



Review Article

Topical roflumilast – A novel molecule for immunodermatological diseases

Abhishek De¹, Disha Chakraborty², Shreya Datta³, Sushil Singh¹

¹Department of Dermatology, Calcutta National Medical College and Hospital, Kolkata, West Bengal, India, ²Department of Dermatology and Rheumatology, VA Medical Center Sacramento, Rancho Cordova, California, USA, ³Department of Rheumatology and Immunology, Calcutta National Medical College and Hospital, Kolkata, West Bengal, India.

ABSTRACT

Topical roflumilast (ROF) is a recently approved phosphodiesterase 4 inhibitor for the treatment of psoriasis. It has strong anti-inflammatory effects which are quite helpful in the management of the distressing symptoms of psoriasis, as seen in several clinical trials. It also displayed a wide range of safety and, hence, can be utilized in patients without fearing the advent of any dangerous side effects. However, more clinical data are required to find out the extended properties of this molecule and future applications in other dermatological conditions. In 2011, oral ROF (Daliresp®) received Food and Drug Administration (FDA) approval for patients with severe chronic obstructive pulmonary disease and recurrent exacerbations. More recently, in 2022, topical ROF 0.3% cream (Zorvye™) obtained FDA approval for the management of plaque psoriasis in patients aged 12 years and older.

Keywords: Atopic dermatitis, Phosphodiesterase 4 inhibitor, Psoriasis, Roflumilast

INTRODUCTION

Psoriasis affects both sexes, but males tend to have more severe cases. Its prevalence in Europe and North America is around 2%, increasing from 0.12% at age 1 to 1.2% at age 18.^[1,2]

Complex interactions among various cell types contribute to the development of psoriasis, primarily involving dendritic cells and T-cells. Dysregulation of cutaneous cells, including keratinocytes, occurs through the tumor necrosis factor (TNF) alpha and interleukin-23/Th17 pathways, leading to psoriasis.^[3-5] Treatment options for psoriasis include phototherapy, topical or systemic medications, and biologic agents. Topical agents and phototherapy are commonly used as initial treatment, while systemic therapies such as biologics, apremilast, and roflumilast (ROF) are also available.^[3,4,6] However, biologics may be less popular in the Indian market due to their higher cost.^[5] [Figure 1]

ROF, a Phosphodiesterase 4 (PDE4) inhibitor, has been approved for the treatment of psoriasis. In 2011, oral ROF (Daliresp®) received Food and Drug Administration (FDA) approval for patients with severe chronic obstructive pulmonary disease and recurrent exacerbations. More recently, in 2022, topical ROF 0.3% cream (Zorvye™) obtained FDA approval for the management of plaque psoriasis in patients aged 12 years and older. The other formulations available include 0.1% cream and foam (0.3%).

PDE4 INHIBITORS

A superfamily of 11 enzymes known as phosphodiesterase governs intracellular levels of cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP) and, as a result, plays a key role in a variety of cellular processes. Important secondary messengers in signaling, cAMP, and cGMP are involved in cellular proliferation, cell-cycle modulation, and energy metabolism. Activated adenylyl cyclase (AC) and guanylyl cyclase, which catalyze the conversion of adenosine triphosphate and guanosine triphosphate to cAMP and cGMP, respectively, and cyclic nucleotide phosphodiesterases (PDEs), which catalyze their destruction, work in conjunction to regulate the levels of intracellular cAMP and cGMP. PDE4 is one such PDE that has elevated expression in psoriasis and is connected to pro-inflammatory cytokines.^[7] There are now many applications for both non-selective and selective PDE inhibitors. Pentoxifylline and theophylline are two examples of non-selective PDE inhibitors. These, however, do not appear to benefit in treating psoriasis. Since PDE4 inhibition results in a decrease in these pro-inflammatory cytokines and has been clinically demonstrated to be effective in psoriasis and other dermatological conditions, selective PDE-4 inhibitors have been researched across a wide variety of dermatologic

*Corresponding author: Abhishek De, Department of Dermatology, Calcutta National Medical College and Hospital, Kolkata, West Bengal, India.
dr_abhishek_de@yahoo.co.in

