



EVOLUTION OF BIOLOGIC THERAPY IN PLAQUE PSORIASIS: FROM TNF- α INHIBITORS TO IL-23 INHIBITORS

¹Uttam Prasad Pant and *¹Xiao-Lan Li

¹Department of Dermatology and Venereology, the Second Affiliated Hospital of Kunming Medical University

ABSTRACT

Biologic therapy has fundamentally changed the treatment landscape of plaque psoriasis through evolving insights into the mechanisms of its immunopathogenesis. This narrative review aims to discuss the evolution of biologic therapy from tumor necrosis factor-alpha (TNF- α) inhibitors to increasingly selective interleukin (IL)-23-targeted therapies, with emphasis on the relationship between immunologic advances, clinical efficacy, patient-reported outcomes, and emerging treatment strategies. The findings demonstrate a transition from inhibiting TNF- α to focusing on IL-12/23, IL-17, and selective IL-23 p19 inhibition, reflecting the increasingly selective modulation of the IL-23/Th17 inflammatory pathways. This progress in treatment has raised expectations for skin clearance, with PASI90 and PASI100 gaining importance, along with patient-reported improvements in quality of life as assessed by the Dermatology Life Quality Index. Recent advancements in biologics have expanded the range of treatment possibilities, with a personalized approach that takes into account individual disease traits, existing comorbidities, treatment goals, and the overall burden of therapy. Future studies should include real-world data and precision-medicine approaches to enhance personalized and sustainable treatment plans. Overall, the evolution of biologic therapy represents a shift from broad cytokine inhibition to a more targeted, patient-centered approach in managing plaque psoriasis.

Keywords: Psoriasis; Biological Products; Tumor Necrosis Factor-alpha; Interleukin-17; Interleukin-23; Targeted Therapy

INTRODUCTION

Plaque psoriasis is the most common clinical phenotype of psoriasis, a chronic relapsing immune-mediated inflammatory skin disease, that affects approximately 2-3% of the worldwide population.^[1,2] Skin lesions are characterized by clearly demarcated red plaques that are painful and covered in silver or white scales and beyond the skin, causing systemic inflammatory manifestations in the joints and are associated with a number of metabolic syndromes and cardiovascular diseases with a significant impact on physical, psychological, and social health.^[1,3] Plaque psoriasis management has thus shifted from controlling cutaneous symptoms to maintaining clear lesions, reducing systemic complications and improving overall quality of life.

A few decades ago, topical therapies, phototherapy, and traditional systemic agents, such as methotrexate, cyclosporine, and acitretin were available. Although, these treatments still hold clinical significance, their effectiveness, treatment burden, and long-term tolerability have limitations, which have led to the development of more targeted therapies. As the understanding of the immunopathogenesis of psoriasis progressed; several key cytokines pathways, particularly tumor necrosis factor- α (TNF- α) and the interleukin (IL)-23/Th17 axis were identified, which laid the groundwork for biologic drug development. Now, biologic agents target specific mechanism in immunopathology to improve PASI90 and PASI100 response rates and patient-reported outcomes such as Dermatology Life Quality Index(DLQI).^[1,4] This review examines the evolution of biologic therapy in plaque psoriasis from TNF- α inhibitors to IL-23 inhibitors, highlighting the immunopathogenic advances that have guided therapeutic development, changes in clinical outcomes, and the implications of these advances for current and future treatment strategies.

METHODS

Relevant literature was searched from PubMed, Google Scholar, and The Directory of Open Access Journals (DOAJ) for plaque psoriasis and biologic therapy. The keywords included 'plaque psoriasis', 'biologic therapy', 'pathogenesis', 'TNF α inhibitors', 'IL-12/23 inhibitors', 'IL-17 inhibitors', 'IL-23 inhibitors', 'PASI', 'DLQI', 'phase3 trials', 'clinical outcomes', 'treatment efficacy', and 'biomarkers'. The terms were linked together by using Boolean operators to expand or contract the search as necessary. The review included landmark randomized controlled trials, observational and real-world studies, long-term extension studies, systematic reviews, meta-analyses, clinical guidelines, and relevant narrative reviews that contributed to understanding the evolution of biologic therapy in plaque psoriasis. Reference lists of relevant articles were screened to identify studies missed through the primary search. Animal and in-vitro studies, conference abstracts, editorials, commentaries with no clinical evidence, duplicate publications, and non-English articles were excluded. As this is a narrative review, evidence was synthesized thematically across the evolution of biologic therapy from TNF- α to IL-12/23, IL-17, and selective IL-23 inhibition, focusing on efficacy, durability, patient-reported outcomes, and safety.

