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SYSTEMATIC REVIEW

Efficacy and Safety of Topical Roflumilast for the Treatment of Psoriasis: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

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Abstract

Background and Objective Plaque psoriasis is commonly treated topically with glucocorticoids and vitamin D derivatives. However, potential side effects such as skin atrophy underscore the need for safe and effective alternative topical therapies. Recently, the US Food and Drug Administration (FDA) and Health Canada approved roflumilast 0.3% cream as an option for treating this disease. A systematic review and meta-analysis of randomized controlled trials (RCTs) was conducted to assess the efficacy and safety of topical roflumilast 0.3% compared with vehicle for plaque psoriasis.

Methods PubMed, Embase, ClinicalTrials.gov, and Cochrane databases were searched from inception to 1 May 2024, assessing the outcomes of Investigator's Global Assessment (IGA) or body-IGA success (clear or almost clear status plus an at least 2-grade improvement from baseline), Psoriasis Area and Severity Index (PASI)-50, PASI-75, PASI-90, intertriginous-IGA success (clear or almost clear status on the intertriginous-IGA plus an at least 2-grade improvement from baseline), and adverse events (AEs). Statistical analysis was performed using Review Manager, R software, and RStudio. Heterogeneity was determined using the Cochran Q test and I^2 statistics.

Results Four RCTs were included, comprising a total of 1403 patients, of whom 885 (63.1%) received topical roflumilast 0.3% and 518 (36.9%) received vehicle. At week 8, the achievement of IGA or body-IGA success was significantly higher among those treated with topical roflumilast than in the vehicle group [relative risk (RR) 5.07; 95% confidence interval (CI) 3.55–7.23; $p < 0.01$]. Similar findings were observed at week 8 for PASI-50 (RR 2.73; 95% CI 2.27–3.29; $p < 0.01$), PASI-75 (RR 4.48; 95% CI 2.26–8.89; $p < 0.01$), and PASI-90 (RR 5.61; 95% CI 2.57–12.25; $p < 0.01$). Corresponding outcomes were found at weeks 2, 4, and 6. Additionally, a higher percentage of patients treated with topical roflumilast 0.3% once daily achieved intertriginous-IGA success, compared with those receiving vehicle, at week 8 (71.9% versus 20.5%; RR 3.32; 95% CI 2.11–5.22; $p < 0.01$), with similar findings at weeks 2, 4, and 6. While a significant difference was observed in the overall incidence of AEs between the topical roflumilast and vehicle groups, there was no difference in treatment-related AEs, serious AEs, or AEs leading to study discontinuation.

Conclusion These findings support the superiority of topical roflumilast 0.3% over vehicle and suggest its use as a valuable asset for the treatment of plaque psoriasis.

Protocol registration International Prospective Register of Systematic Reviews (PROSPERO), CRD42023456494.

1 Introduction

Psoriasis is a chronic, immune-mediated disease that affects approximately 125 million people worldwide [1], with a prevalence of 1.5–5% in most developed countries [2]. This condition can impact the skin, nails, and joints and is associated with various comorbidities such as cardiovascular disorders, diabetes, metabolic syndrome, and depression [3]. The presentation of psoriasis on the skin is highly heterogeneous, with numerous phenotypes. However, chronic plaque psoriasis is the most prevalent form, accounting for over 80% of cases [1, 4, 5].

Topical treatments remain a fundamental component in the management of psoriasis, often chosen as initial therapies for individuals with mild-to-moderate disease, but also commonly employed in association with systemic treatments

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Key Points

This systematic review and meta-analysis revealed that topical roflumilast 0.3%, compared with vehicle, led to a higher achievement of clinical milestones, with a favorable safety profile.

These findings suggest that topical roflumilast 0.3% could represent an alternative option to address an unmet gap in the topical treatment of plaque psoriasis.

or phototherapy [6, 7]. Currently, available topical therapies for plaque psoriasis include corticosteroids, vitamin D derivatives, calcineurin inhibitors, retinoids, coal tar, salicylic acid, and dithranol, with corticosteroids and vitamin D derivatives, either alone or in combination, being the most frequently prescribed options [7–9]. High-potency topical glucocorticoids are effective in the management of chronic plaque psoriasis [9], but are associated with several adverse effects, such as skin atrophy and striae [10]. Vitamin D analogs are less effective and more likely to cause local irritation [11]. This highlights the necessity of exploring alternative topical treatments, such as roflumilast 0.3%, approved by the US Food and Drug Administration (FDA) in 2022 and by Health Canada in 2023.

