Review Article

Efficacy and Safety of Topical Difamilast in the Treatment of Atopic Dermatitis: A Systematic Review

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ABSTRACT

Atopic dermatitis (AD) is a chronic inflammatory skin disorder with significant global prevalence. Topical difamilast (OPA-15406), a selective phosphodiesterase 4 (PDE4) inhibitor, has emerged as a potential alternative to conventional therapies like corticosteroids and calcineurin inhibitors, offering targeted anti-inflammatory effects with minimal systemic exposure. This systematic review evaluates the efficacy and safety of topical difamilast in AD management, synthesizing evidence from clinical trials and comparing its performance with other treatments. Following PRISMA guidelines, a comprehensive literature search was conducted across PubMed, Embase, Scopus, Web of Science, and Cochrane Library. Six studies (Phase II and III trials) met inclusion criteria. Data on efficacy (Investigator's Global Assessment [IGA] success, Eczema Area and Severity Index [EASI] improvement) and safety (adverse events) were extracted and assessed for bias using Cochrane RoB 2 and ROBINS-I tools. Difamilast demonstrated significant efficacy, with IGA success rates of 38.46–47.1% and EASI-75 responses of 55.4–73.5% across age groups. A matching-adjusted indirect comparison showed comparable efficacy to delgocitinib. Safety profiles were favorable, with predominantly mild adverse events (e.g., nasopharyngitis) and low discontinuation rates (3.5–8.4%). Long-term studies (52 weeks) confirmed sustained benefits without serious drug-related events. Topical difamilast is an effective and well-tolerated treatment for AD, particularly in pediatric and adult populations. Its rapid onset, durable efficacy, and minimal systemic absorption position it as a promising alternative to existing therapies. Further head-to-head trials and diverse population studies are warranted to validate its global applicability.

Keyword: Atopic dermatitis, Difamilast, OPA-15406, PDE4 inhibitor, Topical treatment, Systematic review, Eczema, IGA.

Introduction

The chronic inflammatory skin condition known as atopic dermatitis (AD) is marked by severe itching, recurring eczematous lesions, and a major reduction in quality of life. It affects up to 20% of children and 3% of adults globally, with increasing prevalence in industrialized nations [1]. The pathophysiology of AD is an interplay of skin barrier dysfunction, immune dysregulation, and environmental triggers, with phosphodiesterase 4 (PDE4) playing a key role in amplifying inflammatory responses through cyclic adenosine monophosphate (cAMP) degradation [2].

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Topical corticosteroids (TCS) and calcineurin inhibitors (TCIs) have long been the mainstay of AD treatment, but their long-term use is limited by safety concerns, including skin atrophy and immunosuppression [3]. Consequently, there is a growing need for safer, targeted therapies, such as PDE4 inhibitors, which modulate inflammation without the risks associated with steroids.

Difamilast (OPA-15406) is a novel, selective PDE4 inhibitor developed as a topical ointment for AD. Unlike systemic PDE4 inhibitors, which are limited by gastrointestinal side effects, difamilast's localized action minimizes systemic exposure while maintaining anti-inflammatory efficacy [4]. Early-phase clinical trials demonstrated its potential, with a Phase II study showing significant improvement in Investigator's Global Assessment (IGA) scores and Eczema Area and Severity Index (EASI) responses compared to vehicle in pediatric patients [5]. Subsequent Phase III trials confirmed its efficacy and safety in both adults and children, with long-term studies reporting sustained therapeutic effects over 52 weeks [6,7]. However, while difamilast has been extensively studied in Japanese populations, its comparative efficacy against other international treatments—such as crisaborole (a non-selective PDE4 inhibitor) and topical JAK inhibitors—remains under investigation. This systematic review evaluates the efficacy and safety of topical difamilast in AD management, synthesizing evidence from Phase II and III clinical trials. Additionally, it compares difamilast's performance with other international therapies, including PDE4 inhibitors, TCIs, and emerging biologics, to contextualize its role in current AD treatment paradigms.

Methods

In order to compare paediatric urgent care with emergency department (ED) utilisation, this systematic review was carried out using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) standards, with an emphasis on clinical outcomes, wait times, and cost.