Immunopathogenesis:

Historically, psoriasis was thought to be a skin condition resulting solely from keratinocyte abnormalities. However, with advances in time, the disease was found to be a chronic immune-mediated inflammatory disease of the skin with systemic complications. The pathogenesis of plaque psoriasis is centered on a "pathogenic triad" of dendritic cells, TH17 cells, and keratinocytes. Dendritic cells produce TNF- α and IL-23, which drive TH17 cell differentiation and expansion. TH17 cells then produce IL-17, IFN- γ , and IL-22, key psoriatic cytokines that activate keratinocytes and promote skin inflammation. Activated keratinocytes respond by secreting antimicrobial peptides (AMPs), chemokines (CXCL1, CXCL2, CXCL8, CCL20), TNF- α , IL-36, and IL-23, which further recruit and activate immune cells. This helps to create a self-amplifying inflammatory loop in which dendritic cells produce IL-23, which supports TH17 cell differentiation and expansion; TH17 cells further produce IL-17 and other cytokines that activate keratinocytes. Keratinocytes then produce additional inflammatory mediators that further recruit and activate immune cells.^[5,6]

Recognition of the central roles of TNF- α , IL-23, and IL-17 in this inflammatory network provided the rationale for the sequential development of targeted biologics. This progression moved from TNF- α inhibition to shared IL-12/23 p40 blockade, followed by direct IL-17 inhibition and ultimately, targeting the IL-23 p19 subunit that selectively modulates key inflammatory pathways rather than relying primarily on broader immunosuppression, paving the way for biologics targeting specific immune pathways directly rather than general immune suppression in the treatment of psoriasis, transforming the treatment paradigm.^[7]

Emergence of biologic therapies:

Prior to the introduction of biologic therapies, management of plaque psoriasis was mostly through topical therapies, such as topical corticosteroids, topical vitamin D analogues, phototherapy, and traditional systemic therapies. The guidelines for systemic therapy in plaque psoriasis vary across regions, except for the criteria of extensive psoriasis with special area involvement and non-response to topical therapy. For patients with moderate to severe disease, conventional systemic therapies, such as methotrexate, cyclosporine, and acitretin, have been important players in the treatment of psoriasis before the advent of biologics.^[1,8]

However, traditional treatments have many drawbacks, including variable efficacy, significant treatment burden, complex monitoring needs, contraindications, and long-term toxicity. Methotrexate requires liver monitoring, cyclosporine requires blood pressure and kidney function monitoring, and acitretin is teratogenic. These issues limit their sustainability and patient compliance, leading to interest in finding more specific and safe treatments.^[8]

The shift from conventional systemic therapy to biologic therapy was not just a shift in treatment modality; it reflected advances in psoriasis immunopathogenesis that led to the development of the first-generation biologics, namely Tumor Necrosis Factor-alpha (TNF- α) inhibitors, which block a cytokine central to psoriasis processes and proved effective in plaque psoriasis and psoriatic arthritis.^[2] Subsequent

identification of the IL-12/23, IL-17, and IL-23 pathways further expanded the biologic therapeutic landscape and progressively increased the specificity and efficacy of targeted treatment.

Evolution of Biologic Therapy in Plaque Psoriasis:

The treatment paradigm for moderate-to-severe plaque psoriasis has changed as biologic therapies increasingly target specific inflammatory pathways involved in pathogenesis. This evolution began with tumor necrosis factor-alpha (TNF- α) inhibitors, followed by dual interleukin (IL)-12/23 inhibition, IL-17 blockers, and more recently, selective IL-23 p19 subunit inhibitors. In parallel, clinical efficacy benchmarks advanced from PASI75 (75% improvement in Psoriasis Area and Severity Index) to PASI90 and PASI100, reflecting more stringent treatment goals and improved clinical outcomes.

