Systematic Review / Meta-analysis

ANNALS OF MEDICINE & SURGERY

OPEN

Safety and efficacy of pimecrolimus versus vehicle for the treatment of atopic dermatitis in adults and paediatric population: a systematic review and meta-analysis

Sareema E. Akhtar, MD[a], Saad Shakil, MD[a], Sabeeh K. Farooqui, MD[a], Tarek Khedro, MD[b], Ahmad L. Alzufairi, MD[b], Muhammad A. Niaz, MD[b], Saifullah Syed, MD[b], Riaz Jiffry, MD[b], Abdulla K. Alsubai, MD[b], Abdullah Almesri, MD[b], Hebatalla Ismail, MD[b], Kashif A. Khan, MD[c], Ahmed Al-Hindawi, MD[d], Hussein K. Ali, MD[b], Timothy Falodun, MD[b], Aysa Tabassi, MD[b], Aylin Tabassi, MD[b], Talal Almas, MD[b,*]

Introduction: Atopic dermatitis remains a widespread problem affecting various populations globally. While numerous treatment options have been employed, pimecrolimus remains a potent and viable option. Recently, there has been increasing interest in comparing the safety and efficacy of pimecrolimus with its vehicle.

Methods: The authors conducted a comprehensive search of several databases, including PubMed, COCHRANE, MEDLINE, and Cochrane Central, from inception to May 2022, using a wide search strategy with Boolean operators. The authors also employed backward snowballing to identify any studies missed in the initial search. The authors included randomized controlled trials in our meta-analysis and extracted data from the identified studies. The authors used Review Manager (RevMan) Version 5.4 to analyze the data, selecting a random-effects model due to observed differences in study populations and settings. The authors considered a *P*-value of 0.05 or lower to be statistically significant.

Results: The authors initially identified 211 studies, of which 13 randomized controlled trials involving 4180 participants were selected for analysis. Our pooled analysis revealed that pimecrolimus 1% was more effective at reducing the severity of atopic dermatitis than its vehicles. However, no significant difference was observed in adverse effects between pimecrolimus and vehicle, except for pyrexia, nasopharyngitis, and headache, which were increased with pimecrolimus.

Conclusion: Our meta-analysis showed that pimecrolimus 1% is more effective than vehicle, although the safety profile remains inconclusive. Pimecrolimus reduced the Investigator's Global Assessment score, Eczema Area and Severity Index score, and severity of pruritus when compared to its vehicle, indicating a higher efficacy profile. This is one of the first meta-analyses to assess the efficacy and safety profile of pimecrolimus 1% against a vehicle and may assist physicians in making informed decisions.

Keywords: atopic dermatitis, elidel, eczema and dermatology, pimecrolimus

Introduction

Atopic dermatitis (AD), also known as atopic eczema, is a chronic, relapsing, and inflammatory skin disease that affects both adults and children. The term eczema is closely associated with the disease's clinical manifestation, which involves crusting and serous oozing, as well as the formation of blisters along with erythema and scaling[1]. Globally, ~2.4% of the population suffersfrom AD. The burden of the disease varies significantly among different countries, with reported prevalence rates of 4.9% in the adult population of the US, 2.1% in Japan, and up to

[a]Ziauddin Medical College, Karachi, Pakistan, [b]RCSI University of Medicine and Health Sciences, Dublin 2, [c]National University of Ireland, Galway, Ireland and [d]Royal College of Surgeons in Ireland—Bahrain, Bahrain

Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

*Corresponding author. Address: University Hospitals Galway, National University of Ireland Galway, Galway, H91 YR71, Ireland. E-mail: talalalmas.almas@gmail.com (T. Almas).

Annals of Medicine & Surgery (2023) 85:3563–3573

Received 9 December 2022; Accepted 3 May 2023

Supplemental Digital Content is available for this article. Direct URL citations are provided in the HTML and PDF versions of this article on the journal's website, www.annalsjournal.com.

Published online 22 May 2023

http://dx.doi.org/10.1097/MS9.0000000000000844

20% in Sweden[2]. In developed countries, the incidence of AD is on the rise, affecting ~1–3% of adults and 15–20% of children[3].

Topical agents are the cornerstone of AD treatment, often used in combination with systemic treatment or phototherapy for more severe cases. Topical calcineurin inhibitors, which belong to the second class of anti-inflammatory drugs after topical corticosteroids, are naturally produced by streptomyces bacteria and play a pivotal role in inhibiting calcineurin-dependent T-cell activation, resulting in the suppression of AD-associated inflammatory mediators and proinflammatory cytokines[4]. In two short-term (3–12 weeks) and long-term (up to 12 months) trials, topical tacrolimus ointment (strengths of 0.03 and 0.1%), and pimecrolimus cream (1%) were shown to be superior to vehicle[5,6].

Pimecrolimus is recommended for use in children below 2 years of age and in the adult population. However, more recently, countries like Canada have also authorized its use in infants greater than 3 months of age[7]. The current literature has various randomized controlled trials (RCTs) to evaluate the efficacy and safety of pimecrolimus compared to its vehicle, but these results have not yet been systematically reviewed and pooled. Consequently, this systematic review and meta-analysis is noteworthy since it pools the findings from several RCTs. Given that there is no meta-analysis focusing solely on independent safety and efficacy parameters of pimecrolimus, this meta-analysis provides researchers with essential insight for the clinical use of pimecrolimus. As a result, the objective of this systematic review and meta-analysis was to investigate the efficacy and safety of pimecrolimus.

HIGHLIGHTS

- While a multitude of treatment options has been employed to date, pimecrolimus remains a feasible and potent option.
- The pooled analysis revealed that Pimecrolimus 1% was more effective at lowering the severity of atopic dermatitis when compared to vehicle.
- The differences in all of the three variables were statistically significant and indicated that pimecrolimus was more successful at mitigating the severity of atopic dermatitis compared to vehicle.

Methodology

Data Sources and Strategy

This study has been reported in line with the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) guidelines criteria[8], Supplemental Digital Content 1, http://links.lww.com/MS9/A140. The PRISMA flow chart is included in Figure S1, Supplemental Digital Content 3, http://links.lww.com/MS9/A142. The current study is also in compliance with the AMSTAR 2 guidelines, Supplemental Digital Content 2, http://links.lww.com/MS9/A141, and the quality of the current systematic review is observed to be low in accordance with the guideline[9].

Study Selection

From the beginning until May 2022, two independent reviewers (S.S. and S.E.A.) conducted an exhaustive electronic search of PubMed, MEDLINE, and Cochrane Central using all available terms for AD and pimecrolimus, as well as MeSH terms and the Boolean operators "AND" and "OR." The search strategy is included in Supplementary Table S1, Supplemental Digital Content 3, http://links.lww.com/MS9/A142. For our meta-analysis, the following predetermined criteria had to be met: published RCTs; adult patients (>18 years) and pediatric patients including infants and children. Any disagreement over the choice of the studies between the two independent reviewers (S.S. and S.E.A.) was settled by discussion and agreement with a third investigator (S.K.F.). All the relevant articles that were enrolled first on the basis of title and abstract, later full-text read was given to assess for relevance.

Data extraction and quality assessment of studies

Two independent reviewers (S.S. and S.E.A.) cross-checked the studies retrieved by the search method before compiling them in Mendeley Reference Manager (Version 2.77.0) software, where duplicates were checked for and removed. The full texts of the remaining articles were then carefully read to identify the outcomes and calculate their odds ratio (OR) (for most outcomes) or mean difference (MD) [for the Eczema Area and Severity Index (EASI) score]. Furthermore, the references of these full-text publications were manually checked for any relevant research that the automated search may have missed.

