



Application of Topical Phosphodiesterase 4 Inhibitors in Mild to Moderate Atopic Dermatitis

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Article History :

Received date : 2024/07/26
Revised date : 2024/08/12
Accepted date : 2024/09/23
Published date : 2024/10/08



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E-ISSN :

ISSN 3048-1368



P-ISSN :

ISSN 3048-1376



ABSTRACT

Background: The application of topical phosphodiesterase 4 (PDE4) inhibitors in the treatment of mild to moderate atopic dermatitis (AD) has emerged as a significant area of interest in dermatological research. The literature presents a comprehensive overview of the efficacy, safety, and therapeutic potential of these agents, particularly focusing on crisaborole and difamilast, which have shown promise in clinical settings.

Literature Review: The foundational work by (Li et al., 2018) highlighted the efficacy and safety of crisaborole, establishing it as a viable non-steroidal treatment option for AD. This pivotal study demonstrated the ability of crisaborole to reduce inflammation by inhibiting pro-inflammatory cytokines, a mechanism that is crucial given the chronic nature of AD and the need for effective long-term management strategies. The safety profile of crisaborole, particularly its tolerability in pediatric populations, supports its role as a preferred alternative to traditional corticosteroids, which often come with significant side effects. Further expanding the therapeutic landscape, (Sharma et al., 2018) introduced East Indian sandalwood oil as a PDE4 inhibitor, suggesting its potential as a natural treatment option for inflammatory skin diseases, including AD. This exploration of alternative therapies enriches the available treatment modalities, particularly for patients seeking non-pharmacological interventions. **Conclusion:** In conclusion, the literature collectively supports the therapeutic potential of topical PDE4 inhibitors in managing mild to moderate atopic dermatitis. The studies reviewed emphasize their efficacy in reducing inflammation and pruritus while maintaining a favorable safety profile, thus presenting a promising alternative to conventional treatments. However, ongoing research is essential to fully understand the long-term effects and optimize treatment strategies for diverse patient populations.

Keywords: Topical Phosphodiesterase 4 Inhibitors, Mild to Moderate Atopic Dermatitis

INTRODUCTION

The application of topical phosphodiesterase 4 (PDE4) inhibitors in the management of mild to moderate atopic dermatitis (AD) has garnered increasing attention in recent years, as evidenced by a growing body of literature. The initial exploration of PDE4 inhibitors in inflammatory diseases was highlighted in the work of (Li et al., 2018), which presented a foundational understanding of the efficacy and safety of crisaborole, a 2% topical ointment, along with E6005, in treating AD. This pivotal phase 2a study established the groundwork for future investigations into the therapeutic potential of PDE4 inhibitors, emphasizing their role in mitigating inflammation through the inhibition of pro-inflammatory cytokines.

Building upon this foundation, (Sharma et al., 2018) expanded the discourse by identifying East Indian sandalwood oil as a phosphodiesterase inhibitor, suggesting its potential as a novel therapeutic option for inflammatory

skin diseases, including AD. This review not only underscored the relevance of PDE4 in the inflammatory cascade but also opened avenues for alternative natural treatments, enriching the therapeutic landscape for managing AD.

The insights provided by (Klasa & Cichocka-Jarosz, 2020) further elucidated the pathophysiological role of PDE4 in AD, particularly its heightened expression in lymphocytes associated with the disease. Their findings highlighted the necessity for innovative local treatments that minimize adverse effects, particularly in light of the chronic and relapsing nature of AD. This discussion is vital as it sets the stage for understanding the clinical implications of PDE4 inhibition in the context of long-term treatment strategies.

In 2021, (Bieber, 2021) emphasized the expanding therapeutic pipeline for AD, noting the promising results of various topical PDE4 inhibitors, including crisaborole and emerging agents like lotamilast and difamilast. The

exploration of these compounds, particularly in avoiding gastrointestinal side effects associated with oral formulations, underscores the potential of topical therapies in enhancing patient compliance and safety.

(Saeki et al., 2022) contributed to this discourse with their phase III study on difamilast, highlighting its efficacy and safety profile in both adult and pediatric populations. This study not only reinforced the therapeutic promise of difamilast but also illustrated the critical need for effective long-term treatments that can be safely administered to diverse patient demographics.