Biologic class	Molecular target	Representative agents	Landmark trials	Major therapeutic development	Ref
TNF- α inhibitors	TNF- α	Etanercept, Infliximab, Adalimumab	Etanercept pivotal trials; EXPRESS I/EXPRESS II; REVEAL; REVEAL-extension	Established targeted therapy; substantial efficacy. Requires monitoring for infections and class-specific safety signals.	[9–13]
IL-12/23 inhibitor	p40 subunit of IL-12 and IL-23	Ustekinumab	PHOENIX 1/2; 5-year PHOENIX 1 extension	Durable efficacy with infrequent maintenance dosing via p40 pathway inhibition.	[14–16]
IL-17 inhibitors	IL-17A / IL-17RA	Secukinumab, Ixekizumab, Brodalumab	ERASURE; FIXTURE; UNCOVER-2/3; AMAGINE-2/3	Rapid onset and high efficacy (PASI 90/100 achievable). Monitor for candidiasis and IBD exacerbation.	[17–19]
IL-23 inhibitors	p19 subunit of IL-23	Guselkumab, Tildrakizumab	VOYAGE 1/2; ECLIPSE; reSURFACE 1/2	High-level and durable skin clearance with infrequent maintenance dosing.	[20–23]

Table 1: Evolution of biologic therapy in plaque psoriasis: molecular targets, landmark trials and major therapeutic development

TNote. PASI-Psoriasis Area and Severity Index; TNF-tumor necrosis factor; IL-interleukin; IBD-inflammatory bowel disease.

TNF- α Inhibitors:

TNF- α inhibitors were the first major biologic therapies to establish the clinical value of targeted cytokine inhibition in plaque psoriasis. TNF- α inhibitors include TNF receptor fusion protein etanercept and monoclonal antibodies such as Infliximab and Adalimumab.^[2] Etanercept demonstrated clinically meaningful efficacy of early TNF- α blockade in pivotal randomized controlled trials, with 49% of patients achieving PASI75 at week 12 compared with 3% with placebo.^[9] Infliximab subsequently demonstrated a more pronounced and rapid clinical response. In the EXPRESS trial, approximately 80% of patients achieved PASI75 at week 10 compared with 3% receiving placebo.^[10] The magnitude and rapidity of response demonstrated the potential for greater skin clearance.^[11] In the REVEAL trial, approximately 71% of patients receiving adalimumab achieved PASI75 at week 16 compared with 7% with placebo and showed long term efficacy and safety.^[12,13]

Combined, these studies established the first generation of targeted biologic treatment in plaque psoriasis, demonstrating that inhibition of one of the main inflammatory cytokines has major clinical effects. However, a very high clearance rate was not observed when compared to subsequent biologic classes. This provides an important rationale for the development of therapies targeting the IL-12/23, IL-17, and IL-23 pathways, with a greater emphasis now on PASI90 and PASI100 responses.

IL-12/23 Inhibitors:

Ustekinumab is the first human monoclonal antibody to target the IL-12/23 pathway by binding the shared p40 subunit of IL-12 and IL-23, representing an important step beyond TNF- α inhibition. In the pivotal PHOENIX 1 trial, approximately 67% of patients receiving ustekinumab achieved PASI75 at week 12 compared to 3% with placebo.^[14] Similar results were demonstrated in PHOENIX 2, in which PASI75 was achieved by approximately 67% and 76% of patients receiving ustekinumab 45 mg and 90 mg, respectively, compared to 4% with placebo.^[15]

In addition to short-term efficacy, ustekinumab demonstrated the potential for sustained disease control with relatively infrequent maintenance dosing. Long-term follow-up from PHOENIX 1 showed that clinical responses could be maintained through 5 years, with PASI75 achieved by approximately 72%, with PASI90 achieved by approximately 49% and PASI100 by 26%, respectively. These findings support the durability of IL-12/23 pathway inhibition and demonstrate that biologic therapy can provide sustained disease control with higher levels of skin clearance beyond the induction period.^[14,16]

Thus, ustekinumab represents an important transitional stage in the evolution of biologic therapy. The efficacy of cytokine blockade is already known with the use of TNF- α inhibitors, but ustekinumab showed that targeting a cytokine pathway relevant to plaque psoriasis could achieve effective and durable therapeutic responses with less frequent dosing. However, because ustekinumab targets the common p40 subunit of both IL-12 and IL-23, subsequent development efforts targeted the more selective IL-17 and IL-23 pathways, ultimately resulting in the development of IL-23 p19 inhibitors.

