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Review Article

Systematizing PDE4 Inhibition in Psoriasis Treatment: Roflumilast Leads the Way

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ABSTRACT

Psoriasis, a prevalent autoimmune disorder, presents significant challenges due to its chronic inflammatory nature and multifactorial etiology, involving both genetic tendency and environmental factors. Conventional therapies, while providing symptomatic relief, often stay behind to achieve sustained remission. This review explores advancements in psoriasis treatment, emphasizing the emergence of targeted therapies and biologics as the priority in enhancing disease management. Focus is on plaque psoriasis, the most common clinical subtype and the role of Roflumilast, a Phosphodiesterase-4 (PDE4) inhibitor, in modern therapeutic approaches. Roflumilast exerts immunomodulatory effects by increasing intracellular cyclic Adenosine Monophosphate (cAMP), which attenuates inflammation and keratinocyte hyperproliferation, key pathological features of psoriasis. A comprehensive literature review was conducted using scholarly databases and clinical trial registries. Key terms such as "Psoriasis treatment," "PDE4 inhibitors," "Roflumilast," "Targeted therapy," and "Therapeutic efficacy" guided the search. Priority was given to randomized controlled trials, observational studies and meta-analyses to ensure robust data inclusion. Clinical evidence suggests that Roflumilast exhibits a favorable safety profile compared to conventional treatments. Highlighting findings include rapid clinical improvement, patients achieving clear or almost clear skin within weeks and fewer adverse effects, indicating its efficacy and tolerability. This review brings to light Roflumilast's potential to revolutionize psoriasis treatment, offering improved outcomes and safety. While additional research is inevitable to establish its long-term safety profile, Roflumilast represents a promising step forward in enhancing patient quality of life and reshaping psoriasis management.

Keywords: Psoriasis, Roflumilast, Targeted therapies, Treatment efficacy.

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INTRODUCTION

As an existing non-communicable autoimmune disease, psoriasis affects approximately 3% of the global populace. It manifests as a chronic, inflammatory condition with multifactorial origins, including genetic reasons and environmental triggers.[1] Though it affects individuals across all age groups, around 75% of cases appear before age 46.[2] The disease discomforts affected individuals physically and psychologically, bringing imbalance in their quality of life.[3] Worldwide, approximately 100 million individuals contend with psoriasis, which often comes with comorbidities such as arthritis caused by psoriasis, cardiometabolic diseases and mood disorders.[4]

Psoriasis remains a complex disease, accelerating the development of multifaceted treatment approaches. Conventional therapies may alleviate symptoms, but emerging biologics and targeted therapies can give hope for enhanced results and better quality of life for affected people. Continued research with clinical interventions is imperative to actualize the full potential of these advancements in psoriasis management.

This review provides insights into the treatment options for plaque psoriasis, which totals 80- 90% of cases, while also scrutinizing the role of a Phosphodiesterase-4 (PDE4) inhibitor, Roflumilast, in contemporary treatment. At the same time, conventional therapies encompass topical agents, systemic medications and phototherapy.[5] Despite advancements, a good cure remains far away, necessitating novel therapies with better safety profiles and targeted actions.

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OVERVIEW OF CURRENT TREATMENTS AND CHALLENGES

Conventional treatment landscapes for psoriasis are topical and systemic therapies in addition to phototherapy. In recent decades, biologics have also been used to treat moderate to extremely severe psoriasis. These treatments involve a unique mechanism of action that reduces inflammation and keratinocyte hyperproliferation. However, no complete cure for Psoriasis has been shown by any of these therapies till now. The current scenario recognizes the need for novel therapy that shows reduced adverse effects and site-specific action of the drug.

Topical therapies, including corticosteroids, vitamin D analogues and calcineurin inhibitors, are the initial choice for patients with less than 20% body involvement in psoriasis. Their long-term use shows side effects like skin atrophy, striae and telangiectasia.[6] Vitamin D analogues, such as calcipotriol, normalize keratinocyte proliferation, while calcineurin inhibitors like tacrolimus and pimecrolimus target T-cell activation.[7] These treatments, though effective in mild cases, are often insufficient for moderate to severe psoriasis, necessitating the use of systemic therapies.