Finally, the systematic review and meta-analysis conducted by (Martín-Santiago et al., 2022) provided a comprehensive evaluation of the safety and tolerability of topical PDE4 inhibitors in treating AD. This synthesis of existing studies is crucial for assessing the overall risk-benefit profile of these therapies, informing clinical decision-making, and guiding future research directions.

Through this literature review, the evolving landscape of topical PDE4 inhibitors in the treatment of mild to moderate atopic dermatitis is critically examined, revealing both the therapeutic potential and the challenges that remain in optimizing treatment outcomes for this complex disease.

LITERATURE REVIEW

The article "Phosphodiesterase-4 Inhibitors for the Treatment of Inflammatory Diseases" by (Li et al., 2018) provides a comprehensive overview of the efficacy and safety of various phosphodiesterase 4 (PDE4) inhibitors in the treatment of atopic dermatitis (AD). The authors focus on several key studies, including a phase 2a trial of crisaborole, a 2% topical ointment, which demonstrated promising results in adults with mild to moderate AD. This study is significant as it highlights the potential of crisaborole as a non-steroidal treatment option, addressing a critical need for alternative therapies in managing this chronic inflammatory skin condition.

The in vivo characterization of GSK256066, a high-affinity inhaled PDE4 inhibitor, is also discussed, although its direct application to atopic dermatitis may be less relevant. The article effectively contrasts this with the topical application of E6005, another novel PDE4 inhibitor. The authors report on the efficacy and safety of E6005 through an investigator-blinded, vehicle-controlled study, which adds to the body of evidence supporting the use of topical PDE4 inhibitors in clinical practice.

The safety and tolerability of E6005 ointment were assessed in both healthy volunteers and patients with AD, underscoring the importance of pharmacokinetic studies in informing the clinical use of these agents. The findings suggest that PDE4 inhibitors like crisaborole and E6005 offer a favorable safety profile, which is crucial for long-term management of atopic dermatitis, particularly in pediatric populations where steroid-sparing treatments are highly sought after.

The article provides a critical evaluation of the role of topical PDE4

inhibitors in the therapeutic landscape of atopic dermatitis, emphasizing their mechanism of action in reducing inflammation and pruritus. The authors highlight that while traditional treatments often involve corticosteroids, PDE4 inhibitors present a novel approach that may mitigate the adverse effects associated with prolonged steroid use.

The article "Atopic Dermatitis – Current State of Research on Biological Treatment" by (Klasa & Cichocka-Jarosz, 2020) provides a comprehensive overview of the role of phosphodiesterase-4 (PDE-4) in the pathophysiology of atopic dermatitis (AD) and emphasizes the potential of PDE-4 inhibitors as a novel therapeutic approach. The authors highlight that patients with AD exhibit elevated levels of PDE-4 in lymphocytes, which is closely linked to the synthesis of pro-inflammatory cytokines. This relationship underscores the enzyme's critical role in inflammatory pathways associated with AD.

The discussion on PDE-4 inhibition is particularly relevant, as it presents a promising alternative to

traditional local treatments, such as topical corticosteroids (TCS) and topical calcineurin inhibitors (TCI). The authors point out the limitations of TCS, notably the risks associated with prolonged use, which can lead to significant adverse effects. Given the chronic and relapsing nature of AD, the need for continuous treatment strategies that minimize side effects is paramount. This is where PDE-4 inhibitors may provide a significant advantage, as their mechanism of action targets the underlying inflammatory processes without the same level of risk associated with long-term corticosteroid use.

The article effectively argues that PDE-4 inhibitors could represent a new class of local treatments for AD, offering a balance between efficacy and safety. By blocking the action of inflammatory cytokines, these inhibitors may help manage symptoms more effectively while reducing the likelihood of adverse effects that are often seen with existing therapies. However, while the potential benefits are clear, the authors also imply that further research is necessary to fully

understand the long-term safety and efficacy of these treatments in diverse patient populations.

The article "Atopic dermatitis: an expanding therapeutic pipeline for a complex disease" by (Bieber, 2021) provides a comprehensive overview of the current landscape regarding the application of phosphodiesterase 4 (PDE4) inhibitors in the treatment of atopic dermatitis (AD), particularly focusing on topical formulations for patients with mild to moderate disease.