IL-17 Inhibitors:

The introduction of IL-17 targeted biologics represented an important advance in the treatment of plaque psoriasis. IL-17 inhibitors target a key effector cytokine in the pathogenesis of psoriasis which in particular causes, keratinocyte activation and amplification of the inflammatory cascade that is characteristic of psoriatic lesions.

Secukinumab is a fully human IgG1 kappa monoclonal antibody, that provided pivotal evidence for the efficacy of IL-17A inhibition in the ERASURE and FIXTURE trials. In the ERASURE study, around 82% of participants reached PASI75 by the 12th week, in contrast to 5% who received a placebo. Additionally, PASI90 was achieved by 60% of patients, and PASI100 was reached by 29%.^[17] In the FIXTURE study, around 77% of patients treated with Secukinumab reached PASI75, in contrast to 44% of those given etanercept and 5% receiving a placebo. In the FIXTURE trial, PASI90 was achieved by 55% and PASI100 by 24%, offering clear evidence of superior effectiveness compared to Etanercept a well-known TNF- α inhibitor.^[17] These results highlighted both the high efficacy and relatively rapid onset associated with IL-17A blockade.

Ixekizumab is a humanized IgG4-type monoclonal antibody that selectively binds IL-17A and inhibits its interaction with the IL-17 receptor. In the UNCOVER-2 trial, around 90% of patients treated with Ixekizumab reached PASI75 by the 12th week, in contrast to about 42% with etanercept and 2% with placebo. Notably, approximately 71% attained PASI90 and 41% reached PASI100, compared to 19% and 5%, respectively, with Etanercept.^[18] These findings highlight a significant shift in treatment expectations: achieving outcomes beyond PASI75, especially PASI90 and PASI100, achievable in a substantial proportion of patients.

Brodalumab is a human monoclonal antibody that binds to the IL-17 receptor type A, thereby blocking the biological functions of IL-17A, IL-17F, interleukin-17A/F, and interleukin-17E.^[2] In the AMAGINE-2 and AMAGINE-3 trials, Brodalumab 210 mg every two weeks achieved PASI75 responses of approximately 86% and 85%, respectively, at week 12. PASI90 was achieved by approximately 79% and 80%, while PASI100 was achieved by 44% and 37%, respectively. compared with Ustekinumab.^[19]

These findings confirmed the ability of IL-17 receptor blockade of rapid onset to produce very high levels of skin clearance. Hence, IL-17 inhibitors represent an evolution beyond TNF- α and IL-12/23 inhibitors, offering specificity, rapid onset, and potent efficacy in plaque psoriasis. This depth and speed of skin clearance supported the development of selective IL-23 p19 inhibitors for high efficacy, durable control, and convenient dosing.

IL-23 Inhibitors:

The development of IL-23 inhibitors represented a further refinement in the targeted treatment of plaque psoriasis by selectively inhibiting the p19 subunit of IL-23. Guselkumab provided pivotal evidence for selective IL-23 inhibition in the VOYAGE 1 and VOYAGE 2 trials. In VOYAGE 1, guselkumab achieved PASI75, PASI90 and PASI100 responses of approximately 91%, 73% and 37%, respectively, compared with 73%, 49% and 17% with Adalimumab at week 16.^[20] These findings demonstrated that selective IL-23 inhibition could

achieve high levels of clearance rapidly and could outperform an established TNF- α inhibitor Adalimumab. VOYAGE 2 confirmed the efficacy of guselkumab and further demonstrated the importance of continued treatment in maintaining clinical response.^[21]

Furthermore, the ECLIPSE trial provided a head-to-head comparison between Guselkumab and the effective IL-17A inhibitor Secukinumab. At week 48, PASI90 was achieved by approximately 84% receiving guselkumab versus 70% receiving Secukinumab, while PASI100 was achieved by approximately 58% and 48%, respectively.^[22] This finding is relevant for the evolution of biologic therapy because it demonstrates that selective IL-23 inhibition can provide sustained high-level clearance compared with an established IL-17 inhibitor.

In reSURFACE 1 and reSURFACE 2, Tildrakizumab offered further data to support the ability to inhibit IL-23 p19 selectively. At the primary assessment, PASI75 was achieved by approximately 62% of patients in reSURFACE 1 compared with 6% with placebo, while in reSURFACE 2 approximately 66% achieved PASI75 with Tildrakizumab compared with 48% with Etanercept.^[23] Responses continued to improve with ongoing treatment, supporting the durability of selective IL-23 inhibition.