Systemic therapies are mainly administered by severe psoriatic patients for short periods. Methotrexate inhibits DNA synthesis and reduces the rapid turnover of skin cells, while cyclosporine suppresses immune activity by inhibiting calcineurin, thereby reducing cytokine production.[8] Retinoic acid derivatives, combined with PUVA therapy, are more effective in chronic plaque psoriasis treatment.[9] The most serious side effect of drugs, including Etretinate and Acitretin, is teratogenicity, which makes it crucial to avoid pregnancy during the treatment.[10] Low dose treatment for three months shows improvement in the patients, while higher doses are associated with adverse effects, including hepatotoxicity, nephrotoxicity and increased risk of infection.[11]

Patients with moderate to severe cases may often undergo phototherapy, which proves effective even in extensive areas where topical application is difficult or ineffective. Phototherapy targets affected areas by utilizing UVA and UVB radiations.[12] Localized psoriasis benefits from targeted phototherapy, while full-body sessions are necessary for severe cases. Combined with coal tar, intermittent phototherapy yields optimal therapeutic outcomes, benefiting nearly 80% of patients.[13] Excimer laser treatment is gaining popularity for localized psoriasis management.[14] Long-term effects, including photodamage and increased cancer risk due to cumulative UV radiation exposure, are noted alongside short-term effects like burning and pruritis.[15] Biologic agents reformed the treatment of psoriasis, offering targeted inhibition of specific immune system components. TNF-α inhibitors, such as etanercept, certolizumab infliximab and adalimumab, block the activity of TNF-α, a key driver for inflammation.[16] Interleukin inhibitors, including IL-17 and IL-23, target more defined pathways in immune response. While biologics are incredibly effective, they are expensive and require careful monitoring for increased risk of infections and malignancies. Combining topical treatments with systemic agents and biologics enhances efficacy, safety and long-term outcomes.

EMERGING TREATMENTS

Janus Kinase inhibitors, such as tofacitinib, baricitinib and ruxolitinib, selectively target JAK1, JAK2, JAK3 and TYK2 modulating immune responses via cytokine receptor interactions.[17] One of the most exciting areas of emerging psoriasis treatments is the innovation of nanoparticle-based drug delivery systems. Nanomedicine harnesses more precise delivery of drugs to affected skin areas, enhancing bioavailability and minimizing systemic side effects. Innovations in psoriasis management offer significant advancements, but a complete cure remains elusive. While conventional therapies provide relief, their limitations necessitate the need for targeted therapies. Emerging treatments like PDE4 inhibitors offer efficacy with fewer adverse effects. As research progresses, the future promises transformative therapies, improving the quality of lives of those affected.

ADVANCES IN PSORIASIS TREATMENT: A FOCUS ON PDE4 INHIBITOR-ROFLUMILAST

Phosphodiesterase-4 regulates inflammatory responses across various cell types, including brain, epithelial and immune cells.[18] Among the different families of phosphodiesterase enzymes, PDE4 is the most prevalent, specializing in the breakdown of cAMP, a key signaling molecule in immune and central nervous system functions.[19] The pharmaceutical industry has developed several PDE4 inhibitors to address inflammatory conditions. While selective PDE4 inhibitors have shown promise in dermatologic conditions, systemic administration of oral PDE4 inhibitors often comes with drawbacks, such as a narrow therapeutic window and adverse effects, such as vomiting, headache, nausea, hair loss and depression.[20] Consequently, ongoing research now focuses on exploring their topical administration for conditions like psoriasis, aiming to avoid these systemic side effects while maintaining therapeutic efficacy. This limitation necessitates focusing on the topical administration of Roflumilast, which offers improved safety, efficacy and a broader therapeutic window in psoriasis treatment. Roflumilast, a selective PDE4 inhibitor, was initially designed for COPD treatment.[21] However, its potent anti-inflammatory activity made it a promise for psoriasis treatment. By controlling immune responses and limiting pro-inflammatory cytokine production, Roflumilast paved the way for targeted therapy with fewer side effects. Moreover, developments in drug delivery systems have enhanced their bioavailability, efficacy and safety profile.

