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Advances in biologic therapy for the treatment of moderate to severe psoriasis: a systematic review

Avances en la terapia biológica para el tratamiento de la psoriasis de moderada a grave: una revisión sistemática

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ABSTRACT

We summarize that biologic therapies for moderate to severe psoriasis development has advanced enough as these therapies encompass biologic factors such as TNF-α inhibitors, IL-12/IL-23 inhibitors, and IL-17/IL-23 pathway inhibitors for psoriasis. First-generation biologics like etanercept, infliximab, and adalimumab offer substantial clinical improvements but carry risks of infections and malignancies. Second-generation agents, such as ustekinumab, provide targeted efficacy with fewer adverse effects. Third-generation biologics, including secukinumab, ixekizumab, brodalumab, guselkumab, and tildrakizumab, present highly specific mechanisms, achieving remarkable efficacy with manageable safety profiles. Despite challenges such as cost and long-term monitoring, these biologics represent a paradigm shift in psoriasis management, enhancing patient outcomes and quality of life.

Keywords: psoriasis, biologic therapy, immunotherapy, monoclonal antibodies, cytokine inhibitors, severe psoriasis.

RESUMEN

Resumimos que las terapias biológicas para el desarrollo de psoriasis moderada a grave han avanzado lo suficiente ya que estas terapias abarcan factores biológicos como inhibidores de TNF-α, inhibidores de IL-12/IL-23 e inhibidores de la vía IL-17/IL-23 para la psoriasis. Los productos biológicos de primera generación como etanercept, infliximab y adalimumab ofrecen mejoras clínicas sustanciales, pero conllevan riesgos de infecciones y tumores malignos. Los agentes de segunda generación, como ustekinumab, proporcionan una eficacia específica con menos efectos adversos. Los productos biológicos de tercera generación, incluidos secukinumab, ixekizumab, brodalumab, guselkumab y tildrakizumab, presentan mecanismos muy específicos y logran una eficacia notable con perfiles de seguridad manejables. A pesar de desafíos como el costo y el seguimiento a largo plazo, estos productos biológicos representan un cambio de paradigma en el tratamiento de la psoriasis, mejorando los resultados de los pacientes y la calidad de vida.

Palabras clave: psoriasis, terapia biológica, inmunoterapia, anticuerpos monoclonales, inhibidores de citocinas, psoriasis grave.

INTRODUCTION

Psoriasis is a lifelong immune-mediated inflammatory disorder that affects the skin. Psoriasis presents clinically heterogeneous, manifesting as plaque, flexural, guttate, pustular, or erythrodermic forms. Statics says it affects an estimated 60 million individuals worldwide, with a prevalence of 1.52% in the UK. Genetic mutations cause psoriasis, and it can lead to

various comorbidities, including psoriatic arthritis, cardiovascular disease, and psychological conditions. Hence, it needs a comprehensive and multidisciplinary approach for its management. Traditional treatments encompass topical agents, phototherapy, and systemic therapies, yet these methods often require more efficacy and safety (Raharja et al., 2021). Since biologic therapies were introduced, these have revolutionized their management by targeting specific immune pathways implicated in psoriasis, revolutionizing the treatment paradigm for moderate to severe cases. These biologics, which include tumor necrosis factor (TNF) inhibitors and interleukin (IL)-17 and IL-23 inhibitors, offer targeted and highly effective treatment options, significantly improving patient outcomes Raharja et al stated. In this systematic review, we aim to explore the latest advances in biological therapy for psoriasis, assess their efficacy and safety profiles, and discuss potential future developments. Our ultimate goal is to provide a detailed analysis of how these innovations are reshaping the management of moderate to severe psoriasis, offering new hope and improved quality of life for patients affected by this chronic condition.

METHODOLOGY

Literature Search Strategy

To systematically review the mechanism, efficacy, and safety, various biologics treatments for the treatment of moderate to severe psoriasis, a comprehensive literature search was conducted and we decided to run our research onPubMed, Cochrane Library, Embase, and Web of Science. We decided on proper inclusion and exclusion criteria, and papers will be selected only from 2014 to June 2024 for up-to-date evidence.

We selected the main primary keywords that are Psoriasis, biologic therapy, immunotherapy, monoclonal antibodies, cytokine inhibitors, severe psoriasis, treatment advances, targeted therapy, therapeutic outcomes, disease progression and these were combinedwith secondary keywords to generate Mesh.