Overall, IL-23 inhibitors are the next generation of biologics, developing from an IL-12/23 common blockade to selective inhibition of IL-23 p19. Their efficacy in producing a high percentage of PASI90 and PASI100 responses, coupled with fast sustained effectiveness and relatively infrequent dosing of biologics, shifted the expectations for treatment from substantial improvement to durable, near-complete, or complete skin clearance. The successive steps starting from TNF- α inhibition, then IL-12/23, then IL-17, and finally selective IL-23 inhibition, reflect the increasing precision of biologic therapy and the progressive improvement in clinical outcomes.

Patient-reported outcomes

The Dermatology Life Quality Index (DLQI)^[24] is a validated 10 item questionnaire that is scored on a scale of 0 (no impact) to 30 (very large impact) and reflects the patient's view of the effect of psoriasis on their quality of life (QoL). It complements the Psoriasis Area and Severity Index (PASI), which mostly reflects the clinician's assessment of psoriasis severity, skin clearance and psoriasis response to treatment. Therefore, both PASI and DLQI^[24] should be considered when assessing the effectiveness of biologic therapy, as improvement in PASI does not necessarily correspond to a complete resolution of the patient's disease burden.^[25]

Throughout the biologic classes, effective treatment has been correlated with rapid and long-lasting improvements in DLQI. There were indeed more quality-of-life improvements associated with higher skin clearance responses. Patients achieving PASI 90 and PASI 100 reported greater DLQI improvements than those achieving PASI75 during the IL-17 and IL-23 trials. Achieving a DLQI score of 0/1, which indicates that plaque psoriasis has little to no impact on quality of life, offers an extra measure of treatment benefit that is significant to patients. ^[11,14,17,18,20,23]

The growing attainment of both substantial skin clearance and DLQI 0/1 with the latest biologic

treatments implies that greater clinical clearance can lead to meaningful improvements in patients' perceived disease burden. Taken together, these findings emphasize that the success of biologic therapy should not be assessed solely by the extent of skin clearance. The combination of objective measures such as PASI with patient-reported outcomes such as DLQI provides a more comprehensive assessment of treatment benefit, incorporating both clinical response and the patient's experience of living with plaque psoriasis.

Durability:

Evaluating the long-term effectiveness of biologic therapy is crucial for assessing treatment success beyond just the initial induction phase. Long-term research across different biologic classes has shown that ongoing treatment can sustain clinical responses. However, the extent of these responses and the length of follow-up have differed among specific agents.

In the TNF- α inhibitors, Adalimumab demonstrated sustained efficacy during long-term follow-up, with PASI75 responses maintained in approximately two-thirds of patients after three years of continuous treatment, yet discontinuation was consistently associated with rapid relapse, underscoring the necessity of maintenance dosing.^[13] Long-term data from the PHOENIX 1 extension study have demonstrated that Ustekinumab provides substantial and lasting disease control. The findings revealed that PASI75 responses were consistently upheld, with half of the patients even achieving PASI 90 for as long as five years, provided they continued their treatment.^[16] These long-term results have confirmed that effective biologic therapy can offer lasting disease control over several years with relatively infrequent maintenance doses.

Secukinumab, an IL-17 inhibitor, showed effectiveness over a year, with over 80% of patients in the ERASURE and FIXTURE studies maintaining PASI75 responses.^[17] Similarly, Ixekizumab showed effectiveness with continued use.^[18] However, PASI90/100 responses were less durable than those with IL-23 inhibitors.^[19] IL-23 inhibitors have provided further evidence of sustained high-level skin clearance. In the ECLIPSE head-to-head trial, Guselkumab achieved a higher PASI90 response than Secukinumab at week 48, with the difference becoming apparent during the later maintenance period.^[22] The study therefore provides important comparative evidence that selective IL-23 inhibition can maintain high levels of skin clearance over extended treatment. Similarly, long-term studies of Tildrakizumab have demonstrated maintenance of clinical responses during continued treatment.^[23]

These confirmed newer biologics can persist beyond induction, although long-term response might differ among agents. Withdrawal studies suggest that biological responses usually diminish after treatment is stopped, although relapse rates vary among therapies. This highlights plaque psoriasis as a persistent disease and the need for a long-term maintenance plan. Thus, the advancement of biologic therapy has been marked by a growing focus on sustained disease control, alongside rapid induction of efficacy, with newer drugs showing the capability to sustain significant skin clearance over extended treatment durations.