IMMUNOMODULATORY EFFECTS OF ROFLUMILAST-THE MECHANISM

Phosphodiesterase enzymes play an essential role in cellular signaling by regulating the levels of cAMP and cGMP.[22] The various cell types, including the myeloid cells, lymphoid cells, smooth muscle cells, keratinocytes, endothelial cells and sensory and memory neurons, are specific areas where the PDE4 is expressed.[23] The mechanism involves hydrolysis and degradation of cAMP and cGMP into 5'-nucleotide monophosphates.[24] These cyclic nucleotides attach to their respective receptors and activate downstream signaling pathways. This action of PDE4 ensures precise control over the duration and intensity of cAMP and cGMP signaling, contributing to fine-tuning various cellular processes, including immune response, smooth muscle contraction, cell proliferation and neurotransmission.[25] Roflumilast selectively inhibits the PDE4 enzyme, thereby prolonging cAMP's presence in the body. The Elevated cAMP levels control inflammation and impact cellular growth and communication. When cAMP levels rise, they activate Protein Kinase A, which delays the activity of NF-kB. By blocking NF-kB, the production of inflammatory proteins like TNFα, IFNγ and IL-17 is reduced.[26] Additionally, cAMP can activate CREB protein, initiating the release of anti-inflammatory proteins like IL-10. Roflumilast thus lowers the levels of both pro-inflammatory proteins and anti-inflammatory proteins. This effect of balancing the immune response proves advantageous in conditions such as psoriasis, where inflammation reduction and immune response equilibrium are essential.[27]

ROFLUMILAST-PHARMACOKINETICS

The pharmacokinetic profile of Roflumilast reveals some vital attributes, which include high bioavailability, extensive protein binding and primarily urinary elimination. Topical roflumilast 0.3% cream (Zorvye™) emerged as an exceptional advancement in dermatology upon its approval by the FDA in 2022. During the study, after 15 days of daily 0.3% topical roflumilast cream application (3-6.5 g), roflumilast and its active metabolite, roflumilast N-oxide, were quantifiable in 22 out of 24 patients. Plasma protein binding was 99% for roflumilast and 97% for roflumilast N-oxide. Metabolism involves cytochrome P450 and conjugation. The mean half-life post topical application was 4 days for roflumilast and 4.6 days for roflumilast N-oxide. Knowing these pharmacokinetic properties is strong enough to optimize Roflumilast's use as a therapeutic agent, thereby maximizing its benefits in managing inflammatory conditions like psoriasis.[28] Crafted specifically for plaque psoriasis treatment in patients 12 years and older, it marks the first instance of a topical PDE4 inhibitor being approved to manage psoriasis. Extensive clinical trials exhibited efficacy, with remarkable improvements observed in two weeks of application. The topical roflumilast exhibits a good safety profile, with minimal side effects localized to the application site and mild gastrointestinal discomfort. Roflumilast's potential to integrate with other treatments, like biologics or phototherapy, is a better alternative to psoriasis treatment. This innovation markspsoriasis management as a more targeted, effective and safer alternative. Overall, roflumilast's advantages over existing PDE4 drugs position it as a preferred option for managing psoriasis and other inflammatory conditions. Nanoparticles, the latest advancement in therapy, provide enhanced drug delivery by improving bioavailability, enabling targeted action and offering controlled release, changing the landscape of modern medical and therapeutic applications. Additionally, nanotechnology has significantly optimized drug delivery methods in dermatology.