The primary focus of this study was to evaluate the safety and efficacy of pimecrolimus in comparison to delivery vehicles in AD. Data pertaining to the outcomes of pimecrolimus versus vehicle were extracted from the selected studies and recorded in Excel spreadsheets. The extracted data included information on the author names; publication date; sample size; Investigator's Global Assessment (IGA) score, a standardized indicator of AD severity based on clinical examination, which reflects the severity of pruritis and inflammation; EASI score; severity of pruritus; and safety parameters such as pyrexia, nasopharyngitis, headache, respiratory symptoms, gastrointestinal symptoms, and other dermatological manifestations. Additional variables such as control, time duration, age, severity of AD, number of participants, sex, and race were also recorded. The age groups represented in the studies were as follows: four studies included children aged 3–23 months; three studies included children and adolescents aged 2 to 17 years; one study included participants aged 1–17 years; one study included participants aged 3 months to 17 years; one study included participants aged 12 and over; one study included participants aged 2–49 years; and two studies included adults aged 18 years and older.

Quality evaluation of the included studies was conducted using the Cochrane Risk of Bias tool[10], which was applied to the studies listed in Supplementary Table S2, Supplemental Digital Content 3, http://links.lww.com/MS9/A142. Two reviewers (S.S. and S.E.A.) performed independent data extraction and quality assessment before including the studies in the review. Continuous data were extracted for the outcome EASI, while dichotomous data were preferred for all other outcomes, including pruritus score, IGA score, and safety outcomes. Baseline participant

Table 1

Baseline study characteristics of included studies

References	Intervention and control	Setting	Participants	Definition of AD	Outcomes of efficacy	Outcomes of safety	Severity of AD	Age of participants
Lawrence F Eichenfield [13]	Pimecrolimus 1% b.i.d and Vehicle b.i.d	6 weeks DB, Randomized	589	Hanifin and Rajka[14]	IGA; EASI	—	Mild to very severe	3 months–17 years
Alexander Kapp[15]	Pimecrolimus 1% b.i.d and Vehicle b.i.d	12 months DB, Randomized	251 Infants	.Seymour *et al.*[16]	Incidence of flares; TCs requirement; IGA; EASI; Pruritus score; Patient's global assessment of disease control.	Nasopharyngitis, Otitis Media, URTI, Cough, Bronchitis, Rhinitis, Diarrhea, Gastroenteritis, Impetigo, Bacterial Infection, Herpes Simplex, Pyrexia.	Mild to very severe	3–23 months
Roland Kaufmann[17]	Pimecrolimus 1% b.i.d and Vehicle b.i.d	Four weeks DB, followed by 12 weeks OL	196 Infants	.Seymour *et al.*[16]	Onset of effectiveness; Incidence of flares at EOS; EASI; IGA; Caregiver's assessment of pruritus severity and sleep loss.	Nasopharyngitis, Cough, Bronchitis, Rhinitis, Diarrhea, Gastroenteritis, Pyrexia.	Mild to very severe	3–23 months
Richard G B Langley[13]	Pimecrolimus 1% b.i.d and Vehicle b.i.d	6 wk DB followed by 20 weeks OL	403 Children and adolescents.	.Williams *et al.*[18]	IGA; EASI and pruritus assessment.	Nasopharyngitis, Otitis Media, URTI, Bacterial Infection, Influenza.	Mild to very severe	2–17 years
D F MURRELL[19]	Pimecrolimus 1% b.i.d and Vehicle b.i.d	6 weeks DB followed by 6 weeks OL	200	Hanifin and Rajka[14]	IGA; EASI; Pruritus score; Dermatitis score.	Nasopharyngitis, URTI, Herpes simplex, influenza, Headache.	Mild to moderate	12 years or over
D Y M Leung[20]	Pimecrolimus 1% b.i.d and Vehicle b.i.d	6 weeks DB, randomized.	73	Hanifin and Rajka[14]	IGA; EASI; Pruritus score; Patients AD assessment; TLS	—	Mild to severe	2–49 years
Kristine Breuer[21]	Pimecrolimus 1% b.i.d and Vehicle b.i.d	4 weeks DB, Randomized followed by 12 weeks OL.	195 Infants	.Seymour *et al.*[16]	IGA, EASI, SCORAD	—	Mild to very severe	3–23 months
Lawrence F Eichenfield[5]	Pimecrolimus 1% b.i.d and Vehicle b.i.d	6 weeks DB, randomized	403 Children and adolescents	.Williams *et al.*[18]	IGA; EASI; Pruritus score; Patient's global assessment of disease control.	Nasopharyngitis, URTI, Application of site burning, Headache	Mild to moderate	1–17 years
Vincent C. HO[22]	Pimecrolimus 1% b.i.d and Vehicle b.i.d	6 weeks DB, randomized followed by 20 weeks OL	186 Infants	.Williams *et al.*[18]	IGA; EASI; Pruritus Score	Nasopharyngitis, URTI, Bronchitis, Rhinitis, Diarrhea, Gastroenteritis, Bacterial Infection, Pyrexia & Influenza.	Mild to moderate	3–23 months
T. LUGER[23]	Pimecrolimus 1% b.i.d and Vehicle b.i.d	3 weeks DB, randomized.	260 Adults	Hanifen and Rajka[14]	Adapted EASI; Pruritus score; Patient's self-assessment of disease control.	—	Moderate to severe	> 18 years
B Sigurgeirsson[24]	Pimecrolimus 1% b.i.d and Vehicle b.i.d	26 weeks, DB, Randomized	521 Children	Williams *et al.*[18].	Number of TCS free days; number of flares.	Nasopharyngitis, Otitis Media, URTI, Cough, Bronchitis, Rhinitis, Gastroenteritis, Impetigo, Pyrexia, Influenza, Application of site burning, Headache.	Mild to moderate	2–17 years
Ulrich Wahn[25]	Pimecrolimus 1% b.i.d and Vehicle b.i.d	12 month DB	711 Children and adolescents.	.Williams *et al.*[18]	Incidence of flares at 6 and 12 months; TCs requirement; Time to first flare; IGA; EASI.	Impetigo, Bacterial Infection and Herpes Simplex.	Moderate to very severe	2–17 years
Micheal Meurer[26]	Pimecrolimus 1% b.i.d and Vehicle b.i.d	24 weeks DB, randomized	192 Adults	Rajka and Langland[27]	Incidence of flares; TCs requirement; IGA; EASI; Pruritus score; Patient's global assessment of disease control.	Application of Site Burning	Moderate to severe	> 18 years

AD, Atopic Dermatitis; B.i.d, Twice daily; DB, Double Bind; EASI, Eczema Area and Severity Index; IGA, Investigators Global Assessment; OL, Open Label; URTI, Upper respiratory tract infection.

