International Platform of Registered Systematic Review and Meta-analysis Protocols

INPLASY

Effectiveness and safety of topical phosphodiesterase 4 inhibitors in children with Mild to Moderate Atopic Dermatitis: systematic review and meta-analysis

INPLASY202520121

doi: 10.37766/inplasy2025.2.0121

Received: 27 February 2025

Published: 27 February 2025

Wang, L; Zeng, LQ; Wu, YY; Zhong, M; Zhang, LZ; Li, C.

Corresponding author:
Long Wang

wangloogn@126.com

Author Affiliation:
Department of Dermatology and Venereology, Zhongshan City People's Hospital.

ADMINISTRATIVE INFORMATION

Support - No financial support.

Review Stage at time of this submission - Completed but not published.

Conflicts of interest - None declared.

INPLASY registration number: INPLASY202520121

Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 27 February 2025 and was last updated on 27 February 2025.

INTRODUCTION

Review question / Objective This meta-analysis aimed to quantitatively synthesizes the current evidence on the efficacy and safety of topical phosphodiesterase 4 inhibitors in the treatment of children with mild to moderate atopic dermatitis, aiming to organize the current situation and provide more details for future clinical decision-making.

Condition being studied Atopic dermatitis (AD) is a chronic inflammatory skin disease that an increased risk of skin and systemic infections can accompany. Studies show that about 85% of AD occurs in children, with 30% of patients continuing to be affected into adulthood. The incidence of AD is on the rise worldwide, especially in urbanized countries in northern latitudes. Moreover, limited treatment options impose significant economic and social burdens on AD individuals, families, and public health systems. Studies in the United States show that AD causes $4.2 billion in healthcare costs per year, with personal healthcare costs for people with AD ranging from 28.3% to 67.9% higher than those without AD.

Currently, there is no ideal standard care plan for AD treatment and clinical guidelines state that treatment tailored to individual needs is the most suitable option. As the first-line treatment option, topical intervention is currently the main regimen for AD treatment. However, the potential local and systemic side effects of existing topical agents limit their clinical use. Topical calcineurin inhibitors, the second-line anti-inflammatory drugs for AD, work on the principle of inhibiting calcineurin-dependent T-cell activation, reducing epidermal dendritic cell activation, and inhibiting mast cell activation to achieve long-term maintenance and localized application effects. However, black box warnings that topical use of calcineurin inhibitors may lead to malignancy have reduced patient adherence to treatment. Therefore, there is an urgent need for new local therapies to improve the current high-risk status of AD treatment.

Phosphodiesterase 4 (PDE-4) inhibitors, a new class of non-steroidal anti-inflammatory drugs, are promising in current AD and psoriasis treatment. By degrading cyclic adenosine phosphate, PDE-4 regulates AD inflammatory cytokine production. PDE-4 inhibitors impact several aspects of the allergy/inflammation process. Skin dendritic cell migration is inhibited, which is accompanied by the inhibition of MMP-9 activity in the epidermis and dermis, and the cytokine secretion (TNFα, IL-1β, and IL-12) from human and mouse dendritic cells is impaired. Thus, reduced chemokine secretion leads to a diminished inflammatory response in allergic skin diseases due to decreased influx of inflammatory cells (macrophages, T cells, neutrophils). The oral PDE-4 inhibitor Apremilast has been approved for moderate-to-severe plaque psoriasis and psoriatic arthritis, but dose-titration is required to avoid gastrointestinal side effects (nausea and diarrhea) caused by PDE-4 inhibition in non-target tissues. Conversely, topical PDE-4 inhibitor formulations may provide targeted inhibition of inflammation in skin diseases while minimizing unwanted side effects. There are currently three common PDE-4 inhibitors: Crisaborole is approved by the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for the treatment of AD patients over 2 years old. Difamilast is a new selective PDE-4 inhibitor that has shown significant efficacy and safety in mild to moderate AD in Phase II trials in children and adults in the United States and Japan. Topical E6005 has also been shown to improve topical rashes and pruritus in children and adults with AD without serious side effects, although the number of studies was limited.

