

Advances in the Study of PDE4 Inhibitors in Dermatological Disorders

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Abstract: Since the 1980s, phosphodiesterase 4 (PDE-4) has been one of the most prominent targets for the treatment of inflammatory diseases. More recently, a number of synthetic ligands targeting PDE-4 have received more attention in the academic and pharmaceutical communities and are expected to have applications in these diseases. Due to various potential side effects of PDE-4 inhibitors, there are several obstacles to the clinical translation of specific PDE-4 inhibitors from the preclinical to the clinical phase. Therefore, similar to roflumilast in chronic obstructive pulmonary disease, many PDE-4 inhibitors can take up to 30 years or even longer from development to clinical application. This article is a review of the development of PDE-4 inhibitors, such as crisaborole and apremilast, for use in skin disorders.

Keywords: Phosphodiesterase 4 inhibitor; dermatological disorders; cAMP-PKA signaling pathway; apremilast; crisaborole.

1. Introduction

The discovery of PDEs by Sutherland and Rall in 1958 has led to extensive research into their active modifications in the medicinal chemistry community[1]. PDEs hydrolyse the phosphodiester bond of c-AMP and c-GMP to form two biologically inactive substances, AMP and GMP[2-4]. In fact, inhibition of PDEs can elevate cyclic nucleotide levels and thus act as a second messenger, exerting physiopathological regulation in secretion, contraction, metabolism and proliferation[5].

The PDEs superfamily is divided into 11 species, ranging from PDE1-PDE11[6]. PDE-4 is currently the most diverse subfamily of PDEs and is widely expressed in a variety of cell types[6,7]. These enzymes are intimately involved in a variety of physiological activities such as brain function, phagocyte/monocyte activation, cardiomyocyte contraction, vascular smooth muscle proliferation and neutrophil infiltration, to name a few. In addition, PDE-4 may be closely involved in the development of autoimmune diseases, tumours and cardiovascular diseases[8].

There are four isoforms of PDE-4, namely PDE-4A, PDE-4B, PDE-4C and PDE-4D[9]. All PDE-4s have UCR conserved domains in the N-terminal region that are intimately involved in the transcriptional and translational regulation of PDE-4. PDE-4 has a catalytic domain in the C-terminus, which usually consists of 300-350 amino acids[6].

2. Inflammation and PDE-4

Nuclear factor κ -light-chain-enhancer of activated B cells (NF- κ B) is known to mediate specific responses, and pharmacological blockade of NF- κ B activity can be used to therapeutically control inflammatory diseases[6]. c-AMP can inhibit signal transduction downstream of the NF- κ B pathway, and c-AMP levels are positively correlated with immunosuppressive and anti-inflammatory effects[6,10,11]. Since PDE-4 can hydrolyse c-AMP, it could be a key target in the treatment of inflammatory diseases by modulating the NF- κ B pathway[9]. Macrophages exposed to ethanol for a long

time can inhibit TNF- α mRNA expression by inhibiting PDE-4, and inhibition of PDE-4 not only inhibits the NF- κ B-TNF- α pathway, but also activates PKA and induces the expression of IL-10[8].

Thus, PDE-4 inhibitors may play an important role in the negative and positive regulation of gene expression[8]. In T lymphocytes, both PDE-4 and c-AMP have been reported to be involved in the regulation of their proliferation, expression of TNF- α and other interleukins (IL-2, IL-4 and IL-5)[12]. By cross-linking with T cell membranes (e.g. CD4-positive and TH2 subsets), c-AMP can also inhibit T cell proliferation by acting as a regulator of T cells[7]. In terms of inflammatory regulation, PDE-4 may be involved in the regulation of eosinophil and neutrophil chemotaxis and degranulation[7,8]. These effects are mediated by PDE-4-mediated increases in IL-8, leukotriene B4 and superoxide anion levels in neutrophils. In addition, PDE-4 is involved in the regulation of adhesion molecules such as the β 2 integrin Mac-1 in neutrophils, thereby enhancing their adhesion to vascular endothelial cells[8,13].

3. PDE-4 Inhibitors and Atopic Dermatitis (AD)

Atopic dermatitis (AD) is a chronic inflammatory skin disease with a prevalence of approximately 2-3% and an increasing trend over the years[6]. The main manifestations of AD are recurrent pruritus, skin hypersensitivity and erythema, and there is considerable evidence that immune and inflammatory cells are closely involved in the pathogenesis of AD[14]. Current treatment for AD consists of moisturising the skin, topical steroids (e.g. hydrocortisone, betamethasone and clobetasol) and topical calcineurin inhibitors (tacrolimus, pimecrolimus)[14]. In December 2016, crisaborole, manufactured by Pfizer, was approved for topical use in the treatment of AD[8,14,15]. Although crisaborole has been shown to have anti-inflammatory effects in vivo, in vitro animal and cellular studies[16]. However, in clinical trials, topical application of 2% crisaborole twice daily was found to be the most effective in controlling the condition of AD and improving itching compared with the control group[16].

Other drugs (E6005, GW842470XOPA-15406, apremilast) are currently being investigated for the treatment of AD[8].

4. PDE-4 Inhibitors and Psoriasis

Psoriasis is a relatively common chronic inflammatory skin disease that mainly affects the skin, nails and joints[8]. Mild psoriasis is treated with principles similar to those used for AD, such as topical steroids, TCIs and vitamin D analogues; psoriasis may be associated with arthritis, synovitis and may affect up to 30% of psoriasis patients[2,4]. In the skin, PDE-4 is predominantly expressed in Langerhans cells, neutrophils, keratinocytes and T cells, which are intimately involved in plaque formation, and mRNA levels of PDE-4 are significantly higher than in healthy controls[5,6,17]. Apremilast, an oral form of the PDE-4 inhibitor, was approved in 2014 for the treatment of psoriatic arthritis and plaque psoriasis[8,18]. Oral apremilast was shown in in vivo studies to be effective in improving psoriasis lesion thickness and levels of the local inflammatory molecules ICAM-1, HLA-DR and TNF- α [19]. The Phase III study found that 33.1% of patients with psoriasis achieved a 75% reduction in their baseline Psoriasis Area and Severity Index (PASI-75) with oral apremilast, compared to 5.3% in the control group[20].