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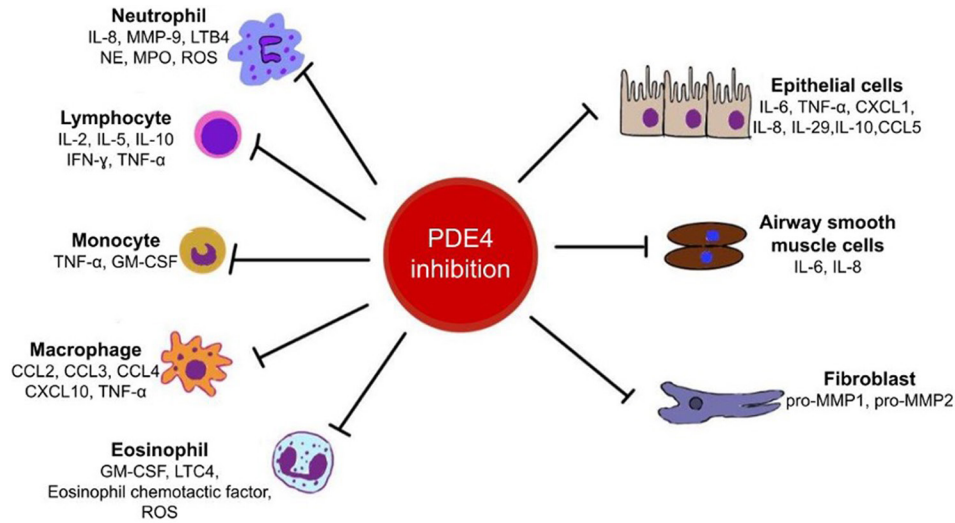


Figure 1: Phosphodiesterase 4 inhibition and its effects on the whole body. IL: Interleukin, IFN: Interferon, TNF: Tumor necrosis factor, GM-CSF: Granulocyte macrophage colony stimulating factor, ROS: Reactive oxygen species, PDE: Phosphodiesterase

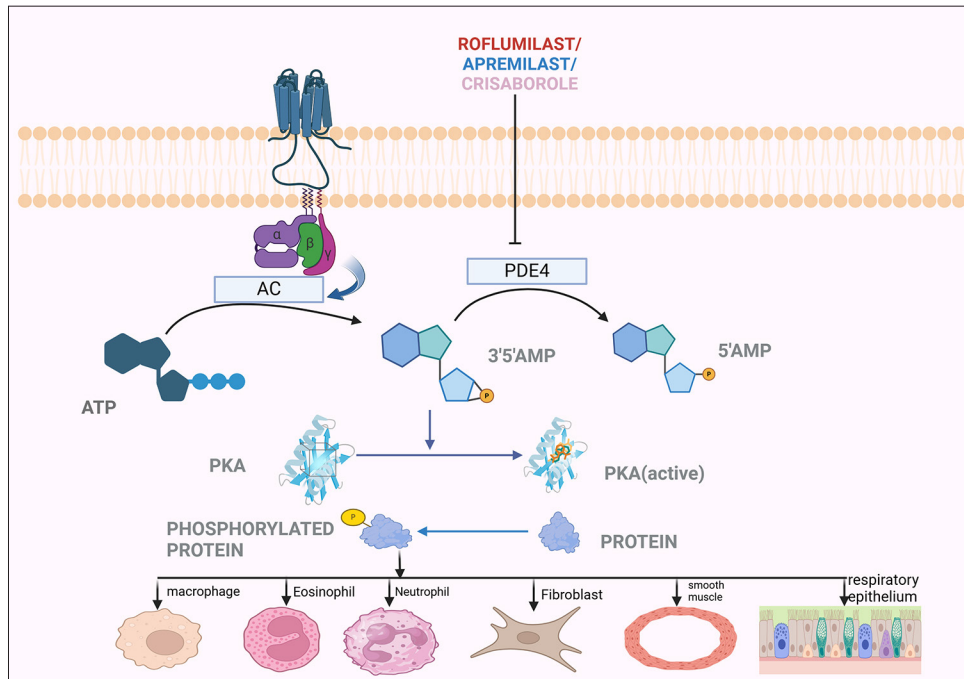


Figure 2: Mechanism of action of phosphodiesterase 4 inhibitors. Created in BioRender. Singh, S. (2025). AC: Adenyl cyclase, PDE: Phosphodiesterase, ATP: Adenosine triphosphate, PKA: Protein Kinase A, AMP: Adenosine monophosphate

inflammatory conditions, including psoriasis [Figure 2]. For this reason, several PDE4 inhibitors have been utilized, including apremilast, crisaborole, and ROF^[8] [Figure 2].

