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Advances in Biologic and Monoclonal Antibody Therapies for the Management of Psoriasis: A Comprehensive Overview

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Abstract

Background: Psoriasis is a chronic inflammatory skin disorder affecting approximately 3% of the global population, significantly impacting quality of life and incurring substantial healthcare costs. Recent advancements in biological therapies, particularly monoclonal antibodies targeting specific cytokines, have transformed the treatment landscape for moderate to severe psoriasis.

Methods: This review encompasses a thorough analysis of current literature on biologic therapies and monoclonal antibodies for psoriasis management, focusing on their mechanisms of action, efficacy, and safety profiles. The review includes data from clinical trials, meta-analyses, and real-world studies published up to 2023.

Results: The review highlights several biologic therapies, including TNF-α inhibitors (e.g., adalimumab, etanercept) and IL-17 inhibitors (e.g., secukinumab, ixekizumab), which have demonstrated significant efficacy in reducing psoriasis symptoms and improving patient quality of life. Emerging therapies targeting IL-23, such as guselkumab and tildrakizumab, show promise in providing sustained remission. The efficacy of these biologics is often accompanied by manageable safety profiles, although some patients experience adverse effects that necessitate careful monitoring.

Conclusion: Biologic therapies and monoclonal antibodies represent a significant advancement in the management of psoriasis, offering targeted treatment options that improve patient outcomes. Continued research is essential to explore the long-term effects of these therapies, address any emerging safety

concerns, and assess their impact on comorbid conditions associated with psoriasis. Future directions include the development of novel agents that enhance therapeutic efficacy while minimizing side effects.

Keywords: Psoriasis, biologic therapies, monoclonal antibodies, cytokine inhibitors, treatment outcomes.

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1. Introduction

Psoriasis is a chronic skin disorder influenced by several factors and mediated by biological defense systems, affecting around 3% of the general population. It is associated with considerable comorbidities, diminished productivity, employment restrictions, and healthcare expenditures above USD 40 billion each year [1,2]. Numerous studies in the literature have shown that the prevalence of psoriasis varies from around 30 to 320 cases per 100,000 population. This disorder has relationships with parameters like age, gender, ethnic origin, and other genetic and environmental effects [3-5]. The ongoing detrimental effect on quality of life and financial strain highlights the need for efficient long-term illness treatment. The severity of the disease is affected by variables like lesion size, location, and comorbidities such as psoriatic arthritis [6,7].

Effective therapy entails attaining either remission or near remission, which is associated with improved quality of life. Furthermore, a growing body of data indicates that psoriasis is a systemic disorder associated with several comorbidities, including cardiovascular diseases, psoriatic arthritis, metabolic syndrome, depression, and anxiety [8,9]. Therefore, it is essential to tackle both the comorbidities linked to psoriasis and the condition itself to formulate prompt intervention and treatment strategies. In recent years, there has been the development of very successful targeted therapeutics, including conventional, biological, and oral small-molecule treatments. These biological therapies include various classes, such as tumor necrosis factor (TNF)-α inhibitors, Interleukin (IL)-17 inhibitors, IL-23 inhibitors, and an IL-12/23 inhibitor [10-13].

Despite advancements in therapy effectiveness and safety, there is still a need for innovative medicines that provide enhanced skin remission and durability. Moreover, several medicines exhibit diminishing effectiveness over time, prompting the investigation of alternate solutions. Recent advancements in the comprehension of psoriasis pathophysiology have catalyzed the identification of novel therapeutic targets, such as IL-36 inhibitors, phosphodiesterase (PDE)-4 inhibitors, Janus kinase (JAK) inhibitors, tyrosine kinase 2 (TYK2) inhibitors, RORγt inhibitors, and A3 adenosine receptor agonists [13-15]. This narrative review examines recent advancements in biological therapies, oral small molecules, and novel biosimilar medications for the treatment of psoriasis.

This review is to examine all therapies for moderate to severe psoriasis, beginning with biological agents and monoclonal antibodies, and progressing to the latest oral medications including small molecules. The metabolic component is succinctly examined to introduce the pathophysiology, followed by a discussion of the pharmaceutical therapy. Outdated therapies, including seldom used oral drugs for moderate to severe conditions and topical treatments that provide just symptomatic relief without systemic curative effects, are excluded from consideration. The efficacy and usefulness of each medicine might differ according to the patient's clinical circumstances, making it hard to uniformly assess or favor one treatment over another. The prescribing physician must consistently assess the patient's clinical circumstances, therapeutic appropriateness, and associated expenses. In treatment-naive patients, etanercept or adalimumab, now accompanied by biosimilar options, should consistently be used as first-line therapies when their effectiveness is comparable to that of newer, more expensive medications.