TRIALS ASSESSING THE EFFICACY OF ROFLUMILAST IN TREATING PSORIASIS

Lebwohl *et al*., in 2020, performed a phase 2b, double-blind trial todiscover the efficacy and safety of roflumilast cream to treat chronic plaque psoriasis. In the trial, 331 adults were randomly given 0.3% roflumilast cream, 0.15% roflumilast cream, or placebo cream once daily for 12 weeks. The patients getting clear or very near to clear skin ratio in the 6th week was judged as the initial endpoint per the IGA. The 28% of patients in the 0.3% roflumilast group and 23% in the 0.15% roflumilast group achieved the primary endpoint, compared to 8% in the placebo group. Secondary efficacy outcomes included significant improvements in IGA scores in intertriginous areas and reductions in PASI scores in every treatment group. The roflumilast cream safety profile was favorable, with similar rates of application site reactions observedin both roflumilast and placebo groups. The authors concluded the study that the application of roflumilast cream once daily led to better efficacy compared to a placebo, with a good count of patients getting clear skin by week 6. The authors also suggested that higher concentrations of roflumilast may offer greater benefits and recommended lengthy and bigger trials to assess the safety and durability of roflumilast in psoriasis treatment.[29] Lebwohl *et al*., intheir 2022 study, studied the safety and tolerability of 0.3% roflumilast cream, two weeks once daily application in psoriasis patients, through phase III randomized, double-blind, controlled, multicentred trials conducted at multiple centers in the US and Canada. The trials, DERMIS-1 (Trial 1, n=439) and DERMIS-2(Trial 2, n=442), included patients with plaque psoriasis covering 2% to 20% of their Body Surface Area (BSA). A total of 881 patients were enrolled. In week 8, roflumilast treated patients showed higher success rates in the IGA than the vehicle group. IGA success rates were 42.4% in trial 1 and 37.5% in trial 2 for roflumilast versus 6.1% and 6.9% for the vehicle, respectively. Researchers continued the study for a long-term trial, DERMIS-3, for up to 64 weeks with 73.5% of patients. In the continued study, 45% of patients achieved clear skin by week 52. Roflumilast cream also improved intertriginous psoriasis and itching and reduced the burning sensation of plaques. In their study, some adverse