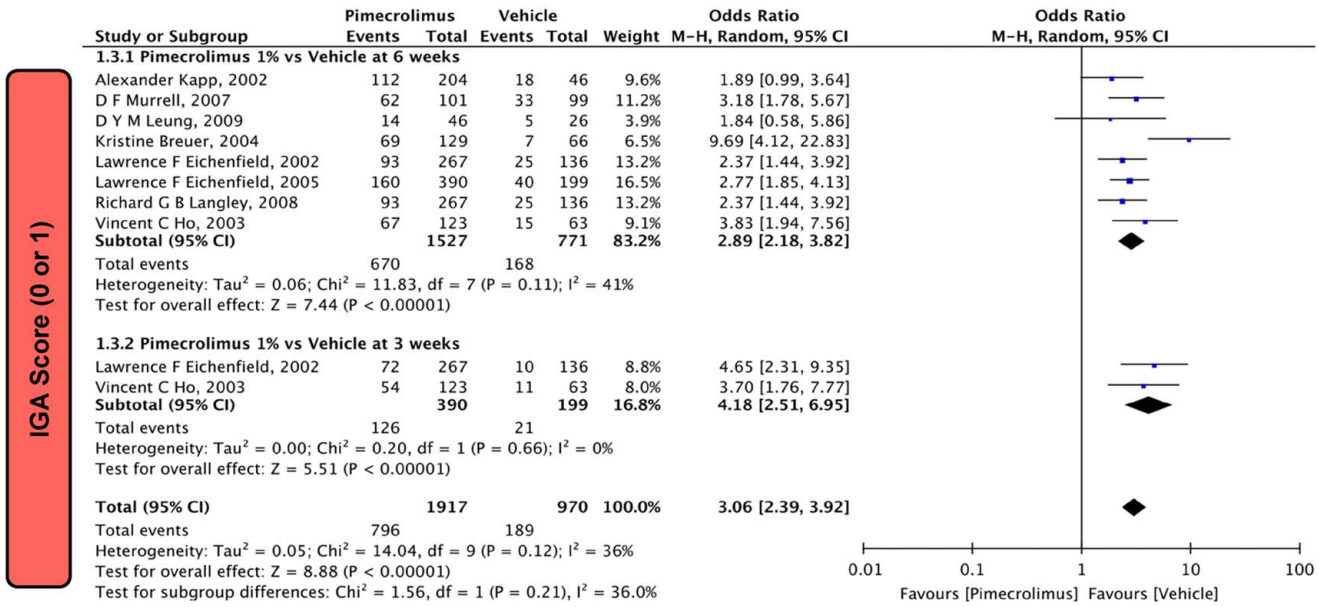

Figure 1. Forest plot of IGA score (0 or 1) of pimecrolimus versus vehicle.

information was also extracted to reduce the likelihood of selection bias.

Statistical Analysis

The extracted data was assessed using the software Review Manager (RevMan), Version 5.4. (the Cochrane Collaboration). The random-effects model was selected due to the observed differences between the study populations and study settings. A $P < 0.05$ or less was regarded as significant. OR were calculated for the majority of the outcomes, whereas EASI results were presented as a MDs with corresponding 95% CIs.

The heterogeneity of effect sizes was assessed using Higgin's I^2 statistics, with an I^2 value greater than 50% considered significant[11]. Additionally, funnel plots (Figure S2–S19, Supplemental Digital Content 3, http://links.lww.com/MS9/A142) were generated and the Begg's test was performed to check for publication bias. A $P < 0.05$ was considered significant for all analyses mentioned above[12].

Results

The study process is encapsulated in the PRISMA flow chart (Figure S1, Supplemental Digital Content 3, http://links.lww.com/MS9/A142). Initially, 211 articles were retrieved from PUBMED, of which 175 were removed after screening for duplicates, titles, abstracts, and full-text. Following the application of inclusion criteria, data from 13 RCTs comparing pimecrolimus 1% with vehicle ($n = 4180$) were collected. While some studies reported both safety and efficacy outcomes, most only reported one or the other. Among the shortlisted studies, 10

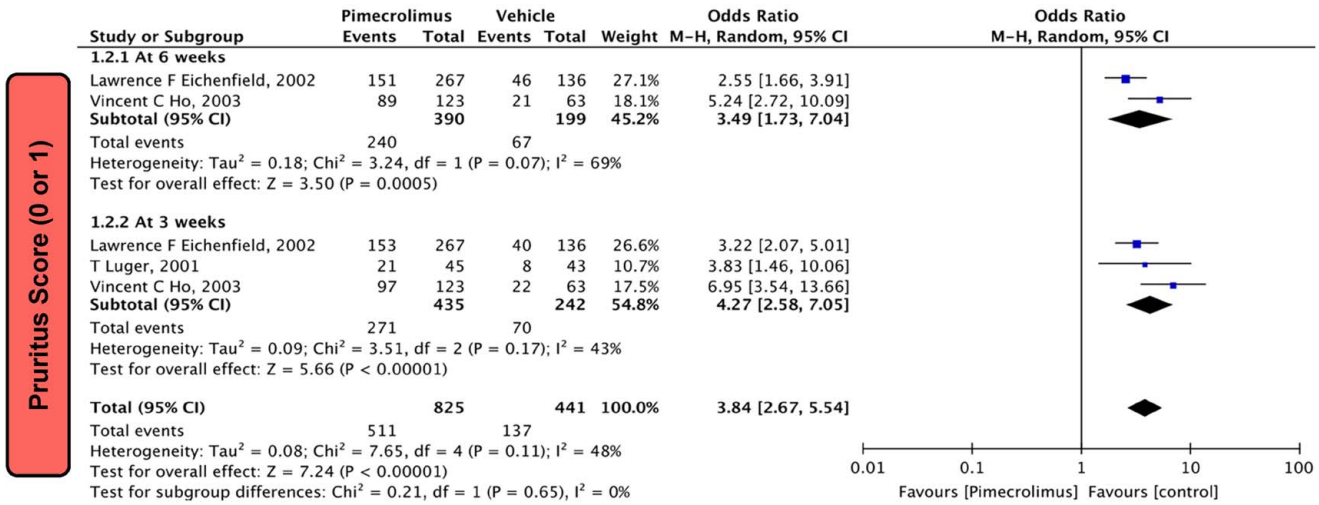

Figure 2. Forest plots evaluating pruritus score (0 or 1) of pimecrolimus versus vehicle.

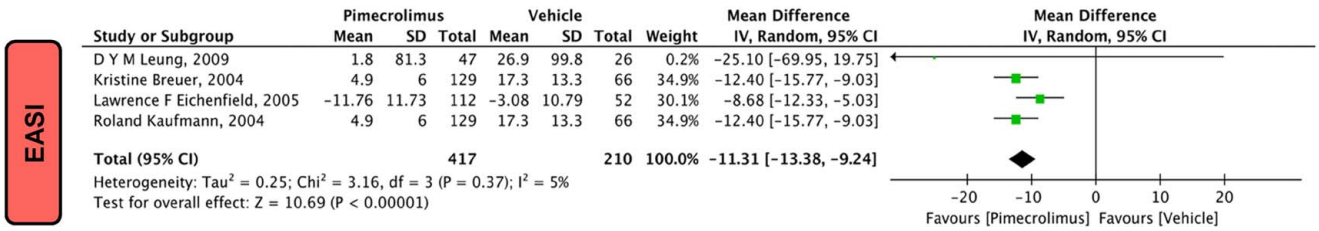

Figure 3. Forest plots evaluating EASI of pimecrolimus versus vehicle.

reported efficacy outcomes ($n=2110$), while nine reported safety outcomes ($n=2986$). Detailed baseline study characteristics, including individual efficacy and safety outcomes reported by the studies, are presented in Table 1 of this manuscript. Patient characteristics of the included studies are presented in Supplementary Table S3, Supplemental Digital Content 3, http://links.lww.com/MS9/A142.