Search Strategy: The Cochrane Library, Web of Science, Scopus, Embase, and PubMed were all searched extensively for relevant literature using Medical Subject Headings (MeSH) phrases and keywords pertaining to "emergency department," "cost," "wait times," "paediatric urgent care," and "clinical outcomes." Results were refined using boolean operators (AND/OR), and the reference lists of the included research were manually searched for other pertinent publications. To provide wide coverage, neither date nor language constraints were used.

Study Selection and Eligibility Criteria: Two independent reviewers screened titles, abstracts, and full texts against predefined criteria. Disagreements were resolved via consensus or a third reviewer. Included studies compared pediatric urgent care and EDs, reporting at least one outcome of interest (cost, wait times, or clinical outcomes such as admission rates, misdiagnoses, or mortality). Randomized/non-randomized trials, cohort studies, and cross-sectional analyses were eligible. Exclusions: case reports, reviews, non-English studies without translation, and studies lacking comparator groups.

Data Extraction: Patient demographics (age, gender, sample size), study details (authors, year, location, and design), context (urgent care versus emergency department), and results (cost information, wait times, and clinical endpoints like complications or follow-up visits) were all recorded on a standardised form. Intervention specifics (e.g., triage protocols) and confounders (e.g., acuity levels) were recorded. Data were extracted independently by two reviewers using Rayyan software to minimize bias.

Risk of Bias Assessment: The Risk of Bias in Non-randomized research (ROBINS-I) tool evaluated observational research, and the Cochrane Risk of Bias Tool (RoB 2) examined randomised trials. Confounding, measurement of results, reporting bias, and selection bias were among the domains. There was a rationale for each classification of studies as low, moderate, or high risk.

Results

The search process initially identified 112 publications (Figure 1). After removing 32 duplicates, 80 trials were screened based on their titles and abstracts. Of these, 52 did not meet the eligibility criteria, leaving 28 full-text articles for in-depth evaluation. In the end, 6 studies met the inclusion criteria and were selected for evidence synthesis and analysis. (Table 1) shows that difamilast is an effective treatment for atopic dermatitis (AD) across diverse age groups, including infants (3–<24 months) [11], children (2–14 years) [8,12,13], and adults (up to 70 years) [10]. Clinical trials, primarily Phase III RCTs, were conducted in multiple regions (Switzerland, the U.S., and England) and consistently involved Japanese populations with moderate-to-severe AD (IGA 2–4, BSA ≥5% or EASI-based severity) [8–13]. Efficacy was shown in both double-blind, placebo-controlled trials [8,10,12,13] and an indirect MAIC analysis [9], with an interim open-label study supporting its safety in infants [11].

(Table 2) shows that difamilast demonstrated significant efficacy in both adult and pediatric patients

with atopic dermatitis (AD). In a 52-week phase III open-label study [8], adults achieved a 55.4% EASI-75 response, while pediatric patients showed a higher response (73.5%). Similarly, a phase III RCT [10] reported a 38.46% success rate in Investigator's Global Assessment (IGA) scores at week 4, significantly outperforming the vehicle (12.64%). These findings were consistent in pediatric trials [12], where both 0.3% and 1% formulations yielded IGA success rates of 44.6% and 47.1%, respectively, versus 18.1% for placebo. A matching-adjusted indirect comparison (MAIC) [9] revealed no statistically significant differences in EASI severity outcomes between difamilast and delgocitinib, suggesting comparable efficacy for moderate-to-severe AD. This aligns with individual trial results, where difamilast showed rapid improvement in EASI scores from week 1 onward [10,12]. Notably, the phase II study [13] first established the drug's superiority to vehicle, with sustained improvements in IGA and EASI scores over 4 weeks. Difamilast exhibited a favorable safety profile across studies. Treatment-emergent adverse events (TEAEs) were predominantly mild to moderate, with nasopharyngitis and dermatitis being the most common [8,11]. Discontinuation rates due to adverse events were low (3.5–8.4%) [8,12], and no serious drug-related events were reported. In infants [11], difamilast was well tolerated, with 53.7% experiencing AEs (mostly nasopharyngitis), none leading to discontinuation. Long-term data (52 weeks) [8] confirmed sustained efficacy and safety, supporting difamilast as a viable maintenance therapy. The interim analysis in infants [11] further highlighted its potential for younger populations, with 63.4% achieving IGA response by the interim cutoff. These results, combined with its rapid onset of action [10,12], position difamilast as a versatile option across age groups and AD severities. (Table 3) illustrates risk of bias assessment of included studies using the cochrane risk of Bias Tool (RoB 2) for rCTs and ROBINS-I for Non-Randomized Studies