Bieber discusses the oral PDE4 inhibitor apremilast, which has shown efficacy in moderate to severe psoriasis but has not advanced significantly in the context of AD. The article highlights the mixed outcomes of clinical trials, noting that while pilot studies indicated potential benefits, a phase II randomized controlled trial (RCT) revealed substantial improvement only at high doses, leading to the trial's discontinuation due to adverse events. This underscores the complexities involved in translating systemic therapies to dermatological applications, particularly in

populations with varying disease severity.

The potential for topical PDE4 inhibitors emerges as a promising alternative for managing mild to moderate AD. The article identifies crisaborole as the only approved topical PDE4 inhibitor, while also noting that several other compounds are currently in development. Notably, lotamilast in cream formulation has yielded encouraging preliminary results, and difamilast has demonstrated effectiveness in both adolescents and adults, with a phase IIa study indicating a significant clinical efficacy endpoint achievement compared to placebo. This suggests that, while systemic therapies might face challenges, topical formulations could provide a viable option for patient management.

Bieber's evaluation of other PDE4 inhibitors, such as roflumilast and LEO 29102, reveals a mixed bag of results. The proof-of-concept study with roflumilast did not meet its primary endpoint, although it did not raise safety concerns, which is a critical aspect in the treatment of

chronic conditions like AD. Similarly, LEO 29102 showed beneficial effects on pruritus but failed to demonstrate superiority over existing treatments like pimecrolimus.

The article concludes with a cautious optimism regarding the safety profiles of topical PDE4 inhibitors, emphasizing that while they appear to be generally well-tolerated, their efficacy remains limited when compared to traditional therapies such as topical steroids and calcineurin inhibitors. This critical evaluation highlights the need for ongoing research to establish the role of these agents in the therapeutic arsenal for atopic dermatitis, particularly as new compounds like Hemay-808 and PF-07038124 are still under investigation.

The article "Difamilast Ointment in Japanese Adult and Pediatric Patients with Atopic Dermatitis: A Phase III, Long-Term, Open-Label Study" by (Saeki et al., 2022) provides a comprehensive evaluation of difamilast, a topical phosphodiesterase 4 (PDE4) inhibitor, in the treatment of atopic

dermatitis (AD). The authors highlight the chronic nature of AD, which significantly impacts the quality of life for patients, particularly in developed countries where prevalence rates are notably high.

In their study, the authors effectively contextualize the limitations of existing treatments, such as topical corticosteroids (TCSs) and topical calcineurin inhibitors (TCIs), which, while commonly used, are often associated with adverse events that can hinder long-term use. This sets the stage for the introduction of difamilast as a potential alternative therapy, especially given its mechanism of action targeting the PDE4 enzyme, which plays a crucial role in the inflammatory processes associated with AD.

The article details a phase III, long-term, open-label study designed to assess the safety and efficacy of difamilast in both adult and pediatric populations. The findings indicate that difamilast not only demonstrates superior efficacy compared to vehicle treatments but also has a favorable safety profile, which is critical for encouraging adherence to long-term

treatment regimens. The authors provide robust data supporting the use of difamilast, noting its well-tolerated nature in the study cohort, which is a significant advancement in the management of AD.

Furthermore, the article discusses the implications of these findings within the broader context of AD treatment paradigms. The approval of difamilast in Japan marks a pivotal moment in the search for effective long-term therapies that minimize the risks associated with traditional treatments. The authors' emphasis on the need for new therapeutic options is well-founded, considering the chronic relapsing nature of AD and the psychosocial burdens it imposes on patients.

The article "Safety Profile and Tolerability of Topical Phosphodiesterase 4 Inhibitors for the Treatment of Atopic Dermatitis: A Systematic Review and Meta-Analysis" by (Martín-Santiago et al., 2022) provides a comprehensive evaluation of the safety and tolerability of topical phosphodiesterase 4 (PDE4) inhibitors in the treatment of atopic

dermatitis, specifically in mild to moderate cases. This systematic review and meta-analysis synthesize data from multiple studies, allowing for a robust assessment of the therapeutic profile of PDE4 inhibitors compared to vehicle treatments.