Efficacy of Pimecrolimus 1% versus Vehicle

IGA Score with Pimecrolimus versus Vehicle

In our pooled analysis, eight studies[5,13,15,19–22,28] comprising 2298 participants reported IGA scores at 6 weeks, which were statistically significant. Pimecrolimus 1% was significantly more effective than the vehicle [OR = 2.89 (2.18, 3.82), $P<0.00001$, $I^2=41\%$; Fig. 1] in reducing the IGA scores to clear or almost clear (IGA 0 or 1). Two studies[5,22] comprising 589 participants reported IGA at 3 weeks, which was also statistically significant. Pimecrolimus 1% was significantly more effective than the vehicle [OR = 4.18 (2.51, 6.95), $P<0.00001$, $I^2=0\%$; Fig. 1] in reducing the IGA scores to clear or almost clear (IGA 0 or 1).

Severity of Pruritus

In our meta-analysis, two studies[5,22] involving 589 participants reported the severity of pruritus at 6 weeks, which was statistically significant. Pimecrolimus 1% was significantly more effective than vehicle [OR = 3.49 (1.73,7.04), $P=0.0005$, $I^2=69\%$; Fig. 2]. Similarly, three studies[5,22,23] comprising 677 participants reported the severity of pruritus at 3 weeks, which was also statistically significant. Pimecrolimus 1% was significantly more effective than vehicle [OR = 4.27 (2.58,7.05), $P<0.00001$, $I^2=43\%$; Fig. 2].

EASI Score

In our pooled analysis, four studies[17,20,21,28] comprising of 784 participants reported EASI that was statistically significant. Pimecrolimus 1% effectively decreased the EASI score compared to the vehicle [MD = −11.31 (−13.38, −9.24); $P<0.00001$, $I^2=5\%$; Fig. 3].

Safety of Pimecrolimus 1% Versus Vehicle

The use of pimecrolimus resulted in a statistically significant increase in three safety outcomes, namely headache, nasopharyngitis, and pyrexia, compared to vehicle use. However, other adverse effects were not statistically significant in this analysis. Therefore, the safety profile of pimecrolimus has not been fully assessed.

Pyrexia

Our pooled analysis included four studies[15,17,22,24] with a total of 1138 participants reporting pyrexia. The results showed that pimecrolimus 1% significantly increased the risk of pyrexia compared to the use of a vehicle [OR = 1.65 (1.03, 2.63), $P=0.04$, $I^2=31\%$; Fig. 4].

Nasopharyngitis

In our pooled analysis, seven studies[5,13,15,17,19,22,24] comprising 2145 participants reported nasopharyngitis. Our pooled analysis demonstrates that pimecrolimus 1% significantly increases the risk of nasopharyngitis compared to vehicle [OR = 1.61 (1.24,2.10), $P=0.0004$, $I^2=0\%$; Fig. 5].

Headache

In our pooled analysis, three studies[5,19,24] comprising of 1109 participants reported headache. Our pooled analysis demonstrates that pimecrolimus 1% significantly increases the risk of

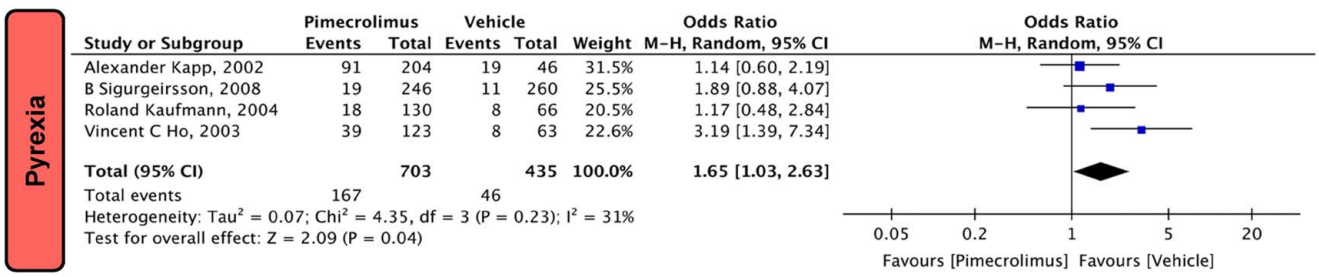

Figure 4. Forest plots evaluating the safety outcomes of pyrexia of pimecrolimus versus vehicle.

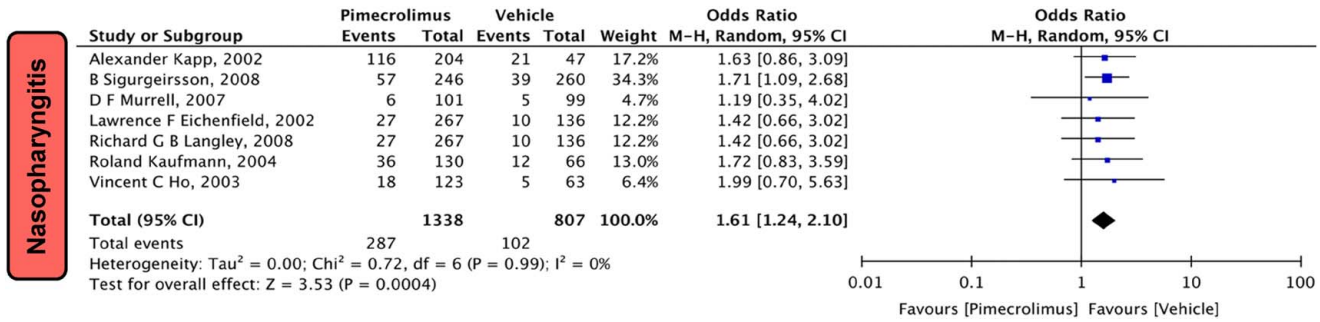

Figure 5. Forest plots evaluating the safety outcomes of nasopharyngitis of pimecrolimus versus vehicle.

beadache compared to vehicle [OR = 1.70 (1.00,2.87), $P = 0.05$, $I^2 = 0\%$; Fig. 6].

Respiratory Symptoms

Pimecrolimus 1% given to patients with AD did not increase the risk of respiratory symptoms such as upper respiratory tract infection [OR = 1.19 (0.87, 1.63), $P = 0.26$, $I^2 = 0\%$] six studies [5,13,15,19,22,24], cough [OR = 1.22 (0.73, 2.02), $P = 0.45$, $I^2 = 0\%$] three studies[15,17,24], influenza [OR = 1.58 (0.55, 4.50), $P = 0.39$, $I^2 = 46\%$] four studies[13,19,22,24], rhinitis [OR = 0.77 (0.39, 1.53) four studies[15,17,22,24], $P = 0.46$, $I^2 = 56\%$], and bronchitis [OR = 0.85 (0.52, 1.38), $P = 0.51$, $I^2 = 0\%$], four studies[15,17,22,24] when compared to vehicle (Fig. 7).

Gastrointestinal Symptoms

Upon evaluating the safety profile of pimecrolimus 1% and the vehicle regarding gastrointestinal symptoms, it was revealed that pimecrolimus did not significantly increase the risk of diarrhea [OR = 1.27 (0.56, 2.88), $P = 0.58$, $I^2 = 30\%$] three studies[15,17,22] and gastroenteritis [OR = 0.95 (0.44, 2.05), $P = 0.89$, $I^2 = 37\%$] four studies[15,17,22,24] when compared to the vehicle (Fig. 8).