2. Presently Accessible Biologic Treatments for Psoriasis

The results from many genome-wide association studies (GWAS) and clinical trials confirm the crucial role of TNF/IL-17/IL-23 signaling pathways in the genesis of psoriasis [16-19]. TNF-α functions as a pivotal inflammatory cytokine significantly implicated in psoriatic lesions, playing a fundamental role in the pathogenesis of psoriasis. The importance of this is shown by the efficacy of medicines aimed against TNF-

α [20-22]. TNF-α, produced by several cell types linked to psoriasis such as keratinocytes, neutrophils, dendritic cells (DCs), mast cells, Th22 cells, Th17 cells, and NKT cells, has dual effects. It significantly impedes plasmacytoid dendritic cells from producing interferon (IFN)-α, often leading to worse or paradoxical psoriasis after TNF-α inhibitor therapy [25,26]. Conversely, TNF-α enhances the maturation of pDCs into a more dendritic cell phenotype, hence promoting the production of IL-23 [27].

Furthermore, TNF-α promotes the production of IL-18 and IL-12, which are strong inducers of IFN-γ, thereby aiding in the modulation of the Th1 response [28]. Additionally, TNF-α collaborates with IL-17A to co-regulate cytokines and keratinocyte genes linked to psoriasis, therefore affecting keratinocyte function [29]. These data jointly demonstrate TNF-α's crucial function as a primary regulator within the IL-23/IL-17 axis. IL-23 is a heterodimeric protein mostly released by dendritic cells, with increased levels seen in psoriasis [30]. The quantity of IL-23 protein in psoriatic lesions significantly exceeds that in unaffected skin [31,32]. Thus, it may be inferred that IL-23 is closely associated with the pathophysiology of psoriasis. IL-23 modulates T cells, namely CD4+ helper T cells (Th17 cells), via a receptor complex. IL-23 subsequently induces Th17 cells to secrete IL-17, a vital cytokine associated with psoriasis, via the activation of signaling pathways [33,34]. The IL-17 family includes six structurally similar cytokines, ranging from IL-17A to IL-17F [35].

Research has identified IL-17A as the cytokine with the most significant biological action, demonstrating the highest levels in psoriasis [36-38]. Thus, IL-17A, often referred to as IL-17, has attracted considerable attention owing to its pro-inflammatory properties and role in autoimmune diseases [39]. IL-17 releases, especially IL-17A and IL-17F, primarily influence keratinocytes, stimulating the production of molecules like β-defensins, antimicrobial peptides (AMPs), and cytokines. Furthermore, IL-17 induces the synthesis of chemokines, often heightened in psoriatic lesions, to attract neutrophils, lymphocytes, and macrophages [40]. Moreover, IL-17 has been associated with the stimulation of keratinocyte proliferation [41]. Psoriasis involves a complex network of interactions among many cellular components and molecular entities. The progression of illness is fundamentally influenced by the complex interaction between the adaptive and innate immune systems. This dynamic interaction stimulates the production of several cytokines that maintain typical psoriatic features in both the dermis and epidermis. Moreover, keratinocytes have a role in inflammation and localized activation. Additional pathways associated with psoriasis, including CCL20-CCR6, the IL-36/IL-1 route, the IFN pathway, and those involving cytokines such as IL-22 and IL-6, are being explored as prospective targets for novel drug development. Figure 1 illustrates a schematic illustration of all these relationships.