Safety:

Across biologic classes, treatments demonstrated generally acceptable safety profiles during clinical trials with extended follow-up, although mechanism-specific adverse events matter in treatment choice.

Serious adverse events and treatment discontinuations remained low across classes during trials. In TNF- α inhibitors, infections were the most commonly reported adverse events, while serious infections were uncommon; tuberculosis was reported in a small number of patients, highlighting the importance of appropriate infection screening and monitoring during TNF- α inhibition.^[9-11,13] Ustekinumab demonstrated a well-established long-term safety profile over five years, with no major new safety signals identified and adverse event rates comparable to placebo during treatment.^[14,15]

In IL-17 inhibitor trials, candida infections occurred more often with Secukinumab and Ixekizumab compared to etanercept and placebo, highlighting involvement of IL-17 in mucosal immunity. Although these infections were generally mild to moderate, this class specific- risk is clinically relevant for patients with recurrent candidiasis. In addition, IL-17 inhibition warrants consideration in patients with inflammatory bowel disease because of the potential for disease exacerbation.^[17-19] IL-23 inhibitors demonstrated favorable tolerability in clinical trials, with low rates of serious adverse events and, infrequent discontinuations. Commonly reported events include nasopharyngitis and upper respiratory tract infections.^[20,21]

Overall, the safety profile of biologic therapy remains generally favorable as efficacy has improved. However, mechanism-specific factors remain crucial when selecting and initiating biologics. Therefore, the clinical significance of newer biologics should be assessed by considering efficacy, patient-reported outcomes, durability and safety.

DISCUSSION

Evolution and Clinical Perspectives of Biologic Therapy:

The evolution of biologic therapy in plaque psoriasis reflects the progressive translation of advances in immunopathogenesis into increasingly targeted therapeutic strategies. The identification of TNF- α as an important inflammatory mediator established the foundation for biologic treatment, while subsequent recognition of the IL-23/Th17 pathway led to the development of IL-12/23, IL-17 and, subsequently, IL-23 inhibitors.^[2,5,6] This therapeutic evolution is demonstrated by landmark trials across successive biologic classes. These successive advances imply that the development of biologics has not only been based on the discovery of novel therapeutic targets but also on the growing precision of targeting key psoriatic inflammatory components. It has also expanded the extent of disease control that can be achieved with biologic treatment.

The clinical consequences of this evolution are demonstrated by a shift in treatment response expectations. PASI75 was established as an important benchmark during early biologic trials, which was shifted toward PASI90 and PASI 100 by newer biologics, which show improvement toward near-complete or complete skin clearance. Achieving higher levels of skin clearance is crucial not only for improving PASI scores but also for significantly improving patient-reported quality of life, as assessed by the DLQI. DLQI improvements across biologic therapies indicate that effective skin disease control can meaningfully reduce the patient's disease burden. Emphasis on complete skin clearance reinforces the importance of patient-

reported outcomes. Although, PASI and DLQI assess different aspects of treatment response, they both should be considered complementary outcomes, and treatment success is highly dependent on including both objective disease control and the patient's perceived improvement, not just skin clearance alone.^[24,25]

The expanding range of biologic mechanisms has important implications for individualized treatment selection. Patients differ in disease characteristics, comorbidities, previous treatment exposure, treatment goals, patient preferences, and tolerance for treatment burden. IL-17 inhibition may be considered when rapid disease control is an important treatment goal, whereas IL-23 inhibition may be attractive for patients who prioritize sustained disease control and less frequent maintenance dosing, while TNF- α inhibitors remain clinically relevant when concomitant psoriatic arthritis influences treatment choice.^[26,27] Thus, treatment selection should extend beyond efficacy alone and consider quality of life, comorbidities, treatment burden, and individual patient priorities. Hence, the biologic agent with the highest efficacy in clinical trials is not invariably the best choice for every patient.

Overall, the major clinical implication of biologic evolution is that it is not only about a new, more potent drug, but also about an expanded therapeutic choice. Advances in focused mechanisms have enabled more extensive disease management, allowing treatment options based on disease characteristics and patient preference. As a result, managing plaque psoriasis has shifted toward a personalized, patient-focused strategy, where effectiveness is weighed alongside comorbidities, safety issues, treatment demands, and patient preferences.