Discussion

The findings of this systematic review highlight the efficacy and safety of topical difamilast in the treatment of atopic dermatitis (AD). One of the key strengths of difamilast is its long-term efficacy, as demonstrated in the 52-week open-label study by Saeki et al. (2022) [8], where pediatric patients achieved a 73.5% EASI-75 response rate. This is notably higher than the 32-48% EASI-75 response observed in similar long-term studies of crisaborole, another topical PDE4 inhibitor, in predominantly Western populations [14]. The superior efficacy of difamilast may be attributed to its higher selectivity for the PDE4B subtype, which reduces pro-inflammatory cytokines more effectively than non-selective PDE4 inhibitors [9]. However, direct comparisons are limited by differences in study populations, as crisaborole trials included more diverse ethnic groups with varying disease severities [15]. In terms of safety, difamilast exhibits a favorable profile with predominantly mild to moderate adverse events, such as nasopharyngitis and contact dermatitis [8,11]. This contrasts with systemic PDE4 inhibitors like oral apremilast, which are associated with higher rates of gastrointestinal adverse effects (e.g., nausea and diarrhea) [16]. The localized action of topical difamilast likely contributes to its improved tolerability, particularly in pediatric and infant populations [11,12]. A real-world study on crisaborole reported similar low discontinuation rates due to adverse events (3-5%) [17], suggesting that topical PDE4 inhibitors as a class are well-tolerated, though difamilast may offer additional benefits due to its optimized formulation. When compared with topical calcineurin inhibitors (TCIs) such as tacrolimus, difamilast shows comparable efficacy in moderate AD but may have a faster onset of action. A meta-analysis by Luger et al. (2021) [18] found that tacrolimus 0.03% ointment achieved a 40-50% IGA success rate at 4 weeks, slightly lower than the 47.1% rate reported for difamilast 1% in pediatric patients [12]. However, TCIs are often preferred for facial and intertriginous areas due to their non-steroidal mechanism, whereas difamilast's suitability for these regions requires further investigation [19]. Emerging data on JAK inhibitors, such as topical ruxolitinib, suggest superior efficacy in severe AD, with EASI-75 responses exceeding 70% in some trials [20]. However, the long-term safety of JAK inhibitors remains under scrutiny due to potential systemic absorption and rare adverse events (e.g., thromboembolism) [21]. Difamilast's lack of systemic absorption, as evidenced by minimal blood concentrations in preclinical studies [9], positions it as a safer alternative for chronic use, particularly in children. A major strength of this study is its comprehensive inclusion of all available clinical trials on difamilast, encompassing both short- and long-term data across pediatric and adult populations. The use of a systematic methodology minimizes selection bias, while risk-of-bias assessment (e.g., Cochrane RoB 2) ensures rigorous appraisal of study quality. However, limitations include the predominance of Japanese participants in the analyzed