effects, including insomnia (1.4%), diarrhea (3.1%) and headache (2.4%), were reported in 25.2% and 23.5% of patients in trials 1 and 2, respectively. Drawbacks of roflumilast treatment identified include the cost of the drug, the lack of studies in hepatic patients and the capacity for poor adherence. This study provides valuable insights into the efficacy and profile of the safety of roflumilastcream in treating chronic plaque psoriasis.[30] Snape, Wigger and coworkers evaluated the anti-inflammatory efficacy, local safety, tolerabilityand systemic pharmacokinetics of two topical phosphodiesterase 4 inhibitors, roflumilast and TAK-084, in plaque psoriasis. 15 Patients in the age group of 18-65 with stable chronic plaque psoriasis were included in this randomized, single-center, observer-blind trial. An intraindividual comparisonof five topical products and vehicle control was carried out over three weeks. The study found improvements to a large extent in all treatments. Roflumilast 0.5% and 0.5% TAK-084 showed the most improvement in the depth of skin infiltration caused by psoriasis compared to the vehicle control, with reductions of -237.1 µm and -153.6 µm, respectively. Also, the researchers found that 5% TAK-084 and 0.5% Roflumilast were more effective than calcipotriol 0.005%. Meanwhile, they reported mild adverse effects indicating good tolerability. In general, the study demonstrated the efficacy of topical PDE4 inhibitors in reducing inflammation and improving the severity of psoriasis, with favourable safety profiles. These findings underscore the potential of roflumilast and TAK-084 as promising treatment options for plaque psoriasis.[31] A placebo-controlled randomized trial was conducted by Egeberg et al. to investigate the efficacy of oral roflumilast in moderate to severe psoriasis, particularly in a patient predisposed to psoriasis with comorbidities like COPD and overweight. The patient presented with psoriasis affecting approximately 65% of the BSA and a PASI score of 21.2, along with impaired life quality and symptoms of depression. After four weeks, treatment with oral roflumilast 500 µg OD resulted in a remarkable 75% decrease in PASI scores and a reduction in BSA involvement. Complete disappearance of severe psoriasis plaques was achieved within 24 weeks of roflumilast therapy, as indicated by dermatology and quality of life indices. Also, the patients experienced weight normalization due to the drug's side effect of weight loss, which proved beneficial in this case. The findings underscore the efficiency of oral roflumilast as an effective therapeutic option for moderate to severe psoriasis, especially in patients with associated comorbidities.[32] A study was conducted to find out the pharmacokinetic profile of topical roflumilast cream in psoriatic patients with high BSA≥20% by Archie W Thurston *et al*. The research comprised a Phase I maximal usage study and data from Phase II and III studies involving 26 patients. The study, an open-label, single-arm trial over two weeks, included 6 adolescents and 20 adults with chronic plaque psoriasis. Serial plasma samples collected on days 1 and 15 allowed determination of peak plasma concentration and area under the curve, while terminal half-life ($t_{1/2}$) was assessed at weeks 3, 4 and 5. Results showed a bioavailability of 1.5% for the 0.3% roflumilast cream, indicating slow absorption and a flat plasma concentration-time curve with a peak-to-trough ratio of 1:2. Steady-state conditions demonstrated a peak roflumilast concentration of 3.72% with a corresponding trough value of 1.78 ng/mL after 8 weeks 45. The topical administration of roflumilast cream resulted in significantly higher skin concentrations (125-61.8-fold) compared to plasma levels, suggesting enhanced efficacy locally. Moreover, the favourable pharmacokinetic profile, including a 4-hr half-life and minimal gastrointestinal adverse effects, supports once-daily administration. This study highlights the potential of topical roflumilast cream as an efficient and well accepted treatment option for psoriasis.[33] In 2020, Kim A Papp *et al.* researched the safety and effectiveness of low-dose administration from a phase 1/2 a, randomized controlled study. In this phase ½ a study, two cohorts were enrolled to determine the safety and efficacy of roflumilast cream in chronic plaque psoriasis. Cohort 1 received a single dose of 0.5% cream on psoriatic plaques, while Cohort 2 underwent a 28-day, double-blinded trial with 0.5%, 0.15% roflumilast cream or vehicle. The patients had psoriasis involving ≤5% of body surface area. Results showed that adverse events, mostly light or moderate, were similar across active arms and vehicles, with no severe events reported. The events related to treatment were localized to the site of application and none moved to treatment discontinuation. Both doses of roflumilast cream significantly improved the Target Plaque Severity Score×Target Plaque Area compared to the vehicle, with statistically significant improvements observed as early as 2 weeks. At week 4, an improvement of 66%-67% from baseline was seen with roflumilast cream versus a 38% improvement with the vehicle. In conclusion of the study, roflumilast cream at 0.5% and 0.15% demonstrated safety and high efficacy, presenting as a promising topical therapy of once daily for chronic plaque psoriasis.[34] Lebwohl *et al.* conducted a phase 2b double-blind trial to evaluate the efficacy of roflumilast cream in treating chronic plaque psoriasis. The study included 331 adults randomly assigned to receive once-daily applications of 0.3% roflumilast cream (n=109), 0.15% cream (n=113), or placebo (n=109) for 12 weeks. The important endpoint, the Investigator's IGA status of clear or almost clear skin at week 6, showed significant improvement with roflumilast compared to placebo. Secondary outcomes, including improvement in IGA and PASI scores, also favoured roflumilast treatment. Adverse reactions were similar between Roflumilast and placebo groups, which indicates a favourable safety profile. The study highlights the efficacy of roflumilast cream once daily, particularly at higher concentrations, in achieving clear or almost clear skin by 6 weeks. The authors suggest further research to assess roflumilast's long-term safety and durability in psoriasis treatment. These findings take over the potential of roflumilast cream as a promising therapeutic option for psoriasis management.[35]

DISCUSSION

Clinical trials evaluating roflumilast have shown its significant impact on disease severity, depicting its ability to achieve clear or almost clear skin in moderate to severe psoriasis. The safety profile is favorable, with fewer adverse effects reported, supporting its therapeutic potential.

In the studies conducted, the graphical representations portray the efficacy and safety profile of Roflumilast based on clinical trial data by Lebwohl *et al.* in 2020, comparing adverse events, site pain and discontinuation rates between patients treated with Roflumilast and those who received a placebo. The data shows that Roflumilast has a favorable efficacy and safety profile, with minimal discontinuations and manageable side effects.

The clinical trials discussed in the review of Lebwohl *et al.* 2022, signify the capacity of roflumilast to reduce the severity of psoriasis, as given by the Psoriasis Area and Severity Index (PASI) and Investigator Global Assessment (IGA) scores. The DERMIS-1 and DERMIS-2 trials exhibited that 0.3% Roflumilast cream defined important advancements in skin clearance, while the long-term DERMIS-3 trial confirmed the robustness of the results interpreted in Figure 1.