Although previous studies have evaluated the use of different types and concentrations of PDE4 inhibitors to treat AD patients with different demographics, there is still debate about their effectiveness. A RCT study published in 2016 found no significant difference in reduced severity scores between the PDE4 inhibitor E6005 and loaded therapy, but another large sample static global evaluation clinical trial showed a higher success rate in patients treated with crisaborole compared to loaded therapy.

METHODS

Search strategy Articals published in PubMed, Embase, Web of Science and the Cochrane Library databases were searched, using the MeSH terms ‘Phosphodiesterase 4 Inhibitors’ and ‘Dermatitis, Atopic’.

Participant or population Studies targeted AD patients aged below 18 years old.

Intervention The intervention group received any topical phosphodiesterase 4 inhibitor treatment.

Comparator The control group received a placebo, conventional treatment, or other anti-atopic dermatitis interventions.

Study designs to be included Studies designed as randomized controlled trials were included.

Eligibility criteria

The inclusion criteria were:

1)Studies targeted on atopic dermatitis patients aged below 18 years old;

2) The intervention group received any kind of topical phosphodiesterase 4 inhibitor treatment;

3) The control group received a placebo, conventional treatment, or any other anti-atopic dermatitis interventions;

4)Study endpoints included the treatment response rate and adverse effect.

5)Studies designed as randomized controlled trials were included;

6)Full text available.

The exclusion criteria were

1)Combined intervention can not be included (e.g., PDE4 + conventional treatment vs conventional treatment);

2)Reviews, animal trials, single-arm studies, chapters in handbooks, case reports, dissertations, editorials, and conference papers were excluded;

3)Studies without international peer-review;

4)Studies with duplicate data.

Information sources Information sources included PubMed, Embase, Web of Science and the Cochrane Library databases.

Main outcome(s) Main outcomes included the treatment response rate and adverse effect.

Quality assessment / Risk of bias analysis The Cochrane risk of bias tool was used to assess the risk of bias and quality of evidence. The quality assessment was carried out by two independent researchers. The risk of bias was assessed across five different areas, with the results expressed as "low risk of bias," "some risk," or "high risk of bias." Evaluations in each area influence the overall bias risk judgment.

Strategy of data synthesis All analyses were performed using the Stata 15.1 SE version. Odd ratios (ORs) and their corresponding 95%

confidence intervals (CIs) were used to compare the outcomes. To ensure consistency, changes (endpoints – baseline values) across all study endpoints were calculated for pooled analysis. Cochran' s Q-test, and the I2 index (I2>50% and Q-test P>0.10 indicated high heterogeneity) was used to calculate statistical heterogeneity. Random-effects model was used for high inter-study heterogeneity; otherwise, the fixed-effects model was selected. P-values <0.05 were considered as threshold.

Subgroup analysis Subgroup analysis was conducted based on different topical phosphodiesterase 4 inhibitors (E6005, crisaborole, or OPA-15406), and treatment duration (2 weeks, 4 weeks, or 30 days).

Sensitivity analysis The leave-one-out method was used to evaluate potential confounding effects and the robustness of the pooled results. If the pooled results change significantly after excluding a study, that study is identified as a confounding factor, and the results after exclusion are considered the final findings.

Country(ies) involved China.

Keywords Atopic dermatitis; Phosphodiesterase 4 inhibitors; E6005; Crisaborole; OPA-15406; Adverse effect; Meta-analysis.

Contributions of each author

Author 1 - Long Wang.
Email: wangloogn@126.com
Author 2 - Le-qu Zeng.
Author 3 - Yuyu Wu.
Author 4 - Min Zhong.
Author 5 - Lizhen Zhang.
Author 6 - Chen Li.
Email: 414110094@qq.com