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REVIEW ARTICLE

A Systemic Review on Psoriasis and Its Treatment

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ABSTRACT

Psoriasis is a chronic, systemic immune-mediated disease characterized by the development of erythematous, indurated, scaly, pruritic and often painful skin plaques. Biologic agents for psoriasis treatment have shown efficacy and safety in clinical trials, but are costly, immunogenic, and require intravenous or subcutaneous injections. Oral therapies, specifically small molecule and microbiome therapeutics, have the potential to be more convenient and cost-effective. This manuscript reviews oral therapies for psoriasis identified through a search of ClinicalTrials.gov. Small molecules under development include tumor necrosis factor inhibitors, IL-23 inhibitors, IL-17 inhibitors, phosphodiesterase-4 inhibitors. Oral microbials have also demonstrated success in early phase studies. Real-world data and comparative trials are needed to better inform the use of these new oral therapies among patients. Research aims to further elucidate the efficacy and safety of various systemic treatments for optimizing outcomes in patients with moderate-to-severe psoriasis.
Keywords: Psoriasis, imide derivatives, synthesis, molecular docking, biological activity, TNF-α, IL-17, anti-inflammatory, antiproliferative

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INTRODUCTION

Psoriasis is a painful, disfiguring, debilitating, chronic, noncommunicable disorder that has no cure and significantly lowers the quality of life (QoL) of those who have it. While it can occur at any age, those between the ages of 50 and 69 experience it most often. There are severe cases of psoriasis all across the world; prevalence rates range from 0.09% to 11.4%, according to reports. Worldwide, psoriasis is prevalent. It affects people of various ages, genders, and ethnic backgrounds everywhere. The variation of psoriasis prevalence across different countries is 0.09% to 11.4%. In most developed countries, the prevalence ranges from 1.5 to 5%. There is also evidence that the prevalence of psoriasis is on the rise. Many studies have shown that psoriasis may have a significant influence on QoL even when it affects a relatively small body surface area (BSA)[1]. The disease affects 2–3% of the world's population and is associated with several comorbidities including cardiovascular disease, inflammatory bowel disease, and psoriatic arthritis [2-4]. Treatment requires an individualized approach, as mild cases are often managed with topical therapies, while moderate-to-severe disease (>5–10% body surface area) may require the addition of systemic therapies [5,6].

Pathophysiology

Although there is no clear immunogen associated with psoriasis, the disease's basic pathophysiology is thought to be excessive activation of certain adaptive immune system components [7]. More precisely, a variety of cell types, including T, dendritic, and keratinocyte cells, are responsible for the chronic inflammation that results from their cytokine production [8–12]. Psoriasis can also occur as a result of genetic mutations and heredity, environmental factors, infections, stress, and skin lesions [13,14].

Epidemiology

Psoriasis is a severe public health concern that affects at least 125 million individuals globally. Psoriasis is equally common in men and women [15], although it varies greatly between geographical areas, with rates as low as 0.5% in Asia and as high as 8% in some parts of Europe [15–17]. A little over 3.2% of

adults and 0.13% of children in the US have psoriasis [18–20]. Psoriasis can start at any age, however it usually manifests itself between the ages of 15 and 30 [21]. The age at which psoriasis first appears can be influenced by both genetic and environmental variables. For example, early onset of psoriasis is strongly correlated with the human leukocyte antigen (HLA)-C*06 allele [22]. Besides, patient ethnicity, UV exposure, and the climate they live in are also considered to influence the prevalence of psoriasis, and recent studies have found a weak association between latitude and psoriasis prevalence [23].

Clinical diagnosis

Based on its clinical signs, which include silver-white scales that easily peel off the skin and vivid pink or red lesions with well-defined edges, psoriasis is a common skin disease that most dermatologists can detect with ease. When the scales are scraped off of the damp skin, little bleeding spots will show up on the pink, sensitive, and moist flesh beneath the scales. A clinical examination of the skin and nails, which includes an evaluation of the location and morphology of psoriatic lesions, and an inquiry into any family history of psoriasis would typically be the main emphasis of the diagnosis process. Sometimes, when psoriasis patients have atypical clinical presentations, dermatologists may also use skin biopsies or scrapes and blood analysis to eliminate otherdiseases and to verify the diagnosis. In addition, the Psoriasis Area and Severity Index (PASI) score is widely used to evaluate the severity of lesions in patients with psoriasis [24], and lattice system physician's global assessment (LSPGA) or psoriasis global assessment (PGA) have been used in routine clinical practice [25].