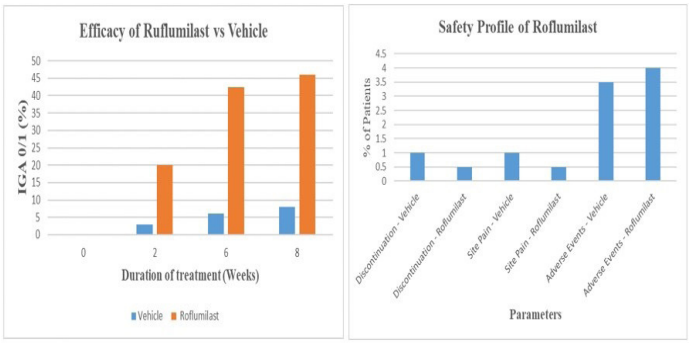

Figure 1: Efficacy and Safety Profile of Roflumilast.

On the safety profile, Roflumilast has been beneficial; topical and oral formulations reported the least adverse events with common side effects, including mild reactions on application sites comparable to placebo. The effectiveness of Roflumilast in short-term and long-term studies is proven, providing a safer and highly potent alternative, especially in cases of plaque psoriasis in sensitive areas.

Nanoparticles, 10 to 200 nanometers in size, offer advantages like increased skin absorption, better drug stability and controlled release. In treating psoriasis, nanoparticles can heighten drugs like Roflumilast by targeting affected areas, reducing side effects. Encapsulating Roflumilast in lipid-based or polymeric nanoparticles improves solubility and bioavailability. Animal studies show nanoparticle formulations reduce epidermal hyperplasia and inflammation more effectively, offering prolonged release and improved adherence.

Going forward, the psoriasis treatments may influence combined targeted therapies that can tune distinct immune response pathways. Due to its anti-inflammatory properties, Roflumilast could be paired with biologics to bring efficacy in patients. Additionally, combining Roflumilast with novel agents like Janus kinase inhibitors or small molecules offers personalized treatment approaches. Further studies are required to understand Roflumilast's long-term safety in comorbid populations and to explore its nanoparticle formulations for broader dermatological applications.

CONCLUSION

In conclusion, psoriasis is a challenging autoimmune disease affecting millions worldwide, with evident physical and psychological impacts. Though conventional treatments provide some relief, they are limited, necessitating the advancement of novel therapeutic approaches. PDE4 inhibitors, especially roflumilast, give a promising alternative for managing psoriasis with improved safety and efficacy.

Roflumilast's mechanism, targeting inflammatory pathways by selectively inhibiting PDE4 and increasing intracellular cAMP, attenuates inflammatory mediators and reduces keratinocyte proliferation. This action results in symptom relief and improved quality of life. Encapsulated nanoparticles also reduce systemic side effects by concentrating the drug in affected areas, making them a promising advancement in dermatological treatments.

Although further research is recommended to assess roflumilast's long-term safety and durability, current clinical trial results hold its role as an excellent treatment option for psoriasis. Roflumilast signals a significant advancement in psoriasis management, enhancing patient outcomes.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

DNA: Deoxy Ribonucleic Acid; **PUVA:** Psoralen combined with Ultraviolet A; **PDE4:** Phosphodiesterase-4 inhibitor; **cAMP:** Cyclic adenosine monophosphate; **PUVA:** Psoralen plus ultraviolet A; **UVA:** Ultraviolet A; **UVB:** Ultraviolet B; **TNF-α:** Tumour necrosis factor-alpha; **IL:** Interleukin; **JAK:** Janus Kinase; **TYK2:** Tyrosine Kinase 2; **COPD:** Chronic obstructive pulmonary disease; **cGMP:** Cyclic guanosine 3'5'- monophosphate; **NF-kB:** Nuclear Factor Kappa B; **IFNγ:** Interferon-gamma; **CREB:** Cyclic AMP Response Element-Binding Protein; **FDA:** Food and Drug Administration; **IGA:** Investigator's Global Assessment; **PASI:** Psoriasis Area and Severity Index; **BSA:** Body surface area.

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