Our mesh terms were

1. ("Psoriasis"[MeSH]) AND ("Biological Therapy"[MeSH] OR "Immunotherapy"[MeSH] OR "Monoclonal Antibodies"[MeSH] OR "Cytokine Inhibitors"[MeSH]) AND ("Severity of Illness Index"[MeSH] OR "Disease Progression"[MeSH]) AND ("Therapeutics"[MeSH] OR "Drug Therapy"[MeSH] OR "Treatment Outcome"[MeSH] OR "Clinical Trials as Topic"[MeSH])

2. ('psoriasis'/exp) AND ('biological therapy'/exp OR 'immunotherapy'/exp OR 'monoclonal antibody'/exp OR 'cytokine inhibitor'/exp) AND ('severity of illness'/exp OR 'disease progression'/exp) AND ('therapy'/exp OR 'drug therapy'/exp OR 'treatment outcome'/exp OR 'clinical trial'/exp)

Inclusion Criteria

Study Population: Adults diagnosed with moderate to severe psoriasis.

Interventions: First-generation biologics targeting TNF-α (e.g., etanercept, infliximab, adalimumab).Second-generation biologics targeting IL-12 and IL-23 (e.g., ustekinumab).Third-generation biologics targeting IL-17 and IL-23 pathways (e.g., secukinumab, ixekizumab, brodalumab, guselkumab, tildrakizumab).

Comparative Studies: Studies comparing the efficacy and safety of biologics to placebo or other active treatments.

Outcome Measures: Clinical efficacy measured by Psoriasis Area and Severity Index PASI 75 and PASI 90 scores.Safety profile, including common and serious adverse effects.

Study Design: Randomized controlled trials (RCTs), cohort studies, and meta-analyses.

Publication Status: Peer-reviewed articles.

Language: Studies published in English.

Exclusion Criteria

Non-Human Studies: Animal studies or in vitro research.

Non-Biologic Therapies: Studies focusing on conventional systemic therapies or topical treatments.

Incomplete Data: Studies with insufficient data on efficacy or safety outcomes.

Short Duration: Studies with follow-up periods of less than 12 weeks.

Non-English Publications: Studies published in languages other than English.

Abstracts and Conference Papers: Non-peer-reviewed articles or those not available in full text.

Synthesis of Data

To systematically synthesize the data on biologic therapies for psoriasis, we followed a rigorous and systematic approach:

Literature Search: We comprehensively searched multiple databases, including PubMed, Cochrane Library, and Embase. Keywords used included "psoriasis," "biologics," "TNF-α inhibitors," "IL-12/IL-23 inhibitors," "IL-17 inhibitors," and specific drug names (e.g., etanercept, ustekinumab, secukinumab).

Study Selection: Two independent reviewers screened titles and abstracts against the inclusion and exclusion criteria. Full texts of potentially eligible studies were then assessed for final inclusion.

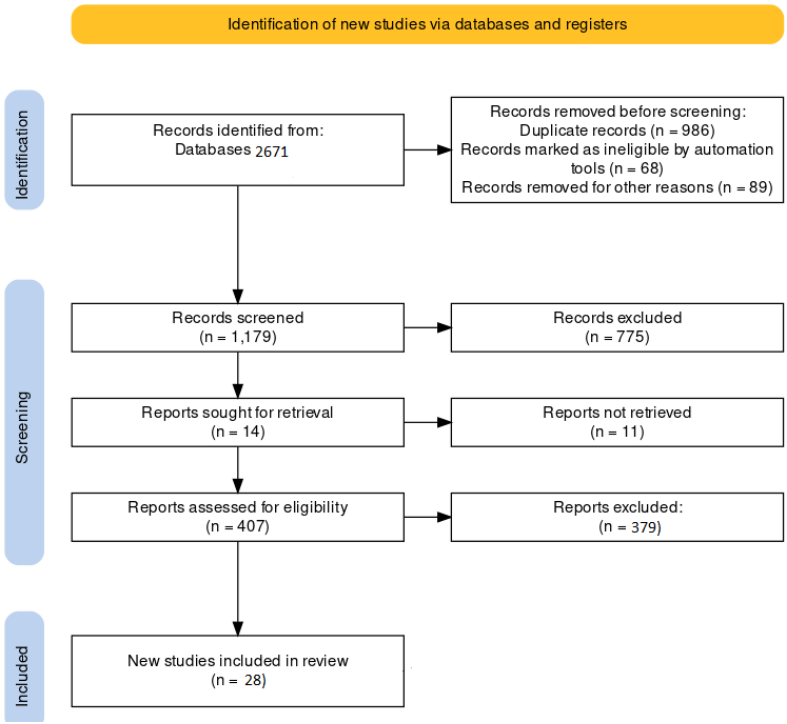
Data Extraction: We extracted data on study design, patient demographics, intervention details, clinical efficacy Psoriasis Area and Severity Index PASI 75 and PASI 90), and safety outcomes. Discrepancies in data extraction were resolved through discussion.