Roflumilast 0.3% is a highly potent phosphodiesterase-4 (PDE-4) inhibitor [12]. PDE-4 is an enzyme involved in mediating inflammatory responses, holding a crucial role in the pathogenesis of psoriasis [13]. A few clinical trials evaluating the efficacy of topical roflumilast 0.3% in treating psoriasis, compared with vehicle, have been conducted [14–16]. These trials have shown positive results in the roflumilast group with a favorable safety profile. Herein, a systematic review and meta-analysis of randomized controlled trials (RCTs) were performed to analyze the efficacy and safety of topical roflumilast 0.3% compared with vehicle in patients with plaque psoriasis, aggregating data from a larger cohort and consequently enhancing the statistical power and confidence in the reported outcomes.

2 Materials and Methods

The systematic review and meta-analysis were conducted following the recommendations of the Cochrane Collaboration and the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement guidelines [17]. The pre-specified research protocol was registered with the International Prospective Register of Systematic Reviews under the protocol number CRD42023456494 on 2 September 2023.

2.1 Eligibility Criteria

Studies were included if they met the following criteria: They (1) were RCTs, (2) compared topical roflumilast 0.3% with vehicle, (3) involved patients diagnosed with plaque psoriasis, and (4) reported at least one outcome of interest. The exclusion criteria included: (1) non-randomized studies, (2) studies with overlapping populations, (3) studies not reporting outcomes of interest, (4) abstracts, (5) post hoc analyses, and (6) studies that included patients receiving concomitant systemic therapies, other topical anti-psoriasis medications, or phototherapy. There were no restrictions regarding the age of the participants, the anatomical location of plaque psoriasis, or the language of the publications.

2.2 Search Strategy and Data Extraction

PubMed, Embase, ClinicalTrials.gov, and Cochrane Library databases were searched systematically from inception to 1 May 2024 for studies that met the selection criteria. The following search terms were included: "roflumilast," "Zoryve," "roflumilast cream," "topical roflumilast," "ARQ-151," "ARQ-154," "psoriasis," and "plaque psoriasis." Additionally, a manual search of references from the incorporated studies and previous reviews was conducted to identify any further studies. The search and the data extraction were conducted by two different authors (RMS and RCC), and disagreements among authors were resolved by consensus.

2.3 Endpoints

The primary efficacy outcome of interest was the percentage of patients achieving Investigator's Global Assessment (IGA) or body-IGA success, defined as clear or almost clear status plus an at least 2-grade improvement from baseline, at week 8. For body-IGA, the scale measures the extent of psoriasis involvement, encompassing all affected areas except the scalp, palms, and soles. The secondary efficacy endpoints were: (1) IGA or body-IGA success at weeks 2, 4, and 6; (2) improvement in Psoriasis Area and Severity Index (PASI) of at least 50% (PASI-50) at weeks 2, 4, 6, and 8; (3) improvement in PASI of at least 75% (PASI-75) at weeks 2, 4, 6, and 8; (4) improvement in PASI of at least 90% (PASI-90) at weeks 2, 4, 6, and 8; and (5) intertriginous-IGA success (achievement of clear or almost clear on the intertriginous-IGA plus an at least 2-grade improvement

from baseline) at weeks 2, 4, 6, and 8. The safety outcomes assessed included: (1) overall adverse events (AEs), (2) treatment-related AEs, (3) serious AEs, and (4) AEs leading to study discontinuation.

2.4 Quality Assessment

Quality assessment of individual studies was analyzed with the Risk of Bias 2 (RoB2) tool [18], as recommended by the Cochrane Collaboration for assessing bias in randomized trials. This tool classifies each study into categories of high risk, some concerns, or low risk of bias. Two independent authors (IPC and RCC) conducted this assessment, and discrepancies were resolved through consensus after discussing the reasons for divergence.