MOLECULAR STRUCTURE

ROF is a PDE4 inhibitor. It is a benzamide obtained by formal condensation of the carboxy group of 3-(cyclopropylmethoxy)-4-(difluoromethoxy) benzoic acid with the amino group of 3,5-dichloropyridin-4-amine [Figure 3]. Used in the management of bronchial asthma and

chronic obstructive pulmonary disease, it has thus displayed its efficacy as a phosphodiesterase IV inhibitor and an anti-asthmatic drug.^[9]

PHARMACOKINETICS

After a single oral dosage of 500 µg, ROF was shown to be promptly and almost entirely absorbed in one trial, with a mean absolute bioavailability of 80%. In healthy participants, the C_{max} of ROF was reached approximately after 1 hour. The active metabolite of ROF, N-oxide ROF, was shown to

be responsible for nearly 90% of the drug's overall PDE4 inhibitory action in another research which happened to be the first to evaluate the pharmacokinetics of ROF. The C_{max} of ROF N-oxide was attained in 4–10 hours and was steady after 6–8 hours. At about 21 and 30 hours, respectively, the t_{1/2} concentrations were reached for ROF and ROF N oxide. However, it was not possible to make an unambiguous conclusion from this investigation regarding whether exposure to ROF and ROF N-oxide in healthy Chinese participants was in a dose-proportional manner.

Plasma concentrations of ROF and its active metabolite ROF N-oxide were quantifiable after 15 days of applying 3–6.5 g of 0.3% topical ROF cream to affected areas of plaque psoriasis. The systemic exposure to ROF and its active metabolite was low after topical administration of ROF cream.

After topical application of 3–6.5 g daily for 15 days, the mean ± SD systemic exposure (AUC 0–24) in adults was 72.7 ± 53.1 and 628 ± 648 h•ng/mL for ROF and the N -oxide metabolite, respectively. The bioavailability of ROF cream 0.3% after topical administration was 1.5%. Unlike after oral dosing, the plasma concentration-time curve was flat, with a peak-to-trough ratio of 1.2. ROF N-oxide concentrations were eightfold higher than ROF concentrations.^[7]

MECHANISM OF ACTION

Depending on the comparator and PDE-4 isoform studied, ROF is between 25 and 300 times more effective than other PDE4 inhibitors such as apremilast or crisaborole based on IC₅₀ values, which are measurements of a drug's potency.^[7] Multiple inflammatory mediators, such as TNF, interleukin (IL)-12, IL-17, IL-22, IL-23, and interferon (IFN)-, are linked in the immunopathogenesis of psoriasis. The cAMP pathway, which primarily mediates signal transmission through protein kinase A (PKA), is inhibited by PDE4 inhibitors like ROF. Following this, PKA activates the protein known as the cAMP response element-binding protein, which oversees the production of IL-2, IL-6, IL-10, and TNF.^[10] AC and phosphodiesterase are responsible for mediating these intracellular cAMP concentrations. PDEs oversee cAMP's degradation. For this function, PDE-4 is the most

prevalent isoenzyme in immune cells such as lymphocytes, granulocytes, and monocytes/macrophages. Because ROF is a PDE-4 inhibitor, it may block the production and release of inflammatory cytokines including IFN- γ , TNF- α and IL-2, IL-12, and IL-23 as well as superoxide production and chemotaxis. Thus, ROF and other PDE-4 inhibitors work to minimize inflammation and treat psoriasis. Numerous cell types, including neutrophils, monocytes, macrophages, CD4+ and CD8+ T-cells, endothelium, epithelial, smooth muscle, and fibroblasts, are impacted by ROF^[11] [Figure 2].