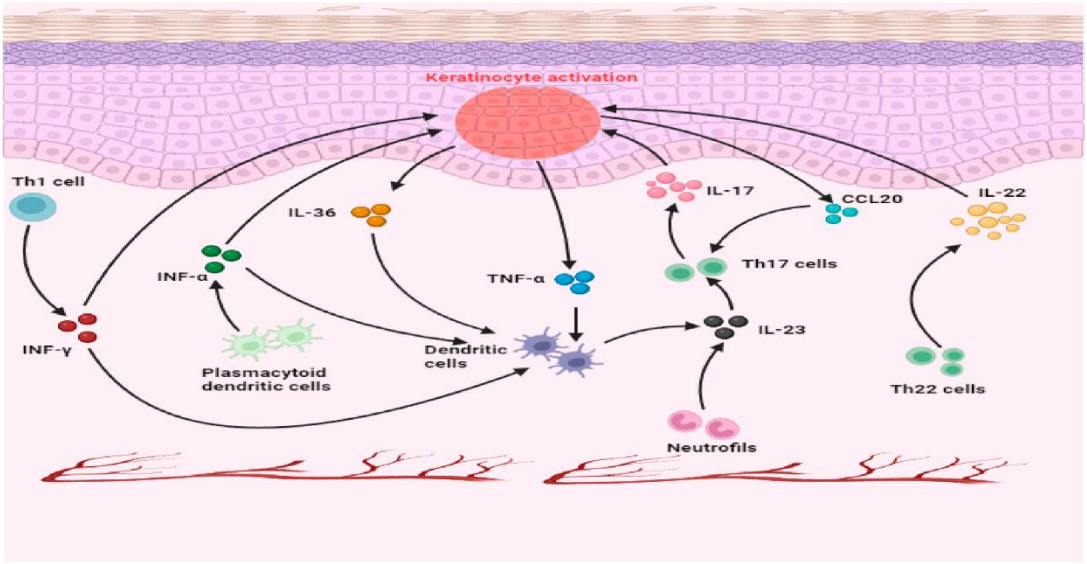

Figure 1. The interaction of cytokine pathways in psoriasis.

3. Novel and Emerging Oral Small Molecules

In the complex domain of investigating novel oral drugs for psoriasis treatment, the JAK-STAT pathway is a pivotal component. This signaling pathway is crucial in cytokine communication, driving inflammation in several autoimmune diseases, hence serving as a significant therapeutic target [42]. This route regulates the action of many cytokines associated with psoriasis, including interferon-α, -β, and -γ. Due to its crucial involvement in the pathogenesis of psoriasis, there is increasing interest in investigating new JAK-STAT inhibitors, in addition to those now used, which provide promising results, to confirm their effectiveness in treating this illness [43]. Certain drugs approved for psoriasis treatment that block this pathway are categorized as first-generation. Tofacitinib, an inhibitor that obstructs the JAK signaling pathway and significantly mitigates all psoriasis-related symptoms, has also attained full FDA clearance after many safety-related occurrences. The medicine may be prescribed with appropriate clinical supervision of the patient. Despite tofacitinib's superiority over placebo in psoriasis therapy, it lacks FDA approval for this use owing to apprehensions over its clinical performance and long-term safety [44].

Numerous studies have shown its benefits, with a phase III study revealing that over 50% of patients on a 5 mg tofacitinib regimen twice daily and more than 60% of those on a 10 mg twice daily treatment saw substantial improvement [45]. Upadacitinib, licensed in 2022 for psoriatic arthritis, has shown favorable outcomes regarding efficacy and safety in clinical studies. Currently, no studies are scheduled to evaluate its efficacy and safety for psoriasis [46,47]. Conversely, baricitinib and ruxolitinib target the same route and operate by inducing Th17 cell death; both are first-generation JAK inhibitors that successfully manage psoriasis [48]. Nonetheless, a meticulous assessment of the safety profile and adverse effects of these medications is crucial, as all first-generation JAK inhibitors focus on the kinase domain of different JAK proteins, increasing the likelihood of nausea, infections, hemoglobin reduction, and possible gastrointestinal perforation [49].

Second-generation JAK inhibitors may preferentially target certain JAK proteins without affecting other cytokines; for example, deucravacitinib (approved by the FDA in 2022) specifically targets TYK2 [50,51]. A recent randomized, double-blind, placebo-controlled phase III study revealed a significant therapeutic response after 16 weeks of daily oral administration of deucravacitinib at a dosage of 6 mg, in comparison to patients receiving placebo [52]. PF-06826647 is a new TYK2 inhibitor that has just completed its phase II study to evaluate its safety and efficacy in individuals with moderate to severe plaque psoriasis [53]. In its preliminary human trial, adverse events and changes in PASI scores were assessed in 40 individuals with plaque psoriasis. Patients were randomly allocated to receive either a placebo or PF-06826647 (400 mg) daily for 28 days. Patients administered 100 mg and 400 mg dosages of PF-06826647 had mean reductions of −14.62 and −24.18 in PASI scores from baseline, respectively, compared to a reduction of −11.13 in the placebo group [54,55].