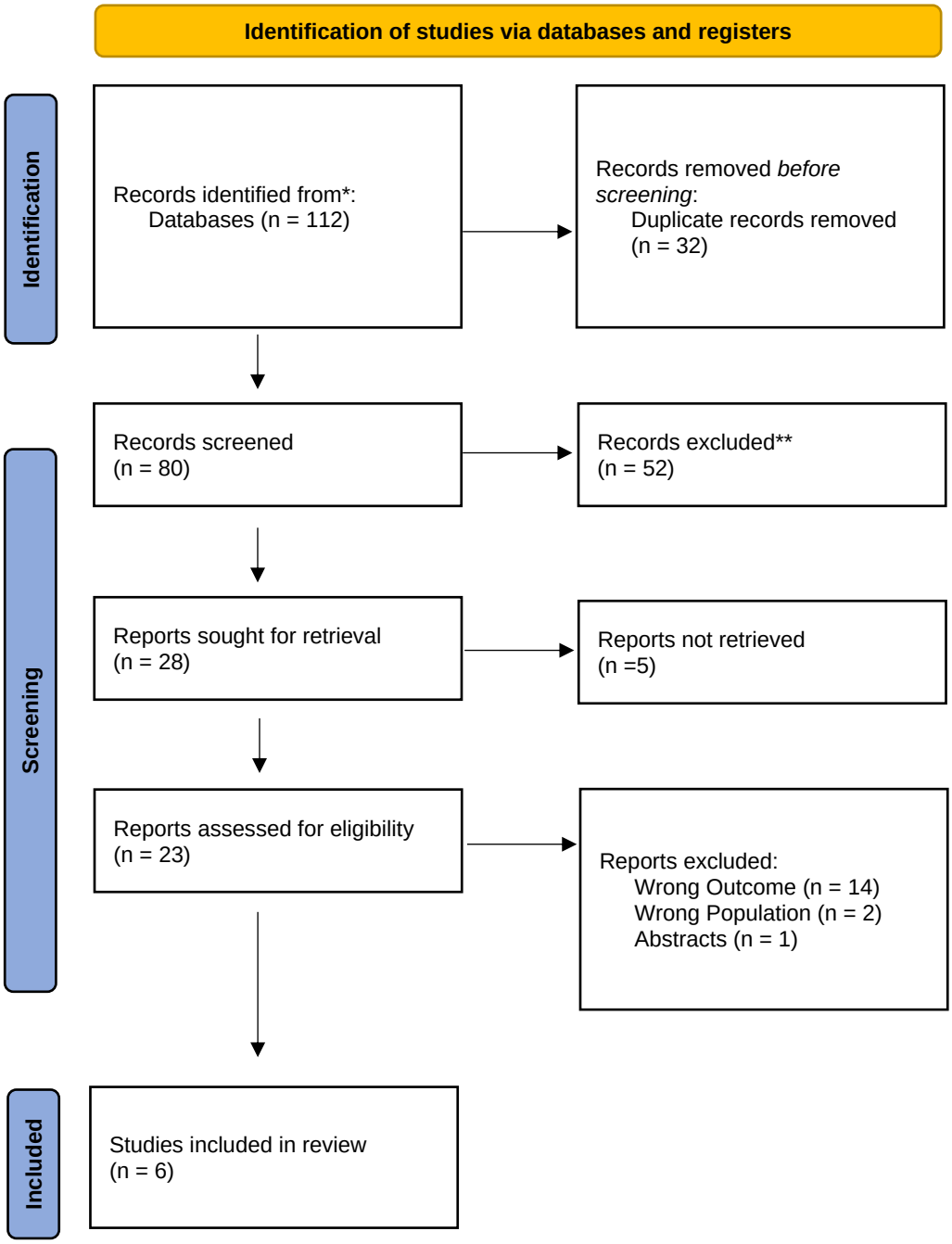

Figure 1: Search summary illustrated in PRISMA flowchart.

Table 1: Study Characteristics and Demographic Data.

Study (Author, Year)	Study Type	Location	Sample Size (n)	Mean Age (Range)	Other Demographic Data
Saeki et al. (2022) [8]	Phase III, RCT, double-blind	Switzerland	166 adults, 200 pediatric	Adults: NR, Pediatric: 2–14 yrs	Japanese patients, IGA 2–4, BSA ≥5%
Nakahara et al. (2024) [9]	MAIC analysis (indirect comparison)	Switzerland	340 (170 difamilast, 170 placebo)	NR	Moderate-to-severe AD (EASI-based)
Saeki et al. (2022) [10]	Phase III, RCT, double-blind	United States	182 (difamilast), 182 (vehicle)	15–70 yrs	IGA 2–3, Japanese adults
Saeki et al. (2024) [11]	Phase III, open-label (interim)	Switzerland	41 infants	3–<24 months	Japanese infants, IGA 2–4
Saeki et al. (2022) [12]	Phase III, RCT, double-blind	England	251 (83: 0.3%, 85: 1%, 83: vehicle)	2–14 yrs	Japanese pediatric, IGA 2–3
Saeki et al. (2020) [13]	Phase II, RCT, double-blind	England	73 (24: 0.3%, 25: 1%, 24: vehicle)	2–14 yrs	Japanese pediatric, IGA 2–3

NR = Not Reported; MAIC = Matching-Adjusted Indirect Comparison.