CLINICAL EVIDENCE

Psoriasis

A double-blind trial by Arcutis Biotherapeutics assessed the efficacy of ROF for psoriasis treatment. Patients were assigned to ROF 0.3% QD, ROF 0.15% QD, or vehicle cream for 12 weeks. By week 6, 28.2% and 22.8% of ROF users achieved "Clear" or "Almost Clear" Investigator Global Assessment (IGA) scores compared to 8.3% in the vehicle group. At week 4, ROF 0.3% showed superiority over the vehicle ($P = 0.015$), with 14% achieving "Clear" or "Almost Clear." The ROF groups also demonstrated significant improvement in modified Psoriasis Area Severity Index (PASI) scores, with a 40.08% reduction at week 4 and -59.48% at week 12.^[12]

The long-term safety profile of ROF was evaluated in a 52-week, multi-center, and open-label research by Gold *et al.*, who extrapolated from this study by enrolling rollover patients from the prior clinical study along with 102 new patients. They were separated into two groups: Cohort 1 consisted of 230 patients who had previously finished 12 weeks of using ROF 0.3% QD, and cohort 2 consisted of 102 patients who had never used ROF 0.3% QD before. Both groups received the same treatment. Fifteen out of 102 patients in the naive cohort reported I-IGA (intertriginous-area IGA) success of clear/almost clear plus a 2-grade improvement at the week 52 mark.^[13] The adverse effects experienced are explained in Table 1.

Another study that coupled the effect of ROF and its impact on itch through patient reported outcomes: Worst Itch

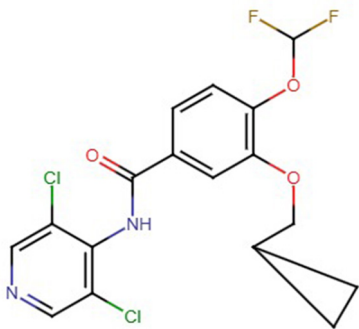


Figure 3: Molecular structure of roflumilast.

Table 1: Adverse effects of roflumilast.

TEAE	Cohort 1 (n=230)	Cohort 2 (n=102)	Total (n=332)
Patients with any TEAE	104	60	164
Patients with any treatment related TEAE	7	5	12
Patients with any SAE	10	2	12
Any treatment-related SAE	0	0	0
Patients discontinuing study due to AE	11	2	13

TEAE: Treatment emergent adverse effects, SAE: Serious adverse event, AE: Adverse events

Numeric Rating Scale (WI-NRS), Itch related Sleep Loss, and Dermatology Life Quality Index (DLQI) revealed that out of the 331 patients who were randomly assigned to receive ROF 0.3%, 0.15%, or vehicle cream, substantial improvement was witnessed in DLQI and WI-NRS scores. Beginning with the 2nd week of treatment, both ROF dosages led to improvements in WI-NRS that were comparable to one another and displayed substantial dominance over the vehicle ($P \leq 0.002$).^[14]

Both DERMIS-1 and DERMIS-2 were two randomized, double-blind, and vehicle-controlled investigations of once-daily ROF cream 0.3% in patients with psoriasis.^[15] For the DERMIS-1 study, 439 patients were chosen, and for the DERMIS-2 study, 442 individuals were selected. A Cochran-Mantel-Haenszel test that was stratified by location, baseline IGA, and baseline intertriginous participation was employed in the analysis of the main outcome. Both phase 3 trials were successful in meeting the main goal of the IGA success at Week 8. ROF provided a significant reduction in itchiness as indicated by the WI-NRS and provided a statistically superior reduction of psoriasis as indicated by percentages of patients achieving PASI-75 and PASI-90.^[15]

A recent pharmacokinetics study found that topical administration of ROF cream 0.3% resulted in a bioavailability of 1.5%. The concentrations of ROF in the skin were significantly higher (126- and 61.8-fold) compared to plasma levels, indicating greater skin exposure than expected with oral dosing. ROF, rather than its active metabolite, is likely responsible for PDE4 inhibition in the skin, as there was no significant conversion to ROF N-oxide. The slow release of ROF from the skin (half-life of 4 days) and a peak-to-trough ratio of 1.2 suggests reservoir formation and drug retention in the stratum corneum.^[7]