Brepocitinib, a powerful selective inhibitor of TYK2 and JAK1, is in development for the treatment of psoriasis. A phase I study including 30 patients demonstrated dose-dependent effectiveness trends, with elevated response rates and more significant decreases in PASI scores in the 30 mg and 100 mg brepocitinib cohorts vs. placebo. The treatment-emergent adverse events were modest, and no significant adverse events were documented. Phase II studies further corroborated brepocitinib's performance, demonstrating substantial enhancements in PASI scores and response rates relative to placebo across many treatment regimens. Safety data revealed a minimal incidence of treatment-emergent adverse events, mostly moderate and treatment-related, with prevalent adverse events including headache, psoriasis aggravation, and upper respiratory tract infections [56].

The bulk of selective JAK inhibitors remain under scientific research and lack market approval, however they are regarded as potential therapeutic medicines because of their improved safety profile. Additional prospective oral medicines include piclidenoson (CF101), an agonist of the adenosine A3 receptor, which has been identified as overexpressed in inflammatory disorders including psoriasis and other autoimmune

illnesses. Initial studies have shown its effectiveness; however, a recent double-blind phase 3 trial (COMFORT-1, NCT03168256) involving 529 patients indicated that piclidenoson exhibited progressively enhanced efficacy responses and a favorable safety profile. These findings further substantiate its continued clinical progression as a therapeutic option for psoriasis. Belumosudil (KD025), a selective inhibitor of Rho-associated kinase (ROCK2), demonstrates effectiveness in individuals with psoriasis vulgaris [57]. A notable study revealed that therapy with belumosulid led to a 50% decrease in psoriasis area and severity index (PASI) scores in 46% of participants. This therapy resulted in reduced epidermal thickness and less T-cell infiltration in the skin [58].

Moreover, substantial decreases in IL-17 and IL-23 levels were seen, accompanied by elevated IL-10 levels among responders. The results demonstrate that oral administration of belumosulid successfully downregulates the Th17-mediated inflammatory response and ameliorates clinical symptoms in psoriatic patients by altering cytokine levels without negatively impacting the immune system [59]. Vimirogant (VTP-43742) is a powerful, selective, and orally bioavailable RORγt inhibitor that has shown encouraging effectiveness in phase II studies for individuals with plaque psoriasis, however it has also been associated with specific side effects [60]. Recent research on individuals with moderate to severe plaque psoriasis has shown good outcomes for Cedirogant (ABBV-157), an orally active RORγt inverse agonist. Recent scientific investigations are concentrating on PDE4, which has shown significant anti-inflammatory properties, attracting considerable interest from researchers on the possible role of its inhibitors in the treatment of numerous dermatological conditions, including psoriasis [61].

In 2014, the oral PDE4 inhibitor apremilast received approval in the United States for adult patients with moderate to severe plaque psoriasis. Clinical research (PALACE 1) revealed that apremilast (30 mg administered bi-daily) attained a response rate twice that of the placebo control group [62]. A phase III clinical study (ESTEEM 1) demonstrated the effectiveness of apremilast in moderate to severe plaque psoriasis, with superior response rates relative to placebo [63]. Notwithstanding these encouraging results, the use of PDE4 inhibitors in psoriasis therapy has been impeded by adverse effects, including emesis. Researchers are actively examining this therapeutic target, fostering optimism that further studies will reveal its full potential and provide new strategies for enhancing patient results.

Recent studies demonstrate that IL-23, generated by CD301b+ cells, may stimulate the localized proliferation of TRM cells, indicating that IL-23 inhibitors or novel therapies aimed at CD301b may provide a viable strategy for addressing disease recurrence and maintaining therapeutic efficacy. However, the implementation of these innovative therapy procedures in clinical practice needs more research. Despite significant advancements in the comprehension and management of psoriasis, several facets remain unexamined. An essential future goal is to create effective treatments for addressing psoriasis comorbidities, especially metabolic and cardiovascular conditions [64].