Quality Assessment: The quality of included studies was evaluated using established tools such as the Cochrane Risk of Bias Tool for RCTs and the Newcastle-Ottawa Scale for cohort studies.

Data Synthesis: We performed a qualitative synthesis of the data, focusing on the mechanisms of action, efficacy, and safety profiles of each biologic therapy. We also compared the outcomes across different generations of biologics to highlight advancements in treatment.

Results Compilation: The extracted and synthesized data were organized into comprehensive tables and narratives, providing a clear comparison of the efficacy and safety profiles of first-, second-, and third-generation biologics.

Figure 1. Identification of new studies databases and registers



Source: the authors.

RESULTS

Findings

Table 1. Advances in Biologic Therapy for the Treatment of Moderate to Severe Psoriasis

Author(s)	Year	Aim	Findings
Blauvelt et al.	2023	To evaluate the efficacy of brodalumab in moderate-to-severe psoriasis using a Delphi consensus.	Brodalumab showed substantial efficacy, with positive consensus on 15/17 treatment statements, aiding dermatologists in patient management.
Puig et al.	2020	To assess the real-world safety and efficacy of IL-23 inhibitors in psoriasis treatment.	IL-23 inhibitors, particularly guselkumab, showed high efficacy and a favorable safety profile, with no active TB cases at 100 weeks.
Warren et al.	2023	To compare the efficacy of risankizumab with other biologics in clinical trials.	Risankizumab demonstrated superior efficacy compared to ustekinumab, secukinumab, and adalimumab, achieving high PASI90 rates.
Reich et al.	2022	To conduct a network meta-analysis on the efficacy of bimekizumab and other biologics.	Bimekizumab showed superior efficacy in achieving PASI90 and PASI100 compared to several biologics, supporting its role in psoriasis management.
Reich et al.	2023	To evaluate the long-term efficacy and safety of bimekizumab.	Bimekizumab demonstrated sustained efficacy with high PASI90 and PASI100 response rates, maintaining safety over long-term use.
Armstrong et al.	2023	To compare the efficacy and safety of deucravacitinib versus other treatments.	Deucravacitinib showed superior efficacy to placebo and comparable efficacy to existing biologics, with a favorable safety profile over the long term.
Langley et al.	2022	To assess the effectiveness of ixekizumab in different patient subgroups.	Ixekizumab proved highly effective across various subgroups, including biologic-naïve and previously treated patients, maintaining high response rates.
Gordon et al.	2022	To investigate the safety and efficacy of risankizumab versus adalimumab.	Risankizumab showed significantly higher efficacy compared to adalimumab, with more patients achieving PASI90 and PASI100, and a similar safety profile.
Lee, H.W. et al.	2023	To assess the safety and efficacy of secukinumab in pediatric patients.	Secukinumab significantly improved psoriasis symptoms in children and adolescents, with a favorable safety profile.
van den Reek, J.M.P.A. et al.	2023	To evaluate the long-term effects of ixekizumab in psoriasis patients.	Demonstrated sustained efficacy and safety of ixekizumab over a 5-year period, showing high rates of skin clearance and manageable side effects.
UCB (FDA Approval)	2023	To evaluate the efficacy of bimekizumab for moderate to severe plaque psoriasis.	Bimekizumab, inhibiting IL-17A and IL-17F, showed unprecedented efficacy with rapid and sustained skin clearance rates, significantly outperforming existing treatments in phase 3 trials.
Fiorillo, G. et al.	2024	To analyze the real-world effectiveness and safety of biologics in very severe psoriasis.	Concluded that biologics are highly effective and well-tolerated for very severe psoriasis, maintaining long-term effectiveness and safety across multiple years.