Dermatological Manifestations

In our pooled analysis, dermatological manifestation reported by different studies revealed that Pimecrolimus 1% when compared to vehicle (Fig. 9) did not significantly increase the risk of Impetigo [OR = 0.77 (0.18, 3.26), $P = 0.73$, $I^2 = 87\%$] three studies[15,24,25]and Application site burning [OR = 0.87 (0.44, 1.72), $P = 0.69$, $I^2 = 33\%$] three studies[5,24,26].

In our pooled analysis, the dermatological manifestations reported by different studies revealed that when compared to vehicle (Fig. 9), pimecrolimus 1% did not significantly increase the risk of impetigo [OR = 0.77 (0.18, 3.26), $P = 0.73$, $I^2 = 87\%$] three studies[15,24,25] and application site burning [OR = 0.87 (0.44, 1.72), $P = 0.69$, $I^2 = 33\%$] three studies[5,24,26].

Other Symptoms

Five other symptoms were reported, which did not fit into the above categories and revealed a statistically nonsignificant association with the use of pimecrolimus 1% and the vehicle in patients with AD (Fig. 10). These symptoms included bacterial infection [OR = 0.76 (0.24, 2.44), $P = 0.64$, $I^2 = 32\%$] four studies[13,15,22,25], otitis media [OR = 1.02 (0.59, 1.75), $P = 0.95$, $I^2 = 0\%$] three studies[13,15,24], and herpes simplex virus (HSV) [OR = 0.79 (0.37, 1.71), $P = 0.55$, $I^2 = 0\%$] three studies[15,19,25].

DISCUSSION

In this meta-analysis of over 4000 patients, we compared the safety and efficacy of pimecrolimus versus a vehicle for treating AD in adult and pediatric populations. To assess pimecrolimus' efficacy, we compared IGA scores, EASI scores, and the severity of pruritus among the 13 studies included in the meta-analysis. The differences in all three variables were statistically significant and indicated that pimecrolimus was more successful than the vehicle in mitigating the severity of AD. We found a significant difference in the incidence of three outcomes; headache, nasopharyngitis, and pyrexia, which were more likely to occur with pimecrolimus use than with vehicle use, among the various safety outcomes evaluated. However, the additional adverse effects evaluated were not statistically significant in our study, making it impractical to assess

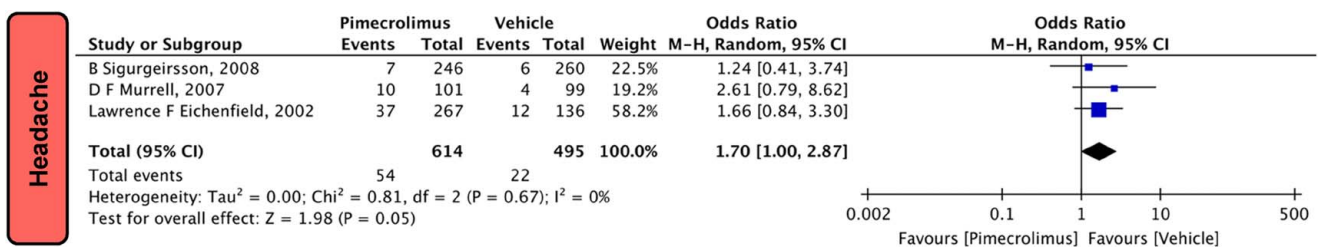

Figure 6. Forest plots evaluating the safety outcomes of headache of pimecrolimus versus vehicle.

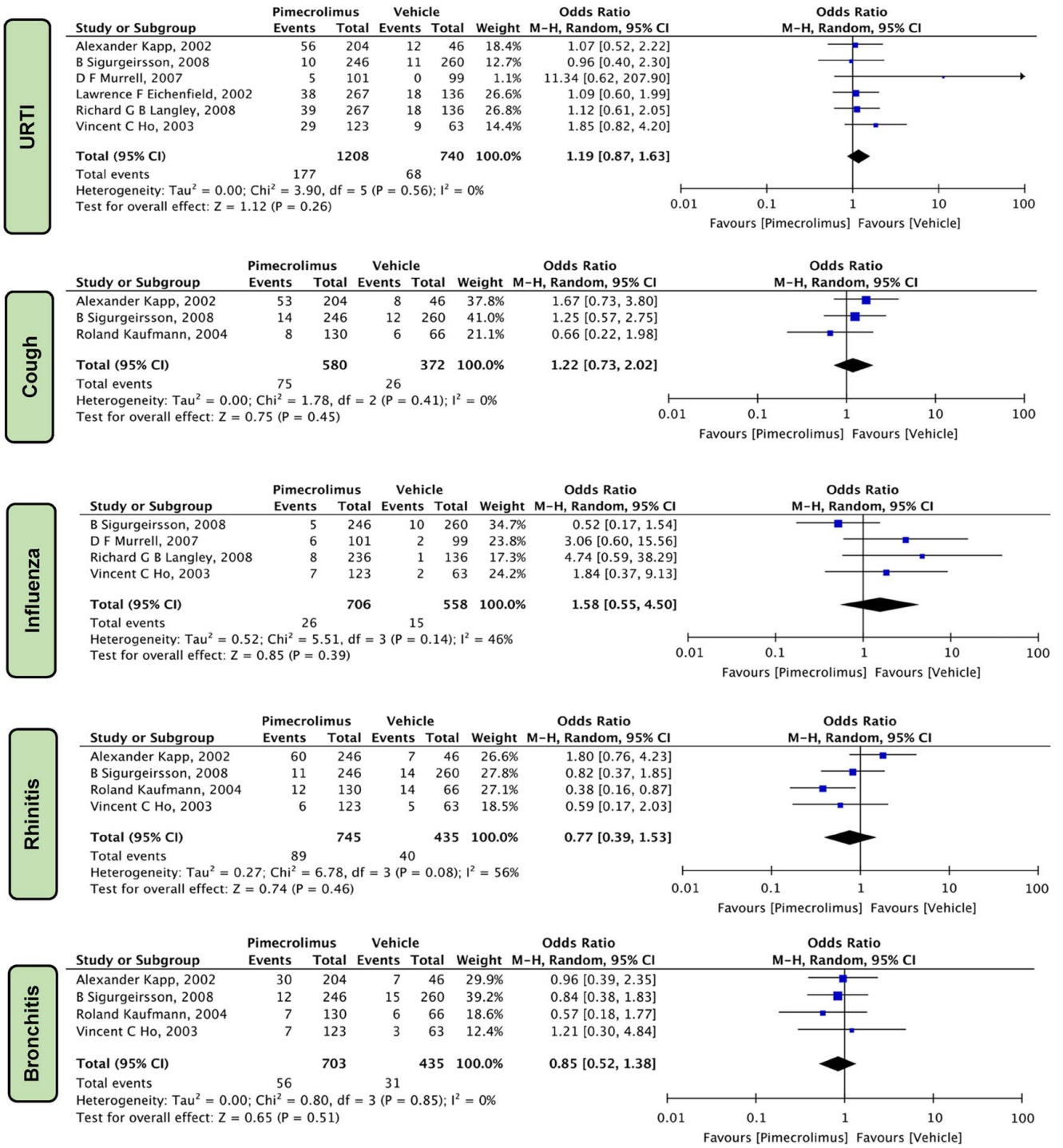

Figure 7. Forest plots evaluating the safety outcomes of pimecrolimus versus vehicle for respiratory symptoms.

pimecrolimus's safety profile. The severity of AD cases ranged from mild to very severe in this pooled analysis, which included both adults and children, implying that the findings held true for all age groups and severity levels. However, there is limited research analyzing the long-term effects of AD medical therapy[25]. Hence, more research is necessary to evaluate pimecrolimus' safety profile.