More recently, a double-blind RCT (N=21) found that topical application of 2% crisaborole was effective in controlling the disease in patients with intertriginous, anogenital and facial psoriasis, and no adverse events were reported[18]. In addition, successful case reports of the use of 2% crisaborole in the treatment of facial, groin and inframammary psoriasis have been reported[6,18]. Therefore, topical crisaborole may also be a non-steroidal choice for the treatment of psoriasis.

5. PDE-4 Inhibitors and Vitiligo

Vitiligo is a chronic autoimmune skin disease with a complex pathogenesis and a prevalence of about 0.5-2%[21]. PDE-4 inhibitors can promote MITF expression by inhibiting c-AMP hydrolysis. MITF can further induce the transcription and synthesis of TYR and TYRP2, thereby enhancing melanocyte proliferation and melanogenesis[7]. PDE-4 inhibitors can effectively block IFN- γ -induced CD8+ T lymphocyte recruitment to the skin and control disease progression[22]. The possible mechanism is that the STAT-JAK pathway of CD8+ T lymphocytes interacts with CXCL chemokine ligand 9 (CXCL9) and CXCL10 of local keratinocytes in the skin and positively recruits CD8+ T lymphocytes to target melanocytes[23]. PDE-4 inhibitors also induced increased levels of cAMP in Th17 lymphocytes, which in turn inhibited its activity, thus avoiding inhibition of the MITF pathway[24]. Majid et al. found that when adult patients (N=13) with non-segmental vitiligo (4%-30% of affected area) were treated with apremilast 30 mg/dose orally twice a day for 3 months, 8 cases (61.5%) showed hyperpigmentation of the face, neck, trunk and hands, with a mean reduction in VASI of 7.11%, and there was no increase in VASI in any of the patients enrolled[22,24]. Tam et al. reported a case of a 71-year-old male patient with vitiligo with lesions on the limbs and trunk involving 10% of the body surface area (BSA), history of atopic dermatitis and ineffective conventional treatment, who was treated with crisaborole ointment, and after 10 months of use, vitiligo hyperpigmentation was evident on the trunk, and after 22 months, the dorsal side of the hands was significantly

hyperpigmented and no longer developing[7,23]. Tausend et al. reported a case of a 40-year-old man with hypopigmented patches on his ears and penis for 20 years, who was treated with crisaborole ointment twice a day externally on the ears and no medication on the penis, and after 1 month there was significant pigmentation on the ears and no significant change on the unmedicated penis[22].

6. PDE-4 Inhibitors and Lupus

Systemic lupus erythematosus (SLE) is a complex autoimmune disease that can affect multiple systemic organs, including the skin, joints, kidneys and nervous system[2]. Currently, the conventional treatment options for SLE include antimalarials, corticosteroids and DMARDs such as methotrexate and rituximab, and PDE-4 inhibitors are also expected to be used in the treatment of SLE due to their anti-inflammatory effects[4]. Apremilast is currently in clinical trials and is expected to become a new treatment option for SLE when the results are reported. The compound NCS613 also showed promising results in the treatment of SLE in mice[9,25]. The possible mechanism is that NCS613 may further regulate the inhibition of TNF- α , IL-6 and IL-8 by inhibiting the phosphorylation of p38 MAPK and the nuclear translocation of NF- κ B[12].

7. PDE-4 Inhibitors and Seborrheic Dermatitis

Seborrheic dermatitis is a common chronic skin condition that can affect both infants and adults[26]. "Greasy" yellow scales and erythema are often found in areas of HIGH sebum production (scalp, eyebrows, nasolabial folds, chest and intertriginous areas)[26]. The exact pathogenesis of seborrheic dermatitis is unclear and may be related to an aberrant inflammatory response, a by-product of Malassezia species, a resident flora of the skin[8]. Topical azole antifungals may have a therapeutic effect by inhibiting Malassezia species or by suppressing the inflammatory response[26]. Topical corticosteroids and calcineurin inhibitors may be used as a routine anti-inflammatory treatment option[26]. Liu et al published a case report that crisaborole 2% ointment was effective in controlling seborrheic dermatitis at the nasolabial fold (50-year-old man)[9]. Further RCTs are needed to validate the clinical efficacy of PDE-4 in seborrheic dermatitis.

8. Conclusion

Inhibition of PDE-4 effectively reduces intracellular cAMP levels, resulting in a variety of anti-inflammatory effects and promising treatments for chronic inflammatory skin diseases. Currently, apremilast has been approved by the FDA for the treatment of psoriasis and psoriatic arthritis, and topical crisaborole ointment has been approved for the treatment of AD. PDE-4 inhibitors are not only effective, but also relatively inexpensive to develop, which is an advantage in the choice of long-term maintenance therapy. Given that PDE-4 inhibitors have only been in clinical use for a relatively short time, large, multi-centre clinical trials are still needed to demonstrate and improve their long-term efficacy and safety, and we look forward to more effective PDE-4 inhibitor-targeted drugs providing viable options for the treatment of chronic inflammatory dermatoses in the future.

CONFLICTS OF INTEREST

The authors declare that they have no conflict of interest.

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