The authors meticulously analyzed existing literature, highlighting the importance of understanding the safety profile of PDE4 inhibitors, which have emerged as a promising option for managing atopic dermatitis. The systematic approach taken in the review ensures that the findings are grounded in a wide array of clinical data, offering a solid foundation for evaluating the efficacy and safety of these agents.

One of the key insights from the article is the favorable tolerability of topical PDE4 inhibitors, with adverse effects being relatively mild and manageable. The authors report that the most common side effects included local skin reactions, which were generally transient and did not lead to discontinuation of therapy. This finding is significant, as it suggests that patients with mild to moderate atopic dermatitis may

benefit from the use of PDE4 inhibitors without experiencing severe or debilitating side effects.

Moreover, the meta-analysis conducted by the authors provides quantitative data that reinforces the safety profile of these agents. By comparing the incidence of adverse events between PDE4 inhibitors and vehicle treatments, the authors demonstrate that the former do not significantly increase the risk of adverse effects, thus supporting their use in clinical practice. This aspect of the article is particularly valuable for clinicians who are considering treatment options for patients with atopic dermatitis.

However, while the article emphasizes the tolerability of topical PDE4 inhibitors, it is essential to consider the limitations of the studies included in the review. The authors acknowledge potential biases in the original studies and the variability in patient populations, which may affect the generalizability of the findings. Furthermore, the long-term safety of these inhibitors remains to be fully established, necessitating ongoing surveillance and further research to

monitor their effects over extended periods.

CONCLUSION

The application of topical phosphodiesterase 4 (PDE4) inhibitors in the treatment of mild to moderate atopic dermatitis (AD) has emerged as a significant area of interest in dermatological research. The literature presents a comprehensive overview of the efficacy, safety, and therapeutic potential of these agents, particularly focusing on crisaborole and difamilast, which have shown promise in clinical settings.

The foundational work by (Li et al., 2018) highlighted the efficacy and safety of crisaborole, establishing it as a viable non-steroidal treatment option for AD. This pivotal study demonstrated the ability of crisaborole to reduce inflammation by inhibiting pro-inflammatory cytokines, a mechanism that is crucial given the chronic nature of AD and the need for effective long-term management strategies. The safety profile of crisaborole, particularly its tolerability in pediatric populations,

supports its role as a preferred alternative to traditional corticosteroids, which often come with significant side effects.

Further expanding the therapeutic landscape, (Sharma et al., 2018) introduced East Indian sandalwood oil as a PDE4 inhibitor, suggesting its potential as a natural treatment option for inflammatory skin diseases, including AD. This exploration of alternative therapies enriches the available treatment modalities, particularly for patients seeking non-pharmacological interventions.

The role of PDE4 in the pathophysiology of AD was further elucidated by (Klasa & Cichocka-Jarosz, 2020), who noted the elevated expression of PDE4 in lymphocytes associated with AD. This finding underscores the enzyme's critical involvement in inflammatory pathways and the potential for PDE4 inhibitors to provide a targeted approach to treatment that minimizes adverse effects.

The systematic review and meta-analysis by (Martín-Santiago et al., 2022) synthesized data from

multiple studies, reinforcing the favorable safety and tolerability profile of topical PDE4 inhibitors. The analysis indicated that while local skin reactions were common, they were generally mild and transient, allowing for sustained treatment without significant discontinuation rates. This aspect is particularly relevant for clinicians considering long-term management options for patients with mild to moderate AD. In terms of emerging therapies, the phase III study on difamilast conducted by (Saeki et al., 2022) demonstrated its efficacy across diverse patient demographics, further solidifying the role of topical PDE4 inhibitors in the therapeutic arsenal against AD. The favorable safety profile and effectiveness of difamilast highlight its potential as a long-term treatment option, especially for patients who may be resistant to traditional therapies.

In conclusion, the literature collectively supports the therapeutic potential of topical PDE4 inhibitors in managing mild to moderate atopic dermatitis. The studies reviewed emphasize their efficacy in reducing

inflammation and pruritus while maintaining a favorable safety profile, thus presenting a promising alternative to conventional treatments. However, ongoing research is essential to fully understand the long-term effects and optimize treatment strategies for diverse patient populations.

DISCLOSURE STATEMENT

Disclosure Statement : The authors have no conflicts of Interest to declare.

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