Source: the authors

Pathophysiology of Psoriasis

Psoriasis is an immune-mediated inflammatory disease, having a complex interplay of genetic material, environmental, and immunological factors. Pathogenesis of psoriasis involves dysregulation of the immune system with aberrant activation of T-cells and the subsequent release of pro-inflammatory cytokines (Rendon & Schäkel, 2019), which orchestrates chronic inflammatory response and accelerates the turnover of skin cells while ultimately resulting in characteristic plaques of psoriasis. The immunopathogenesis of psoriasis is said to be highly mediated by the competent T-helper (Th) cells which include the Th1 and Th17 cells (Hu et al. , 2021). Surprisingly, dendritic cells are the ones that initiate the activation of these T-cells to detect ''antigens'' that target naïve T-cells into becoming Th1 and Th17 types of T-cells. According to Hu et al. (2021), the stimulated t-cells then move to the skin where high levels of cytokines continue to start process of inflammation. Th1 cells are involved in the manufacture of interferon-gamma (IFN-γ) and tumor necrosis factor-alpha (TNF-α), which are key and emotive interplayers in establishing inflammation in psoriasis. TNF-α is an essential cytokine that enhances the activation and survival of numerous immune cells and provides an upregulation of inflammation within the affected psoriatic skin lesions. TNF-α also stimulates the synthesis of other pro-inflammatory cytokines and chemokines to enhance the infiltration of immune cells into the affected tissues (Kurtovic & Halilovic, 2022).On the other hand, Th17 cells which are generate interleukin-17 (IL-17) and Interleukin-22 (IL-22) both of which play crucial role in psoriasis. IL-17, which is highly inflammatory provokes keratinocytes into synthesizing peptides to fight against the microbes and at the same time, chemokines and cytokines to intensify inflammation. In contrast, IL-22 stimulates the proliferation of keratinocytes and increases, epidermal thickness, that are major features of psoriatic plaque. Specifically, the IL-23/Th17 axis is a very active player in psoriasis's progressive and even accumulative inflammation. IL-23 is secreted by dendritic cells and macrophages and is essential for stabilizing and increasing the number of Th17 cells. Plenty of IL-23 expression is observed in the lesions of psoriasis; moreover, genetic polymorphisms of the IL-23 receptor have been associated with an increased risk of developing psoriasis (Deng., 2016) (Hu et al., 2021).

Ortiz-Lopez et al., 2022, explained that the latest literature about psoriasis claims on the critical role of the keratinocyte, the most abundant cells within the epidermis. It has been demonstrated that under the influence of cytokines such as IL-17 and TNF-α, the epidermal keratinocytes proliferate and secrete more pro-inflammatory mediators, enabling continuation of inflammation. This leads to the characteristic hyperproliferative and short-lived keratinocytes in psoriasis vulgaris, leading to a poorly differentiated epidermal layer. To address this, Lee and Kim (2023) stated there has been an emergence of biologic therapies to address each component of this inflammatory network thus, breaking the pathologic cycle and outcomes of significantly improving, the clinical presentation of the patients. Drugs including etanercept, infliximab, and adalimumab, as TNF-α inhibitors, have a high therapeutic impact by binding in the cytokine which leads to the decrease in both inflammation and keratinocyte proliferation with establishing healthy skin in psoriatic patients.

The IL-17 inhibitors such as secukinumab, ixekizumab, and brodalumab are molecules that directly shift course of

actions in anti-IL-17 which means they block the inflammatory signals that are responsible for stimulating keratinocyte proliferation. Thus, these therapies dramatically decrease inflammatory response and hence the clinical manifestations of psoriasis affected individual. There are different targets within this pathway; for instance, ustekinumab targets both IL-12 and IL-23 with utmost emphasis on the p19 subunit of IL-23, while agents such as guselkumab and tildrakizumab are very selective for the p19 subunit of IL-23 that influences the IL-23/Th17 pathway. These treatments are particularly directed towards interfering with the stabilization and proliferation of Th17 cells, which decreases the secretion of IL-17 and IL-22 hence dampening the inflammatory and proliferative processes relevant in psoriasis (Vidal et al., 2021) (Hawkes et al., 2018).