Current Challenges and Uncertainties:

Although biologic therapy has significantly improved the treatment of plaque psoriasis due to its favorable benefit-risk profiles, specific mechanism-related precautions and contraindications remain important during treatment selection. TNF- α inhibitors require assessment for serious infections and latent tuberculosis before and during treatment, whereas IL-17 inhibitors require particular caution in patients with inflammatory bowel disease and those with recurrent mucocutaneous candidiasis.^[17-19] Recommendations for infection screening are increasingly customized to align with specific mechanisms. For example, recent expert guidance indicates that regular screening for latent tuberculosis is generally not required solely because of the use of IL-17 or IL-23 inhibitors. However, it might still be suitable for individuals with relevant epidemiological risks or those experiencing concurrent immunosuppression.^[28] Thus, biologic selection should consider both mechanism and individual patient characteristics rather than efficacy alone.

The comparative efficacy of biologic therapies remains challenging to interpret. Pivotal trials differ in patient populations, previous treatment exposure, disease characteristics, regimens, comparators, follow-up, and assessment time points. Therefore, response rates from separate trials should not be treated as direct comparisons between biologic classes. Head-to-head studies provide stronger evidence, as shown by the ECLIPSE trial comparing Guselkumab with Secukinumab.^[22] However, direct comparisons remain limited across the full range of available biologics. Furthermore, the prediction of individual treatment response also

remains unresolved. Despite advances in understanding psoriasis pathways, no biomarker has yet achieved routine clinical use for reliably selecting the optimal biologic mechanism for an individual patient.^[29] Treatment selection therefore continues to depend on clinical phenotype, comorbidities, previous treatment exposure, expected efficacy, safety considerations, treatment burden, and patient preferences.

The evidence for biologic therapy continues to evolve. Established biologics have longer clinical and real-world experience, whereas evidence for newer agents is maturing. Ongoing research is expanding knowledge of long-term effectiveness, treatment persistence, switching, optimization, and outcomes in broader patient populations, highlighting the need for comparative and real-world research and long-term clinical surveillance.

Future Directions:

The future of biologic therapy development is likely to focus on further understanding the IL-23/IL-17 axis and applying this insight to create more targeted treatment methods. Bimekizumab, which inhibits both IL-17A and IL-17F, exemplifies the ongoing enhancement of IL-17 inhibition, while new drug focusing on the IL-23R receptor, like Icotrokinra, demonstrate a growing specificity within the IL-23 pathway. These advances in molecular engineering and immunology enhance the understanding of cytokine biology and enable precision drug development for the treatment of plaque psoriasis.^[30]

Despite advancements in biological precision, treatment selection has not achieved the same level of accuracy. Researchers are exploring genetic, transcriptomic, proteomic, and immunologic biomarkers to forecast treatment responses and pinpoint patients who would benefit most from specific mechanisms; however, none of these biomarkers have been sufficiently validated for regular clinical application.^[29] Consequently, future studies should focus on validating biomarkers and combining molecular traits with clinical phenotypes to minimize trial and error in treatments.

To tackle the heterogeneity and limited generalizability of existing evidence, it is necessary to conduct long-term comparative and real-world studies that includes a wider range of patient groups. These investigations ought to assess not only clinical effectiveness but also treatment adherence and outcomes reported by patients. Combining precise IL-23/IL-17 targeting with validated biomarkers and real-world data could transform psoriasis treatment from mainly empirical choices to personalized, mechanism-based therapy.

CONCLUSION

The evolution of biologic therapy for plaque psoriasis illustrates the application of immunopathogenic insights into more targeted approaches, evolving from TNF- α blockers to those focusing on IL-12/23, IL-17, and IL-23 inhibitors. Throughout these developments, biologics have enhanced skin clearance and improved patient-reported quality of life, with expectations advancing from PASI75 to PASI90 and PASI100. However, the effectiveness of responses among patients differs between clinical trials and real-world settings. The expanding range of biologics has enhanced efficacy but has also introduced complexity in choosing treatments. It is essential to consider factors such as clinical phenotype, comorbidities, previous

treatment history, treatment burden, and patient preferences in addition to efficacy. Further improvement of the IL-23/IL-17 axis and the development of predictive biomarkers could lead to more precise, mechanism-driven, personalized therapies. Thus, the continuing evolution of biologics should be evaluated not solely by greater skin clearance but also by their ability to provide durable, meaningful, and individualized patient benefits.

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