2.5 Statistical Analysis

Risk ratios (RRs) with 95% confidence intervals (CIs) were used to compare treatment effects for binary endpoints. Heterogeneity was examined with Cochran Q test and I^2 statistics, with $p < 0.10$ and $I^2 > 25\%$ indicative of high statistical heterogeneity. The DerSimonian random effects model was used. Sensitivity analysis was performed using the leave-one-out strategy. The statistical analysis was conducted using Review Manager 5.4 (Nordic Cochrane Center, The Cochrane Collaboration, Denmark), R software, and RStudio version 2022.12.0þ353 (R Core Team, Austria).

3 Results

3.1 Study Selection and Baseline Characteristics

The systematic search yielded 330 results. After removing 115 duplicates and excluding 205 studies based on title and abstract screening, 10 articles remained for full-text assessment according to the eligibility criteria. Ultimately, three reports corresponding to four RCTs were included (Fig. 1).

Study characteristics are presented in Table 1. A total of 1403 patients were included, of whom 885 (63.1%) were assigned to the topical roflumilast 0.3% group, while the remaining 518 (36.9%) participants received vehicle (placebo). In all studies, topical roflumilast 0.3% or vehicle was applied once daily. In all, 576 patients (41.1%) were females, and the mean age ranged from 45.0 to 55.5 years. In the intervention group, the mean baseline PASI score ranged from 6.3 to 7.7, and in the control group, it ranged from 6.8 to 7.6. Most trials utilized a cream vehicle [14, 15], except for Kircik et al. [16], which employed a foam vehicle.

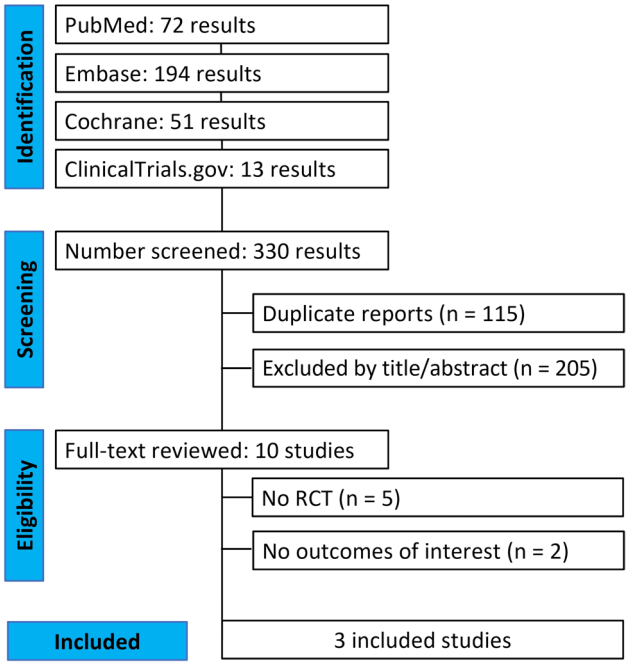

Fig. 1 PRISMA flow diagram of study screening and selection

3.2 Efficacy Endpoints

3.2.1 Primary Endpoint

At week 8, a significantly higher proportion of patients attained IGA or body-IGA success with topical roflumilast 0.3% once daily compared with vehicle (39% versus 7.4%; RR 5.07; 95% CI 3.55–7.23; $p < 0.01$; $I^2 = 11\%$; Fig. 2).

3.2.2 Secondary Endpoints

3.2.2.1 IGA Similar to the findings from week 8, there was a significantly higher rate of IGA or body-IGA success in the roflumilast group compared with vehicle at week 2 (5.4% versus 1.6%; RR 2.68; 95% CI 1.25–5.77; $p = 0.01$; $I^2 = 0\%$), week 4 (19% versus 4.5%; RR 3.73; 95% CI 2.28–6.09; $p < 0.01$; $I^2 = 17\%$), and week 6 (28.4% versus 6.2%; RR 4.37; 95% CI 2.83–6.73; $p < 0.01$; $I^2 = 4\%$) [electronic supplementary material (ESM) Fig. 1].