First Generation Biologics_TNF-α Inhibitors

In moderate to sever psoriasis treatment and biologic therapy, The TNF-α inhibitors have emerged as a groundbreaking improvement in targeted medication These first-generation biologics include etanercept, infliximab, and adalimumab, and these drugs have revolutionized the therapeutic landscape by introducing a novel approach to a disease which was previously resistant to conventional treatments. Mechanism of action of TNF-αpivots on neutralizing tumor necrosis factor-alpha (TNF-α), a pivotal pro-inflammatory cytokine in psoriasis. TNF-α latches onto receptors on immune cells and initiates a sequence of inflammatory signals that call for more cytokines, chemokines, and adhesion molecules, which in turn revs up inflammation as well as keratinocyte proliferation. Hence, through suppression of TNF-α, these biologics discredit this pathological loop, leading to decreased inflammation and enhancement of psoriatic lesions. Etanercept acts in a manner that it binds to TNF-α and prevents it from binding to its receptor and hence leads to the inhibition of further TNF-α which is involved in mediating inflammation. Infliximab is a chimeric monoclonal anti-TNF- α antibody that has a high affinity for both soluble and transmembrane TNF- α and this block the action of the cytokine effectively thus provides a very effective way of managing inflammation (Campa et al., 2015). Jang et al. (2021) state Adalimumab is a fully human monoclonal antibodythat targets TNF-α with high specificity and provides high specificity in blockade of TNF-α signaling. Clinical efficacy is measured using the Psoriasis Area and Severity Index (PASI) in research conducted by Pirzada and his team and in results, significant improvements were seen across these agents. Etanercept achieves a 75% improvement in PASI scores (PASI 75) in 47% of patients after 12 weeks, infliximab reaches PASI 75 in nearly 80% of patients within ten weeks, and adalimumab achieves PASI 75 in 71% of patients at 16 weeks. These results reflectedconsiderable reductions in psoriatic lesion severity, highlighting the transformative impact of TNF-α inhibitors (Pirzada et al., 2018).

However, TNF-α inhibitors have potential risks such as reaction at the site of injection, and immunogenicity resulting in generation of antibodies against the drug that can reduce the effectiveness of the drug. More serious infections like Tuberculosis and opportunistic bacterial, viral, or fungal infections are a major issue owing to the immunosuppressive effect of TNF-α inhibitors. Unfortunately, the long-term dangers of Rituxan include a slightly elevated likelihood of developing malignancies such as lymphoma along with nonmelanoma skin cancer, though conclusive evidence on it is still inadequate. That is why careful safety monitoring for their manifestations and constant evaluations of efficacy and assessment of patients' risks in the long-term management are needed. It is, therefore, essential to maintain an optimal ratio between the clinical efficacy and possible adverse effects to achieve the greatest possible therapeutic effect where TNF-α inhibitors are being used. These biologics are our invaluable assets for moderate to severe psoriasis management. (Henrickson et al., 2016).

Second Generation Biologics: IL-12 and IL-23 Inhibitors

Second-generation biologics targeting interleukins IL-12 and IL-23 are transformed significantly for moderate-severe psoriasis management Campa et al. (2015) stated. Ustekinumab gives targeted approach to interfere and dysregulate immune pathways that cause psoriasis and offer greater effectiveness with small risksthen IL-12 and IL-23 contain a p40 subunit. IL-12 assists in the differentiation of naïve T cells into Th1 cells that release interferon-gamma which promotes inflammation and IL-23 maintains Th17 cells and produce IL-17 and other cytokines conducting to psoriasis (Korta et al., 2023). Targeting the shared p40 subunit IL-12 and IL-23 inhibitors block these cytokinesand, in the meantime, reduce inflammation and keratinocyte proliferation (Guo et al., 2023). Ustekinumab is a fully human monoclonal antibody, binds to the p40 subunit, inhibiting these cytokines' receptor interaction on immune cells. Clinical trials show that ustekinumab significantly reduces psoriatic lesions, with about 67% of patients achieving PASI 75 and 42% reaching PASI 90 at 12 weeks, demonstrating potent anti-inflammatory effects and notable clinical improvements (Ghazawi et al., 2021). Ustekinumab's safety profile is favorable, with fewer serious adverse effects compared to TNF-α inhibitors butmild to moderate upper respiratory infections, headaches, and fatigue are commonwhile serious infections and malignancies are rare but require monitoring. Its dosing schedule, with subcutaneous injections every 12 weeks after initial dosesimproves patient adherence and convenience. Compared to TNF-α inhibitors like etanercept, infliximab, and adalimumab, IL-12 and IL-23 inhibitors such as ustekinumab offer clear benefits. While TNF-α inhibitors are effective as they come with higher immunogenicity risks and infections and potential malignancies due to broader inflammatory pathway inhibition. IL-12 and IL-23 inhibitors gives

targeted approach and reducing adverse effects. Ustekinumab shows superior or comparable efficacy to TNF-α inhibitors achieving higher PASI scores and maintaining long-term disease control (Ghosh et al., 2019).

