician and patient is a significant positive predictor of treatment satisfaction and success.¹²

The most common reasons for treatment discontinuation and/or switching to a new medication are loss of efficacy with time and AEs, followed by overall ineffectiveness and high expense of treatment.^{54,58,59} Commonly reported obstacles to obtaining biologic treatment are issues with insurance approval, cost of treatment, and difficulties related to the pharmacy.⁵⁸

While cessation of treatment is not recommended and will likely lead to a relapse, it may be necessary under certain circumstances such as financial strain, intolerable side effects, pregnancy, scheduled surgery, and extended travel with reduced access to healthcare.⁶⁰ If such situations are known in advance, it is important to consider the benefits of biologic use in these conditions.

Biologics have shown a longer duration of sustained response after cessation of use compared to oral systemics.⁶⁰ The IL-12/23 and IL-23 inhibitors have shown the longest time to relapse (defined by the loss of PASI90), with a duration of 21–42 weeks.⁶⁰ The IL-17 inhibitors have an average time to relapse of 7–24 weeks, and the TNF- α inhibitors have an average time to relapse of 4 weeks.⁶⁰

For both the clinician and patient, long-term benefits and risks associated with treatment are important to discuss when choosing a biologic.⁴⁴ All biologic drugs have shared side effects depending largely on the class of biologic.⁶¹ The most common side effects associated with the IL-17 inhibitors include headache, nasopharyngitis, and infections.³¹ This class of biologics is also most notably associated with induction or worsening of IBD.^{31,62} The most common side effects associated with the IL-23 inhibitors include nasopharyngitis, upper respiratory tract infections, and injection site reactions.^{3,33,55} Collectively, IL-17 and IL-23 inhibitors have good safety profiles and are largely well-tolerated by patients.⁶¹

CONCLUSION

The newer biologics available for treatment of moderate-to-severe plaque psoriasis in adults have shown undisputable superiority in many parameters to older treatment options. Given the significance of this therapeutic arsenal, it is important for providers to be both familiar and comfortable with determining the optimal biologic of choice for each patient. These factors include patient preference and goals, safety, cost, long-term efficacy, rapidity of response, comorbidities, biologic naivety, and the unique features of each biologic described in this review.

The landscape of psoriasis treatment will certainly continue to evolve as researchers identify new potential therapeutic targets, creating a promising future for the treatment of this frequently debilitating and recalcitrant disease.

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