The mechanism of action of pimecrolimus 1% is to inhibit T lymphocyte activation and the synthesis of proinflammatory cytokines such as interleukin-2 and interferon-gamma. This helps to reduce inflammation and pruritus in the affected skin, thereby reducing the severity of AD symptoms[29]. Decreased levels of IGA reflect a reduction in skin itch and inflammation. Pimecrolimus 1% has been shown in clinical studies to

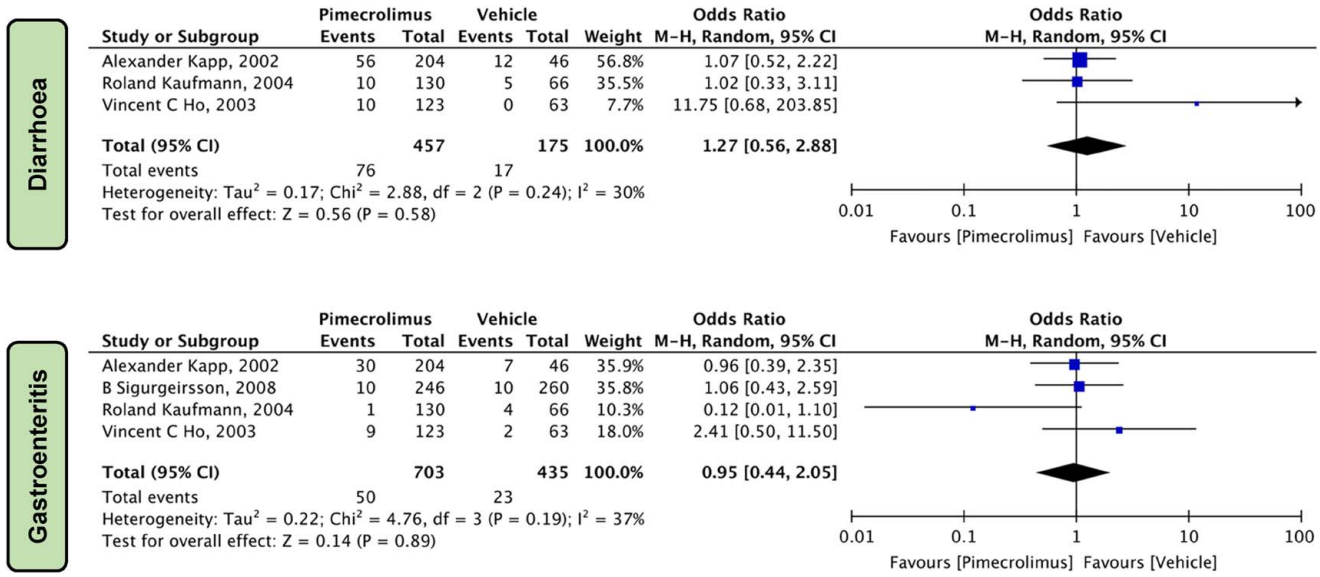

Figure 8. Forest plots evaluating the safety outcomes of pimecrolimus versus vehicle for gastrointestinal symptoms.

significantly reduce the IGA score in individuals with mild to severe AD, compared to placebo medication[5]. Another meta-analysis of RCTs comparing pimecrolimus 1% cream to a control group or alternative therapies for AD patients was conducted by Ashcroft *et al.*[30] in 2007, which revealed that pimecrolimus was more effective in reducing IGA scores than vehicles.

The IGA and the EASI scores, in particular, have suggested that pimecrolimus improves clinical outcomes and reduces pruritus. This meta-analysis consistently shows a superior effectiveness profile of pimecrolimus when compared to a vehicle (also known as a nonactive control). Clinically, pimecrolimus is recommended for use in mild to moderate AD[4]. Another systematic review concluded that pimecrolimus is more effective than the vehicle in terms of efficacy[31]. In short-term (3–12 weeks) and long-term (up to 12 months) studies on adults and children with active disease, topical calcineurin inhibitors, such as pimecrolimus, have been shown to be more effective than the vehicle[4].

Other reviews and meta-analyses have confirmed our findings regarding the efficacy of pimecrolimus over vehicle[30–32]. This was evident even at a pimecrolimus concentration of 0.2%, as demonstrated by a dose-finding study conducted by Luger *et al.*[23]. Interestingly, a 26-week trial by Langley *et al.*[13] suggested that pimecrolimus is more effective in treating AD in the face and neck regions than in other parts of the body. However, this study has limited generalizability since it was only conducted on children aged 12–17. In an infant trial, the onset of action of pimecrolimus was reported to be as early as day 4 of use[17]. Individually, none of the 13 studies included in this meta-analysis reported significant differences in the incidence of adverse events between pimecrolimus and

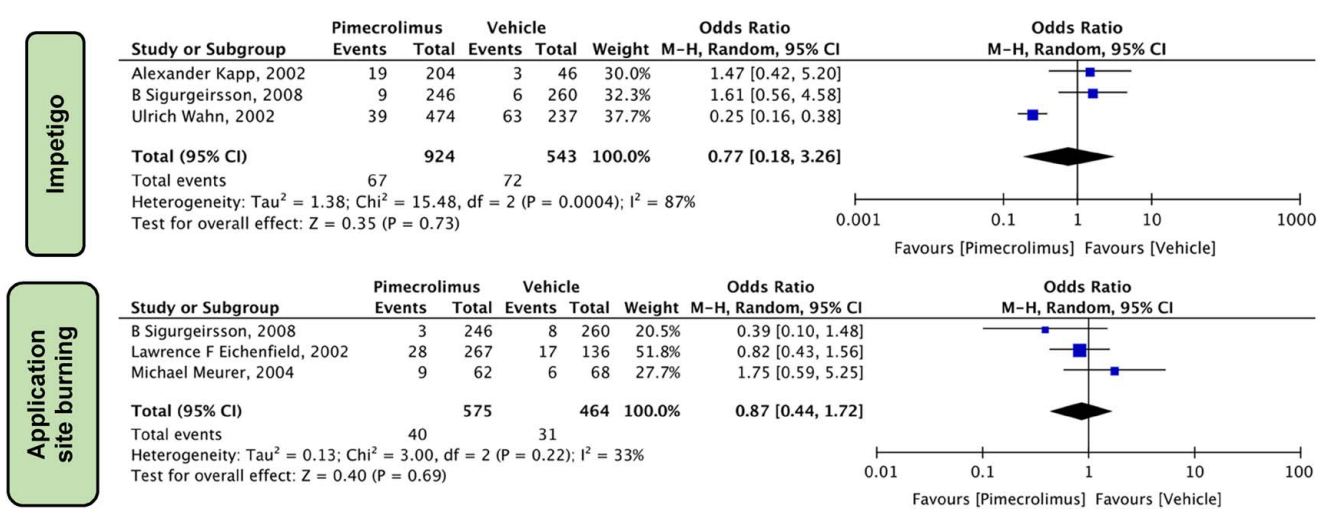

Figure 9. Forest plots evaluating the safety outcomes of pimecrolimus versus vehicle for dermatological manifestations.