Third Generation Biologics: IL-17 and IL-23 Pathway Inhibitors

Third-generation biologic agents with newer targets focusing on the IL-17 and the IL- 23 have enhanced the therapy for moderate to severe psoriasis. These new agents exemplify high specificity in terms of their mechanism of action and thus translate into significant clinical advantages, as well as novel approaches to disease management. Secukinumab and Ixekizumab are among the connector IL-17 inhibitors central to psoriasis management. They aim at IL-17A, which is a cytokine that has widespread roles in the proliferation of keratinocytes and inflammation in regions affected by psoriasis. It substantially decreased clinical severity by neutralizing IL-17A, and these drugs also reduce biomarkers with relevant functions such as TNF-alpha production and inflammatory mediator release. An overview of placebo-controlled trials demonstrates that treatment with Secukinumab leads to up to an 81 % PASI 75 response in psoriasis patients, with approximately 59 % achieving a PASI 90 response in the same time of 12 weeks. Ixekizumab is alike notably effective, where 78% of the patients met PASI 75 and 54% the PASI 90 criteria (Lonnberget al., 2014).

Overall, IL-17 inhibitors have a relatively benign safety profile, although side effects are incurred in over two-thirds of patients, including upper respiratory tract infections, injection site reactions, and candidiasis. There is also potential for increase in severity of IBD, so special care has to be taken in patients affected by this condition. However, these risks are offset by the benefits of having a fast and long-lasting disease control seen with IL-17 inhibitors in some patients with psoriasis (Eshwar et al., 2022). Another study conducted by Fargnoli et al. (2023) mentioned that Brodalumab as one of the developing select IL17 receptor A inhibitors that acts differently by antagonizing almost all IL-17 cytokines. The effectiveness has been proved appreciable, with 83% of patients receiving the PASI 75 and 70% receiving the PASI 90 after twelve weeks. Nonetheless, it is linked to suicidal ideation and behavior that require cautious patient selection and monitoring, and hence, its effectiveness has made it largely restricted from widespread use.

Another research was conducted in 2021 by Ghazawi et al. and authors statedIL-23 inhibitors, like guselkumab and tildrakizumab, target the p19 subunit of IL-23, essential for Th17 cell-mediated inflammation in psoriasis. Guselkumab has demonstrated that up to 85% of patients achieve PASI 75, and 73% reach PASI 90. Tildrakizumab shows PASI 75 responses in 74% of patients and PASI 90 in 54%. Their extended dosing intervals (every 8 to 12 weeks) enhance patient convenience and adherence.IL-23 inhibitors are favorable and safe to use but comes with fewer serious adverse effects than earlier biologics. Common side effects include upper respiratory tract infections, headaches, and injection site reactions. Long-term data indicate a low risk of malignancies and serious infections, making IL-23 inhibitors safe and effective for long-term treatment (Ghazawi et al., 2021).

Table 2. Biologic Therapies for Moderate to Severe Psoriasis: Drug Specifications and Efficacy

Drug Name	Generation	Target	Mechanism of Action	Administration	PASI 75 (%)	PASI 90 (%)	Common Adverse Effects	Serious Adverse Effects	Dosing Schedule
Etanercept	First	TNF-α	Binds to TNF-α, preventing interaction with its receptor	Subcutaneous injection	47%	N/A	Injection site reactions, infections, headache	Serious infections, lymphoma, non-melanoma skin cancers	Twice weekly (50 mg) for 12 weeks, then weekly
Infliximab	First	TNF-α	Chimeric monoclonal antibody neutralizing soluble and transmembrane TNF-α	Intravenous infusion	80%	N/A	Infusion reactions, infections, headache	Serious infections, lymphoma, non-melanoma skin cancers	Weeks 0, 2, 6, then every 8 weeks
Adalimumab	First	TNF-α	Fully human monoclonal antibody targeting TNF-α	Subcutaneous injection	71%	N/A	Injection site reactions, infections, headache	Serious infections, lymphoma, non-melanoma skin cancers	Initial dose, then every other week
Ustekinumab	Second	IL-12, IL-23	Fully human monoclonal antibody binding to p40 subunit of IL-12 and IL-23	Subcutaneous injection	67%	42%	Upper respiratory tract infections, headache, fatigue	Rare: serious infections, malignancies	Weeks 0, 4, then every 12 weeks
Secukinumab	Third	IL-17A	Human monoclonal antibody neutralizing IL-17A	Subcutaneous injection	81%	59%	Upper respiratory tract infections, injection site reactions, candidiasis	Exacerbation of inflammatory bowel disease	Weeks 0, 1, 2, 3, 4, then every 4 weeks
Ixekizumab	Third	IL-17A	Human monoclonal antibody targeting IL-17A	Subcutaneous injection	78%	54%	Upper respiratory tract infections, injection site reactions, candidiasis	Exacerbation of inflammatory bowel disease	Initial dose, then every 2 weeks for 12 weeks, then every 4 weeks
Brodalumab	Third	IL-17RA	Human monoclonal antibody blocking IL-17 receptor A	Subcutaneous injection	83%	70%	Upper respiratory tract infections, injection site reactions, headache	Suicidal ideation and behavior	Weeks 0, 1, 2, then every 2 weeks
Guselkumab	Third	IL-23	Human monoclonal antibody targeting the p19 subunit of IL-23	Subcutaneous injection	85%	73%	Upper respiratory tract infections, headache, injection site reactions	Rare: serious infections, malignancies	Weeks 0, 4, then every 8 weeks
Tildrakizumab	Third	IL-23	Human monoclonal antibody targeting the p19 subunit of IL-23	Subcutaneous injection	74%	54%	Upper respiratory tract infections, headache, injection site reactions	Rare: serious infections, malignancies	Weeks 0, 4, then every 12 weeks