Approach for the treatment of psoriasis

Recent studies have focused on small compounds, which have a molecular weight of less than one kilodaltons and can penetrate cell membranes to obstruct intracellular signaling pathways [26, 27]. These medicines can be applied topically or orally, which improves patient convenience and quality of life. They are also less expensive to produce than biologics [26, 27]. Although studies on oral microbials are still in their early stages, they are being conducted [28]. Apremilast, an inhibitor of phosphodiesterase-4 (PDE4), and deucravacitinib, a tyrosine kinase 2 (TYK2) inhibitor that was just licensed, are two of the available small molecule treatments for psoriasis [29, 30]. Despite being widely used in clinical practice, apremilast is linked to gastrointestinal side effects and low efficacy [31, 32]. Clinical trials have shown that deucravacitinib is more efficacious than apremilast, however, real-world data are lacking, and it remains unclear how this agent will perform against existing biologics [33,34]. New oral therapies are needed for the treatment of psoriasis. TNF-α inhibitors, interleukin-17 (IL-17) inhibitors, IL-12/IL-23 inhibitors, and PDE4 inhibitors have emerged as a promising candidate in clinical treatment.

Phosphodiesterase-4 Inhibitors

The primary phosphodiesterase that is expressed by keratinocytes and immune cells is PDE4 [35]. By hydrolyzing 30–50-cyclic adenosine monophosphate (cAMP), a significant second messenger molecule, to adenosine monophosphate (AMP), it mediates inflammatory reactions [36–38]. Therapeutically, PDE4 enzyme inhibitors are advantageous because they increase intracellular cAMP levels and stimulate mechanisms that promote an anti-inflammatory response by preventing the synthesis of proinflammatory cytokines and promoting the generation of anti-inflammatory mediators [36–38].

In the skin, PDE4 is primarily expressed in keratinocytes, neutrophils, Langerhans cells, and T cells, which contribute to the psoriatic plaque formation[39]. Owing to broad anti-inflammatory activities, PDE4 inhibitors have been investigated and applied for the treatment of various skin disorders or rheumatic diseases, such as psoriasis, psoriatic arthritis (PsA), and AD. Psoriasis is a chronic skin inflammatory disorder, which has an estimated global prevalence of 1–3% [40].

Apremilast is an oral PDE4 inhibitor that inhibits inflammatory responses. It has been tested against various cells and has shown significant effects on psoriasis and arthritis in preclinical models. It also reduces arthritis severity in mice. Apremilast has a wide therapeutic index in ferret lung neutrophilia. It was approved for treatment in 2014 for adults with active PsA and moderate-to-severe plaque psoriasis. However, its exposure is reduced when coadministered with CYP450 inducers, potentially affecting its therapeutic efficacy[41].

Orismilast, an oral PDE4 inhibitor, has shown potential in treating psoriasis, atopic dermatitis, and hidradenitis suppurativa. A phase IIb, randomized, dose-finding study found that orismilast was 2-5 times more potent than apremilast in inhibiting the PDE4 subtype, specifically the PDE4B and PDE4D splice variants linked to inflammation. The study found significant improvements in PASI 75 and 90 responses across all treatment groups. However, tolerability may be a limiting factor to treatment, especially at higher doses. Further phase III studies are needed to better understand the long-term efficacy, safety, and tolerability of orismilast.[42]

ME3183 is a selective PDE4 inhibitor developed by Meiji Seika Pharma. It is 5- to 40-fold more potent than apremilast in inhibiting inflammatory cytokine production. A phase II, double-blind, placebo-

controlled trial showed that ME3183 significantly reduced PASI scores in participants treated once or twice daily. It was well-tolerated with common adverse events like diarrhea, headaches, and nausea[43-44]. Mufemilast, a potent PDE4 inhibitor, is being investigated in phase III for psoriasis patients. The primary endpoint is achieving a PASI 75 response at 16 weeks. Results from previous studies are not yet published[45].

Interleukin-17 (IL-17) inhibitors

The primary effector cytokine in psoriasis is IL-17 [46]. It is generated by Th17 cells, and once created, it acts on keratinocytes to encourage their growth and the release of chemokines, cytokines, and antimicrobial peptides that aid in the development of psoriasis plaques [47–49]. The six subunits that make up the IL-17 family's structure are IL-17A–IL-17F. Particularly connected to psoriasis signaling are IL-17A and IL-17F, which together form the IL-17A/F heterodimer and two homodimers [47–49]. Therapeutic use of antibodies that block these subunits has been effective, and research is currently being done on oral formulations.