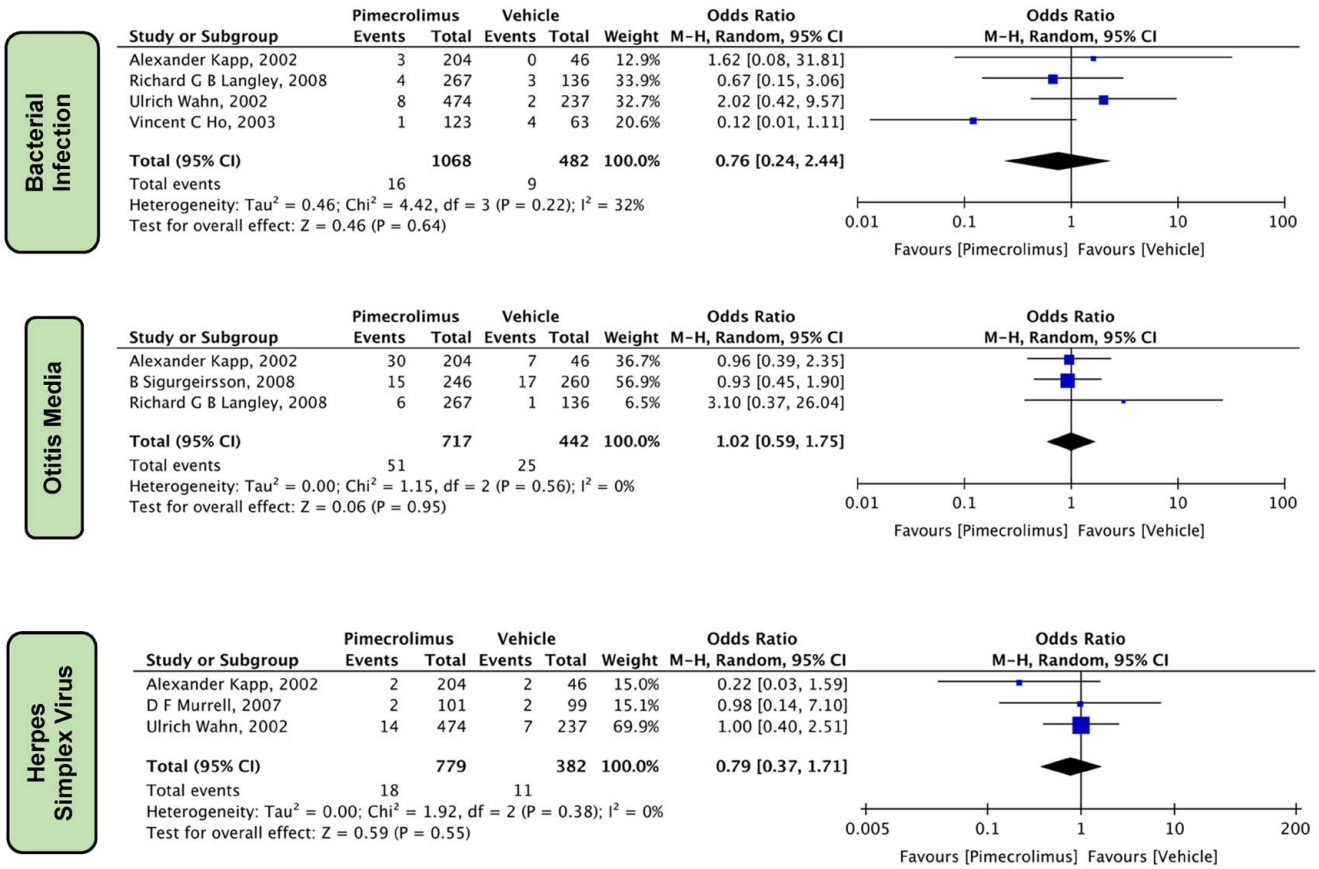

Figure 10. Forest plots evaluating the other safety outcomes of pimecrolimus versus vehicle.

vehicle groups. Still, collectively, our results indicate otherwise. Furthermore, although our meta-analysis found no significant differences in the frequency of HSV infections between pimecrolimus and vehicle groups, a 2009 review found that pimecrolimus use was linked to a slightly higher incidence of HSV infections[32]. The present meta-analysis sought to provide an overview of the safety and efficacy of pimecrolimus versus vehicle in AD. While our goal was indeed to garner an in-depth understanding of these, we did not seek to evaluate the safety and efficacy across the various severity grades. Therefore, we have not included a sub-sectional analysis of the treatments across varying grades of severity.

This meta-analysis has certain shortcomings. Firstly, our results are limited by patient variability, including variations in age, sex, and ethnicity. Due to heterogeneity, the random-effects model was used for statistical analysis. Secondly, the effect of pimecrolimus could not be assessed separately for the pediatric and adult population due to a lack of data comparing pimecrolimus and vehicle in the respective age groups. Therefore, trends regarding the age of patients with AD could not be analyzed. Further prospective studies are required to study the efficacy of pimecrolimus in the pediatric and adult population separately. Thirdly, the safety profile of pimecrolimus could not be completely assessed, as our analysis found most adverse effects to be not statistically significant. Further data from studies are required to evaluate the safety profile of the drug. Fourthly, our meta-analysis excluded studies conducted in any language other than English. Furthermore, this meta-analysis only considered short-term trials. The effectiveness or safety of therapies for chronic illnesses like AD may not be fully reflected by short-term trials, rendering it another limitation of this study. Therefore, long-term study data are required to evaluate the effect of pimecrolimus in all ages. Lastly, the studies included in this meta-analysis were not classified according to the severity of AD. Since the treatment of AD varies according to the severity of AD, the results of this meta-analysis regarding the efficacy of pimecrolimus were only generalized and not specific to different grades of severity of AD. Moreover, data from multicenter studies are required that stratify AD according to severity grades and analyze the efficacy of pimecrolimus and vehicle. However, this meta-analysis is novel since it was the first to assess the safety profile of pimecrolimus in comparison to a vehicle.

CONCLUSION

This meta-analysis highlights the efficacy and safety of pimecrolimus 1% in treating patients with AD (eczema), enabling clinicians to anticipate the course of the condition. The meta-analysis demonstrates a strong correlation between IGA, pruritus score, and EASI, indicating the potency of pimecrolimus in reducing AD compared to the vehicle. However, several notable associations were discovered in the safety profile. Pimecrolimus induced pyrexia, nasopharyngitis, and headaches (in the short-term, given the short follow-up time of individual studies), whereas other side

effects were inconclusive in the analysis; therefore, the safety of pimecrolimus remains inconclusive. Our comprehensive analysis found limited data to answer clinically essential questions about how pimecrolimus and the vehicle compare in terms of effectiveness (particularly as a choice for a long-term treatment strategy), adverse events, tolerability, and financial cost to existing clinically recommended therapies. Future meta-analyses and randomized controlled studies, conducted on larger sample sizes and of longer duration, must bridge the information gap by focusing on additional pimecrolimus safety and long-term effectiveness outcomes across age groups, as well as assessing treatment according to the severity of AD.

Ethical approval

NA.

Consent

NA.

Sources of funding

NA.