Source: the authors

Emerging Biologic Therapies and Future Directions

In the evolving landscape of psoriasis treatment, 2024 promises significant advancements that will shape clinical practice and improve patient outcomes. Psoriasis, once perceived as merely a disorder of epidermal hyperproliferation, is now understood as a complex immune-mediated condition. This shift in understanding has catalyzed the development of therapies targeting specific cytokines implicated in the disease's pathophysiology, particularly IL-23, IL-17, and TNF-α. These biologics represent a paradigm shift from the broad immunosuppressive agents of the past, offering more precise and effective treatment options (Brownstone, 2024).One of the most notable additions to the biologic arsenal is bimekizumab (Bimzelx), approved by the FDA in October 2023. This biologic distinguishes itself by targeting both IL-17A and IL-17F, unlike its predecessors which target only IL-17A or its receptor. Clinical trials, such as the phase 3 BE READY and BE OPTIMAL trials, have demonstrated its superior efficacy, with significant proportions of patients achieving high PASI scores and improved outcomes in psoriatic arthritis. However, bimekizumab's higher incidence of oral candidiasis highlights the importance of monitoring for specific side effects associated with IL-17 inhibition (Brownstone, 2024).

In addition to biologics, the introduction of roflumilast cream, a topical PDE4 inhibitor, marks a significant advancement in the treatment of plaque psoriasis, particularly for intertriginous areas. Approved for adults and adolescents, and pending approval in foam formulation, roflumilast offers a potent, non-steroidal alternative for both psoriasis and seborrheic dermatitis. Its efficacy and safety in these areas suggest it will become a mainstay in topical psoriasis therapy, especially for patients with contraindications to topical steroids.Brownstone (2024) suggested that of biosimilars, particularly for adalimumab (Humira), is poised to impact the treatment landscape significantly. With multiple biosimilars approved and some achieving interchangeable status, these options promise to increase accessibility and reduce costs. However, their integration into clinical practice will require navigating challenges related to formulary preferences, packaging, and patient acceptance.Pediatric psoriasis management also stands to benefit from new therapies. Apremilast, an oral systemic agent traditionally used in adults, shows promise in pediatric populations, providing an appealing alternative to biologic injections. The approval of roflumilast cream for children as young as six further expands treatment options, addressing safety concerns associated with long-term steroid use.

Looking forward, the focus is shifting towards personalized medicine and biomarker-driven therapies. Information from resident memory T cells and their contribution to psoriasis may increase the framework to avoid relapse. Not only so, new and improved oral biologic formulations and peptide based small molecule drugs targeting Il-17 & Il-23 offers a ray of hope for new touch points in oral medicines. The future of psoriasis therapy lies in these targeted, effective, and safe treatments that not only improve skin clearance but also enhance patients' quality of life. The ongoing research and development efforts signal a promising era for both clinicians and patients as they navigate this chronic and often debilitating disease (Brownstone, 2024).