Chinese researchers conducted a study to develop an ROF cream for psoriasis treatment and investigate the role of propylene glycol monocaprylate (PGM) in a cream formulation. The cream formulation was optimized through stability and *in vitro* skin administration studies and further validated through an *in vivo* tissue distribution study. PGM showed an enhanced drug skin retention effect and increased molecular mobility of the cream's oil phase. It also facilitated the orderly flow of stratum corneum lipids and entered the viable epidermis/dermis, promoting drug-collagen miscibility. The study successfully developed an ROF cream and elucidated PGM's molecular-level impact on skin retention.^[16]

Atopic dermatitis (AD)

A phase 2 trial examined the safety and efficacy of ROF cream in patients with mild-to-moderate AD. A total of 136 AD patients aged ≥ 12 years were randomly assigned to receive a once-daily application of ROF cream 0.15%, ROF cream 0.05%, or vehicle cream for 4 weeks. The primary endpoint was the absolute change in the Eczema Area and Severity

Index (EASI) score at week 4. Significant improvements were observed in various efficacy measures, including EASI score, percentage change from baseline in EASI, and patients achieving certain response criteria. Treatment-related adverse events were minimal, with only mild rash and moderate application site pain reported in 2 (2.2%) patients. These findings suggested the need for further large-scale clinical trials to evaluate ROF cream as a potential non-steroidal topical treatment for AD which was demonstrated in the INTEGUMENT-1 and INTEGUMENT-2 phase 3 randomized clinical studies involving patients with AD treated with ROF cream, 0.15%, exhibited improvement across all efficacy endpoints, including a reduction in pruritus within 24 hour post-application, and favorable safety and tolerability profiles with once-daily application.^[10,17]

Seborrheic dermatitis

In April 2023, the United States FDA authorized ROF in a 0.3% foam formulation for the treatment of seborrheic dermatitis.^[18]

A double-blind, vehicle-controlled phase 2a randomized clinical trial conducted on 226 subjects of seborrheic dermatitis above 18 years of age found significant improvement based on the investigator's global assessment in the group that received ROF foam (0.3%) in comparison to vehicle foam at week 2 onwards.^[19]

Phase 3, was a double-blind study involving individuals with standard deviation who were randomly allocated in a 2:1 ratio to receive either once-daily ROF foam of 0.3% or a vehicle foam for a duration of 8 weeks. The principal effective outcome was the IGA success at week 8 with an evaluation of safety. About 79.5% of individuals receiving ROF and 58.0% of those receiving vehicles met the primary objective, demonstrating statistically significant differences in IGA. Success also favored ROF at weeks 2 and 4. ROF has shown good tolerability with a minimal incidence of treatment-emergent side effects.^[18]

Off label uses

Oral ROF has been used in a case of treatment-resistant hidradenitis suppurativa where Ring *et al.*, found a reduction in the number of lesions associated with favorable weight loss in the subject.^[20]

Oral ROF has been used in Behcet's disease as well as in nummular eczema with satisfactory and early response in a few case reports.^[21,22]

Fage and Johansen found satisfactory response with oral ROF in a case of erosive lichen planus which was refractory to other immunomodulators which were well sustained after 3 months of treatment.^[23]

ADVERSE EFFECTS

Topical ROF is generally well-tolerated. Reported side effects are infrequent, mild, and self-limiting. Potential side effects

of topical ROF cream include.

- Application site reactions (such as burning and stinging)
- Gastrointestinal side effects (such as nausea and diarrhea)
- Nasopharyngitis
- Headaches
- Insomnia
- High blood pressure

The safety of topical ROF in pregnancy and lactation is unknown. No formal drug-to-drug interaction studies have yet been conducted.

CONCLUSION

ROF has been proven to be a superior topical PDE-4 inhibitor and a major player in alleviating the symptoms and progression of the disease pathogenesis of psoriasis. It is the first and the only PDE4 inhibitor approved for the topical treatment of psoriasis. Since then, it has been studied for application in a few other dermatological diseases including AD. Following FDA approval, this potent PDE 4 inhibitor with a wide safety profile and powerful anti-inflammatory actions has demonstrated commendable actions in mitigating the disease severity and other associated distressing symptoms of psoriasis. However, further large-scale clinical studies are required to study the varied local and systemic effects of this topical medication on the microbiota of the human skin, especially in the wake of psoriasis.

Ethical approval: The Institutional Review Board approval is not required.

Declaration of patient consent: Patient consent was not required as there are no patients in this study.

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