Author contribution

S.E.A., S.S., S.K.F., and R.J.: conceived the idea, designed the study, and drafted the manuscript; A.K.S., M.A.N., and A.A.: conducted comprehensive literature search, screened the studies for relevant content, and created the literature review table; H.I., K.A.K., and A.A.H.: revised the manuscript critically and refined the literature review table; H.K.A., T.F., A.T., A.T., and S. S.: drafted the discussion part of the manuscript, revised the final version of the manuscript critically based on the reviewer and editorial comments; A.A.P., T.A., A.A., and A.A.: conceived the initial study idea, diagnosed the case, and gave the final approval for publication.

Conflicts of interest disclosure

NA.

Research registration unique identifying number (UIN)

NA.

Guarantor

Saad Shakil. Ziauddin University. E-mail: saadshakil07@gmail.com

Provenance and peer review

Not commissioned, externally peer-reviewed.

Data availability statement

NA.

Disclosures

NA.

References

[1] Hadi HA, Tarmizi AI, Khalid KA, *et al*. The epidemiology and global burden of atopic dermatitis: a narrative review. Life (Basel). 2021;11:936.
[2] Urban K, Chu S, Giesey RL, *et al*. The global, regional, and national burden of atopic dermatitis in 195 countries and territories: an ecological study from the global burden of disease study 2017. JAAD Int 2021;2:12–8.
[3] Overview of Atopic Dermatitis [Internet]. Accessed 8 September 2022. https://www.ajmc.com/view/overview-of-atopic-dermatitis-article
[4] Eichenfield LF, Tom WL, Berger TG, *et al*. Guidelines of care for the management of atopic dermatitis: Part 2: management and treatment of atopic dermatitis with topical therapies. J Am Acad Dermatol 2014;71:116.
[5] Eichenfield LF, Lucky AW, Boguniewicz M, *et al*. Safety and efficacy of pimecrolimus (ASM 981) cream 1% in the treatment of mild and moderate atopic dermatitis in children and adolescents. J Am Acad Dermatol 2002;46:495–504.
[6] Kang S, Lucky AW, Pariser D, *et al*. Long-term safety and efficacy of tacrolimus ointment for the treatment of atopic dermatitis in children. J Am Acad Dermatol 2001;44(1 suppl):S62–3.
[7] Luger T, Paller AS, Irvine AD, *et al*. Topical therapy of atopic dermatitis with a focus on pimecrolimus. J Europ Aca Dermatol Venereol 2021;35:1505–18.
[8] Page MJ, McKenzie JE, Bossuyt PM, *et al*. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. Syst Rev 2021;10:1–11.
[9] Shea BJ, Reeves BC, Wells G, *et al*. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ 2017;358:4008.
[10] Higgins JPT, Altman DG, Gøtzsche PC, *et al*. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ 2011;343.
[11] Higgins JPT, Thompson SG, Deeks JJ, *et al*. Measuring inconsistency in meta-analyses. BMJ 2003;327:557–60.
[12] Operating characteristics of a rank correlation test for publication bias - PubMed [Internet]. Accessed 8 September 2022. https://pubmed.ncbi.nlm.nih.gov/7786990/
[13] Langley RGB, Eichenfield LF, Lucky AW, *et al*. Sustained efficacy and safety of pimecrolimus cream 1% when used long-term (up to 26 weeks) to treat children with atopic dermatitis. Pediatr Dermatol 2008;25:301–7.
[14] Larsen FS, Hanifin JM. Epidemiology of atopic dermatitis. Immunol All Clin 2002;22:1–24.
[15] Kapp A, Papp K, Bingham A, *et al*. Long-term management of atopic dermatitis in infants with topical pimecrolimus, a nonsteroid anti-inflammatory drug. J Allergy Clin Immunol 2002;110:277–84.
[16] Seymour JL, Keswick BH, Hanifin JM, *et al*. Clinical effects of diaper types on the skin of normal infants and infants with atopic dermatitis. J Am Acad Dermatol 1987;17:988–97.
[17] Kaufmann R, Fölster-Holst R, Höger P, *et al*. Onset of action of pimecrolimus cream 1% in the treatment of atopic eczema in infants. J Allergy Clin Immunol 2004;114:1183–8.
[18] WILLIAMS HC, JBURNEY PG, PEMBROKE AC, *et al*. The U.K. working party's diagnostic criteria for atopic dermatitis. III. Independent hospital validation. Br J Dermatol 1994;131:406–16.
[19] Murrell DF, Calvieri S, Ortonne JP, *et al*. A randomized controlled trial of pimecrolimus cream 1% in adolescents and adults with head and neck atopic dermatitis and intolerant of, or dependent on, topical corticosteroids. Br J Dermatol 2007;157:954–9.
[20] Leung DYM, Hanifin JM, Pariser DM, *et al*. Effects of pimecrolimus cream 1% in the treatment of patients with atopic dermatitis who demonstrate a clinical insensitivity to topical corticosteroids: a randomized, multicentre vehicle-controlled trial. Br J Dermatol 2009;161:435–43.

[21] Breuer K, Braeutigam M, Kapp A, *et al*. Influence of pimecrolimus cream 1% on different morphological signs of eczema in infants with atopic dermatitis. Dermatology 2004;209:314–20.
[22] Ho VC, Gupta A, Kaufmann R, *et al*. Safety and efficacy of nonsteroid pimecrolimus cream 1% in the treatment of atopic dermatitis in infants. J Pediatr 2003;142:155–62.
[23] Luger T, van Leent EJM, Graeber M, *et al*. SDZ ASM 981: an emerging safe and effective treatment for atopic dermatitis. Br J Dermatol 2001;144:788–794.
[24] Sigurgeirsson B, Ho V, Ferrándiz C, *et al*. Effectiveness and safety of a prevention-of-flare-progression strategy with pimecrolimus cream 1% in the management of paediatric atopic dermatitis. J Eur Acad Dermatol Venereol [Internet] 2008;22:370–1.
[25] Wahn U, Bos JD, Goodfield M, *et al*. Efficacy and safety of pimecrolimus cream in the long-term management of atopic dermatitis in children. Pediatrics 2002;110(1 Pt 1):e2.
[26] Meurer M, Fartasch M, Albrecht G, *et al*. Long-term efficacy and safety of pimecrolimus cream 1% in adults with moderate atopic dermatitis. Dermatology 2004;208:365–72.
[27] Rajka G, Langeland T. Grading of the severity of atopic dermatitis. Acta Derm Venereol Suppl (Stockh) 1989;144:13–4.
[28] Eichenfield LF, Lucky AW, Langley RGB, *et al*. Use of pimecrolimus cream 1% (Elidel) in the treatment of atopic dermatitis in infants and children: the effects of ethnic origin and baseline disease severity on treatment outcome. Int J Dermatol 2005;44:70–5.
[29] Grassberger M, Steinhoff M, Schneider D, *et al*. Pimecrolimus – an anti-inflammatory drug targeting the skin. Exp Dermatol 2004;13: 721–730.
[30] Ashcroft DM, Dimmock P, Garside R, *et al*. Efficacy and tolerability of topical pimecrolimus and tacrolimus in the treatment of atopic dermatitis: meta-analysis of randomised controlled trials. BMJ 2005;330:516.
[31] El-Batawy MMY, Bosseila MAW, Mashaly HM, *et al*. Topical calcineurin inhibitors in atopic dermatitis: a systematic review and meta-analysis. J Dermatol Sci 2009;54:76–87.
[32] Werfel T. Topical use of pimecrolimus in atopic dermatitis: update on the safety and efficacy. JDDG 2009;7:739–42.