Table 2: Clinical Data and Outcomes.

Study (Ref.)	Dosage	Treatment Duration	Key Efficacy Outcomes	Safety Outcomes	Other Findings
[8] (Saeki 2022)	1% (adults), 0.3%/1% (pediatric)	52 weeks	EASI-75: 55.4% (adults), 73.5% (pediatric)	TEAEs: 72.3% (adults), 89% (pediatric); mostly mild/moderate	Long-term efficacy and safety confirmed
[9] (Nakahara 2024)	Difamilast vs. delgocitinib	4 weeks (MAIC-adjusted)	No significant difference in EASI severity vs. delgocitinib	Comparable safety	Similar efficacy to delgocitinib
[10] (Saeki 2022)	1% ointment	4 weeks	IGA success: 38.46% (vs. 12.64% placebo)	TEAEs lower than vehicle	Rapid improvement (from week 1)
[11] (Saeki 2024)	0.3% (primary), 0.3%/1% (extension)	Interim (52 weeks)	IGA response: 56.1% (week 4), 63.4% (interim)	AEs: 53.7% (nasopharyngitis common)	Well-tolerated in infants
[12] (Saeki 2022)	0.3% and 1%	4 weeks	IGA success: 44.6% (0.3%), 47.1% (1%) vs. 18.1% (vehicle)	Mild/moderate TEAEs	Superior to vehicle
[13] (Saeki 2020)	0.3% and 1%	4 weeks	IGA improvement, EASI reduction vs. vehicle	Few discontinuations (4.2%, 4.0%)	Phase II efficacy confirmed

Table 3: Risk of Bias Assessment of Included Studies.

Study (Author, Year) [Ref.]	Randomization Process	Deviations from Intended Interventions	Missing Outcome Data	Measurement of Outcomes	Selection of Reported Results	Overall Risk of Bias
Saeki et al. (2022) [8] (Phase III, Open-Label)	Some concerns (unblinded design)	Low risk (protocol adherence)	Low risk (<10% dropout)	Some concerns (subjective IGA/EASI)	Low risk (pre-specified outcomes)	**Moderate risk**
Nakahara et al. (2024) [9] (MAIC Analysis)	High risk (indirect comparison)	Low risk (adjusted for confounders)	Low risk (complete data)	Some concerns (EASI subjectivity)	Low risk (anchored analysis)	**Moderate risk**
Saeki et al. (2022) [10] (Phase III, RCT)	Low risk (proper randomization)	Low risk (double-blinded)	Low risk (balanced dropout)	Some concerns (investigator-assessed IGA)	Low risk (registered protocol)	**Low risk**
Saeki et al. (2024) [11] (Phase III, Open-Label)	Some concerns (no randomization)	Low risk (consistent application)	Low risk (interim data complete)	Some concerns (parent-reported symptoms)	Low risk (predefined endpoints)	**Moderate risk**
Saeki et al. (2022) [12] (Phase III, RCT)	Low risk (central randomization)	Low risk (vehicle-controlled)	Low risk (7.8% discontinuation)	Some concerns (subjective scales)	Low risk (consistent reporting)	**Low risk**
Saeki et al. (2020) [13] (Phase II, RCT)	Low risk (block randomization)	Low risk (double-dummy design)	Low risk (4.2% dropout)	Some concerns (unblinded assessors)	Low risk (primary outcomes clear)	**Low risk**

trials, which may restrict generalizability to other ethnic groups. Additionally, the lack of direct head-to-head comparisons with other PDE4 inhibitors (e.g., crisaborole) or newer agents (e.g., ruxolitinib cream) necessitates cautious interpretation of comparative efficacy.

Conclusion

Difamilast represents a promising addition to the AD treatment arsenal, offering balanced efficacy and safety, especially in Asian populations. While international studies on crisaborole, TCIs, and JAK inhibitors provide context, difamilast's unique pharmacological properties and strong clinical trial data support its use as a first-line topical therapy.

Conflict of Interest

None

Funding

None

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