DISCUSSION

Biologic therapies for moderate to severe psoriasis have seen significant advancements, particularly with the introduction of TNF-α inhibitors, IL-12 and IL-23 inhibitors, and IL-17 and IL-23 pathway inhibitors (Wang et al., 2023). First-generation biologics such as etanercept, infliximab, and adalimumab have transformed psoriasis management by neutralizing TNF-α, a crucial cytokine in the inflammatory cascade. Etanercept, a soluble TNF receptor fusion protein, competitively inhibits TNF-α binding, resulting in significant clinical efficacy, with 47% of patients achieving a 75% improvement in PASI scores after 12 weeks. Infliximab, a chimeric monoclonal antibody, offers rapid action with nearly 80% of patients reaching PASI 75 within 10 weeks, while adalimumab, a fully human monoclonal antibody, achieves similar efficacy with 71% of patients attaining PASI 75 at 16 weeks. However, these agents present challenges such as injection site reactions, serious infections including tuberculosis, and the potential development of anti-drug antibodies reducing their efficacy. Long-term risks include a possible increased incidence of malignancies, necessitating vigilant monitoring and individualized patient management (Raychaudhuri & Raychaudhuri, 2024).

Second-generation biologics, notably those targeting IL-12 and IL-23, have further refined psoriasis treatment by disrupting specific cytokine pathways involved in the disease's pathogenesis. Ustekinumab, a fully human monoclonal antibody that binds to the shared p40 subunit of IL-12 and IL-23, demonstrates significant efficacy, with 67% of patients achieving PASI 75 at 12 weeks. The safety profile of ustekinumab is favorable, featuring lower incidences of serious adverse effects compared to TNF-α inhibitors, with common side effects being upper respiratory infections, headaches, and fatigue. Its less frequent dosing schedule enhances patient adherence, although the high cost remains a challenge (Koutruba et al., 2024).

Third-generation biologics are characterised by very selective mode of action, aimed at the attenuation of the

Interleukin-17 and Interleukin-23. Specific IL-17 inhibitors include secukinumab, which binds to IL-17A and has resulted in significant therapeutic outcomes and Ixekizumab also targets IL-17A. Secukinumab has been demonstrated to have 73% of patients achieving PASI 75 and 45% achieving PASI 90 after 12 weeks, and the outcomes of deploying ixekizumab are also similar. nonetheless, these agents carry with them the risk of several side effects, inclusive of upper respiratory infections and in some cases, worsening of inflammatory bowel disease. Brodalumab is another IL-17 inhibitor that is known to bind to both IL-17RA and provides a greater therapeutic benefit: 83% of the patients met PASI 75 and 70% the PASI 90 score in the 12-week study. Although it has potentials, its efficacy is somewhat limited due to psychiatric side effects, most notably, suicidal thoughts, which requires a precise and strict risk assessment and management plan (Schinocca et al., 2021).

Yang et al. (2020) supported that IL-23 inhibitors, including guselkumab and tildrakizumab, bind to the p19 subunit of IL-23 to inhibit the Th17-ce>'+ In managed clinical trials, overall, up to 85% patients witnessed a PASI 75 score with an overall percentage of around 73% achieving PASI 90 following guselkumab therapy while in patients receiving tildrakizumab treatment, the PASI 75 responses were noticed in nearly 74% and PASI 90 in about 54%. They also provide options of more frequent dosing schedules, thus making it easier for patients to adhere to the administration of medication. The safety profile of their current biosimilars is also reasonable with some frequent AE being URI, headache and injection site reaction and relatively less serious AE being reported compared to previous biologics (Yang et al., 2020). However, the use of biologics in rheumatic diseases present some issues for instance, cost, compliance of patients, and harmony between the safety and efficacy of the presented biologic agents. Concerning the long-term effects, especially regarding TNF-α inhibitors, the necessity of patient monitoring and individual therapeutic approaches is obvious. Newer biologic agents with different working mechanisms and safer profiles are the advancements in managing M to S psoriasis yet needs much attention and strict monitoring to get the best result in order to improve the quality of life of the affected populations.

CONCLUSION

Biologic agents have radically changed the management of moderate to severe psoriasis Patients with psoriasis have a wide range of targeted treatment options that have better efficacy than traditional therapies. First-generation TNF-α inhibitors are useful though they have significant side effects that need appropriate monitoring. Actual second-generation IL-12/IL-23 inhibitors and third-generation IL-17/IL-23 pathway inhibitors, therefore deliver much better efficacy and safety. Research advances and specific therapeutic approaches point to further improvement of the care delivery, and, hence, of the overall wellbeing of individuals with psoriasis.

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