The small molecule inhibitor DC-806 (Eli Lilly and Company, Indianapolis, IN, USA) inhibits the IL-17A subunit [50]. Forty subjects in a phase I proof-of-concept research (unlisted) reported a substantially higher mean PASI score reduction after four weeks after receiving DC-806 800 mg twice daily as opposed to those who got a placebo (probability = 0.0008, exploratory p = 43.7% vs. 13.3%) [50]. Therapeutic efficacy from low-dose DC-806 (175 mg twice daily) was not observed. There was no dose-dependent trend and the adverse effects ranged in severity from mild to moderate. Headaches, stomach discomfort, and COVID-19 infection were common side effects. There were no reports of discontinuations because of adverse events or clinically meaningful adjustments to test abnormalities [50].DC-806 is currently being investigated in a phase IIb dose-ranging trial (NCT05896527),with the PASI 75 response at 12 weeks defined as its primary endpoint.

Among the IL-17 inhibitors in the early stages of development are DC-853 (Eli Lilly and Company), a fast follower of DC-806, and LEO 153339 (LEO Pharma, Ballerup, Denmark), which was recently studied in a phase I single ascending dose (SAD) and multiple ascending dose (MAD) trial in healthy subjects (NCT04883333). DC-853 provides better metabolic stability and has a stronger affinity for the IL-17A cytokine, according to Lilly [51]. Nevertheless, there are no published preclinical or clinical trial data on these medications.

IL-12/IL-23 inhibitors

One important regulator of the Th17 pathway is IL-23 [52]. Produced by macrophages and myeloid dendritic cells, it induces naïve T helper cells to differentiate into Th17 lymphocytes and encourages these cells to release pro-inflammatory cytokines such TNF, IL-12, IL-23, and IL-17 [53-55]. Agents that block this pathway typically target either the p19 or p40 subunits of the cytokine and must be administered intravenously or subcutaneously [55]. A comparable method of action is also being studied for oral small compounds.

JNJ-2113 is an orally available peptide that binds to the IL-23 receptor, blocking downstream cytokine signaling. It has shown efficacy in reducing skin thickness and cytokine production in psoriasis-like mouse models. A phase IIb clinical trial showed significant improvements in PASI 75 response and PASI 90 and 100 responses. JNJ-2113 is currently being investigated in two phase III studies for psoriasis, with a 36-week extension study pending results[56, 57].

Tumor Necrosis Factor Inhibitors

A pleiotropic cytokine, TNF has a role in the development of a number of inflammatory and autoimmune disorders [58, 59]. There are two physiologically active forms of it: soluble protein (sTNF) and membrane-bound form (mTNF); the latter is generated when TNF converting enzyme cleaves the former through proteolytic cleavage [60]. When in their trimeric state, both mTNF and sTNF are active and send signals through TNFR1 and TNFR2, two cognate receptors [61-63]. The majority of TNF's biological effects are attributed to TNFR1, which is widely expressed. It does this by triggering the pathways of nuclear factor kappa B (NF-B) and mitogen-activated protein kinase (MAPK) and encouraging a proinflammatory response [63, 64]. The activation of TNFR2, which is limited to immune cells, endothelial cells, and glia and only reacts to mTNF, enhances cell proliferation, survival, andand lineage stability [65, 66]. Psoriasis patients overexpress TNF, causing inflammation through lymphocyte recruitment, adhesion molecules, and keratinocyte differentiation. Current biologic agents inhibit both mTNFand sTNF, making them important therapies for the disease. Oral small molecules with similar mechanisms are under investigation[67-70]. Sanofi's SAR441566 is a small molecule inhibitor of the TNF cytokine, which is used in early phase development for psoriasis. In a phase I, double-blind, placebo-controlled, randomized trial, 58% of participants in the treatment group achieved a one-point reduction in the Investigator Global Assessment score at 4 weeks compared to placebo. Mean changes in Target

Lesion Severity and Psoriasis Area and Severity Index scores also favored the treatment group. The drug was well-tolerated and is currently being investigated in a phase II trial for psoriasis[71, 72].

CONCLUSION

Psoriasis therapy should be cost-effective, easy to use, efficacious, and safe with minimal adverse events. Biologic agents have seen the greatest advancement in psoriasis treatment, with several new agents approved. Oral therapies, despite being more cost-effective and popular, have been slower to follow suit. Current oral agents with well-validated mechanisms of action are under development for psoriasis. JNJ-2113, targeting the IL-23 receptor, is in phase III trials. Orismilast, a selective PDE4 inhibitor, reduced disease severity in phase II trials, but larger trials are needed to determine safety and tolerability. New oral therapies for psoriasis require long-term trials and comparative studies with existing agents to understand their role in the current treatment algorithm. Agent-specific characteristics, including tolerability and dosing regimen, are crucial, especially for medications requiring twice-daily dosing schedules. Studies investigating oral therapies in patients with psoriasis comorbidities will also inform optimal patient selection.

ACKNOWLEDGEMENTS

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