4. Conclusions and Future Outlook

Psoriasis is a chronic inflammatory dermatological illness that significantly burdens people and healthcare systems, highlighting the urgent need for a thorough comprehension of the processes underlying the disease's development. Over the last ten years, progress in comprehending the immunopathology and etiology of psoriasis has resulted in notable treatment advancements. Targeted biologic therapy has created new opportunities for patients, providing significant disease modification and perhaps curative results by inhibiting the formation of tissue-resident memory T cells in the skin. Nonetheless, difficulties remain in the management of psoriasis, including the adverse effects of pharmacological treatments and the potential for disease recurrence upon cessation of therapy. Extended administration of certain pharmaceuticals may result in negative consequences and the establishment of immunological tolerance, thereby restricting their sustained effectiveness.

Moreover, the elevated expense of these medicines often affects the viability of national healthcare systems. An enhanced comprehension of the processes behind illness recurrence underscores the need of early intervention to avert the initiation and expansion of tissue-resident memory T cells. Particular focus

is required for uncommon subtypes of psoriasis, including palmoplantar and pustular psoriasis, which often have a limited response to standard therapies. Moreover, despite the recognition of several putative metabolic molecules, a comprehensive knowledge of the metabolic impacts of psoriasis remains insufficient. The emergence of new technologies like as single-cell metabolomics and spatial metabolomics will enable the construction of a full metabolic network of psoriasis using creative algorithms and integrated analysis. Targeted metabolic medicines remain nascent, probably owing to metabolic variability, adaptability, and unforeseen adverse effects. Identifying more efficacious metabolic targets will be a crucial advancement. We expect that concentrating on psoriasis metabolism and creating a metabolism-focused psoriasis network will emerge as a significant research area in the near future. A crucial domain for future research is assessing the efficacy of genetic biomarkers as preliminary indicators for psoriasis, perhaps enabling earlier diagnosis and more targeted management options.

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التطورات في العلاجات البيولوجية والأجسام المضادة وحيدة النسيلة لإدارة مرض الصدفية: نظرة شاملة

الملخص

الخلفية :الصدفية هي اضطراب جلدي التهابي مزمن يؤثر على حوالي 3% من سكان العالم، مما يترك تأثيرًا كبيرًا على جودة الحياة ويتسبب في تكاليف رعاية صحية باهظة. شهدت العلاجات البيولوجية، وخاصة الأجسام المضادة وحيدة النسيلة التي تستهدف السيتوكينات المحددة، تقدمًا كبيرًا، مما أحدث تحولًا في علاج الصدفية المتوسطة إلى الشديدة.

الطرق :تتناول هذه المراجعة تحليلًا شاملًا للأدبيات الحالية حول العلاجات البيولوجية والأجسام المضادة وحيدة النسيلة لعلاج الصدفية، مع التركيز على آليات عملها وفعاليتها وسلامتها. تشمل المراجعة بيانات من التجارب السريرية والتحليلات التلوية والدراسات الواقعية المنشورة حتى عام 2023.

النتائج :تُبرز المراجعة العديد من العلاجات البيولوجية، بما في ذلك مثبطات TNF-α (مثل *adalimumab* و*etanercept*) ومثبطات IL-17 (مثل *secukinumab* و*ixekizumab*)، والتي أثبتت فعاليتها الكبيرة في تقليل أعراض الصدفية وتحسين جودة حياة المرضى. كما تُظهر العلاجات

الجديدة التي تستهدفIL-23 ، مثل *guselkumab*و*tildrakizumab*، وعودًا بتحقيق فترات هدوء مستدامة. تُظهر هذه العلاجات البيولوجية عادةً ملفات أمان يمكن التحكم فيها، على الرغم من أن بعض المرضى قد يعانون من آثار جانبية تتطلب مراقبة دقيقة.

الاستنتاج :تمثل العلاجات البيولوجية والأجسام المضادة وحيدة النسيلة تقدمًا كبيرًا في إدارة مرض الصدفية، حيث توفر خيارات علاجية موجهة تحسن نتائج المرضى. يُعد البحث المستمر ضروريًا لاستكشاف التأثيرات طويلة الأمد لهذه العلاجات، ومعالجة أي مخاوف أمان ناشئة، وتقييم تأثيرها على الحالات المصاحبة المرتبطة بالصدفية. تشمل التوجهات المستقبلية تطوير عوامل جديدة تُعزز الفعالية العلاجية مع تقليل الآثار الجانبية.

الكلمات المفتاحية :الصدفية، العلاجات البيولوجية، الأجسام المضادة وحيدة النسيلة، مثبطات السيتوكينات، نتائج العلاج.