3.2.2.2 PASI-50 At week 8, a higher percentage of patients treated with topical roflumilast 0.3% once daily achieved PASI-50 compared with those receiving vehicle (69.7% versus 25%; RR 2.73; 95% CI 2.27–3.29; $p < 0.01$; $I^2 = 0\%$; Fig. 3a). Similar findings were observed at week 2 (26.5% versus 8.3%; RR 2.91; 95% CI 1.89–4.46; $p < 0.01$; $I^2 = 27\%$), week 4 (50.4% versus 18.4%; RR 2.62; 95% CI 1.97–3.50; $p < 0.01$; $I^2 = 36\%$), and week 6 (63.5% versus 18.2%; RR 3.41; 95% CI 2.72–4.28; $p < 0.01$; $I^2 = 0$; ESM Fig. 2).

Table 1 Baseline characteristics of included studies [14–16]

Study name or author, year	Country	Eligibility criteria	Treatment duration	Vehicle	Patients (*n*) TR/V	Female (%) TR/V	Mean age (years) TR/V	BSA (%) TR/V	PASI or b-PASI TR/V
DERMIS-1, 2022 [15]	USA, Canada	Patients aged ≥ 2 years; clinical diagnosis of plaque psoriasis ≥ 6 months (≥ 3 months for children); stable disease ≥ 4 weeks; good health; BSA ≥ 20%, not including scalp, palms, or soles; IGA ≥ 2; PASI ≥ 2	8 weeks	Cream	286/153	33.9/37.3	47.6/48.7	6.3/7.4	6.3/6.8
DERMIS-2, 2022 [15]	USA, Canada	Patients aged ≥ 2 years; clinical diagnosis of plaque psoriasis ≥ 6 months (≥ 3 months for children); stable disease ≥ 4 weeks; good health; BSA ≥ 20%, not including scalp, palms, or soles; IGA ≥ 2; PASI ≥ 2	8 weeks	Cream	290/152	39.3/34.2	46.9/47.1	7.1/7.7	6.5/7.0
Kircik, 2023 [16]	USA, Canada, Australia, Bulgaria	Patients aged ≥ 12 years; plaque psoriasis ≥ 6 months; s-IGA ≥ 3; scalp psoriasis ≥ 10% of the total scalp; PSSI ≥ 6; b-IGA ≥ 2; b-PASI ≥ 2; BSA ≤ 25%	8 weeks	Foam	200/104	52.0/54.8	45.2/45.0	8.0/7.6	7.2/6.8
Lebwohl, 2020 [14]	USA, Canada	Patients aged ≥ 18 years; plaque psoriasis ≥ 6 months; IGA ≥ 2; BSA 2–20%; PASI ≥ 2	12 weeks	Cream	109/109	48.6/38.5	51.7/55.5	6.3/6.4	7.7/7.6

TR topical roflumilast 0.3%, *V* vehicle, *PASI* Psoriasis Area and Severity Index, *b-PASI* a modified version of PASI excluding the scalp, palms, and soles, *BSA* body surface area, *IGA* Investigator's Global Assessment, *s-IGA* scalp-IGA, *PSSI* Psoriasis Scalp Severity Index, *b-IGA* body-IGA

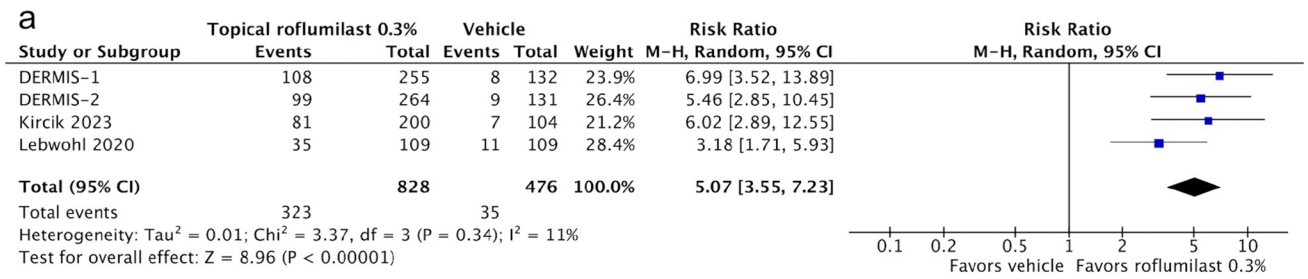

Fig. 2 Forest plot depicting the achievement of the primary outcome: IGA or body-IGA success at week 8. *CI* confidence interval, *df* degrees of freedom, *M–H* Mantel–Haenszel, *IGA* Investigator's Global Assessment

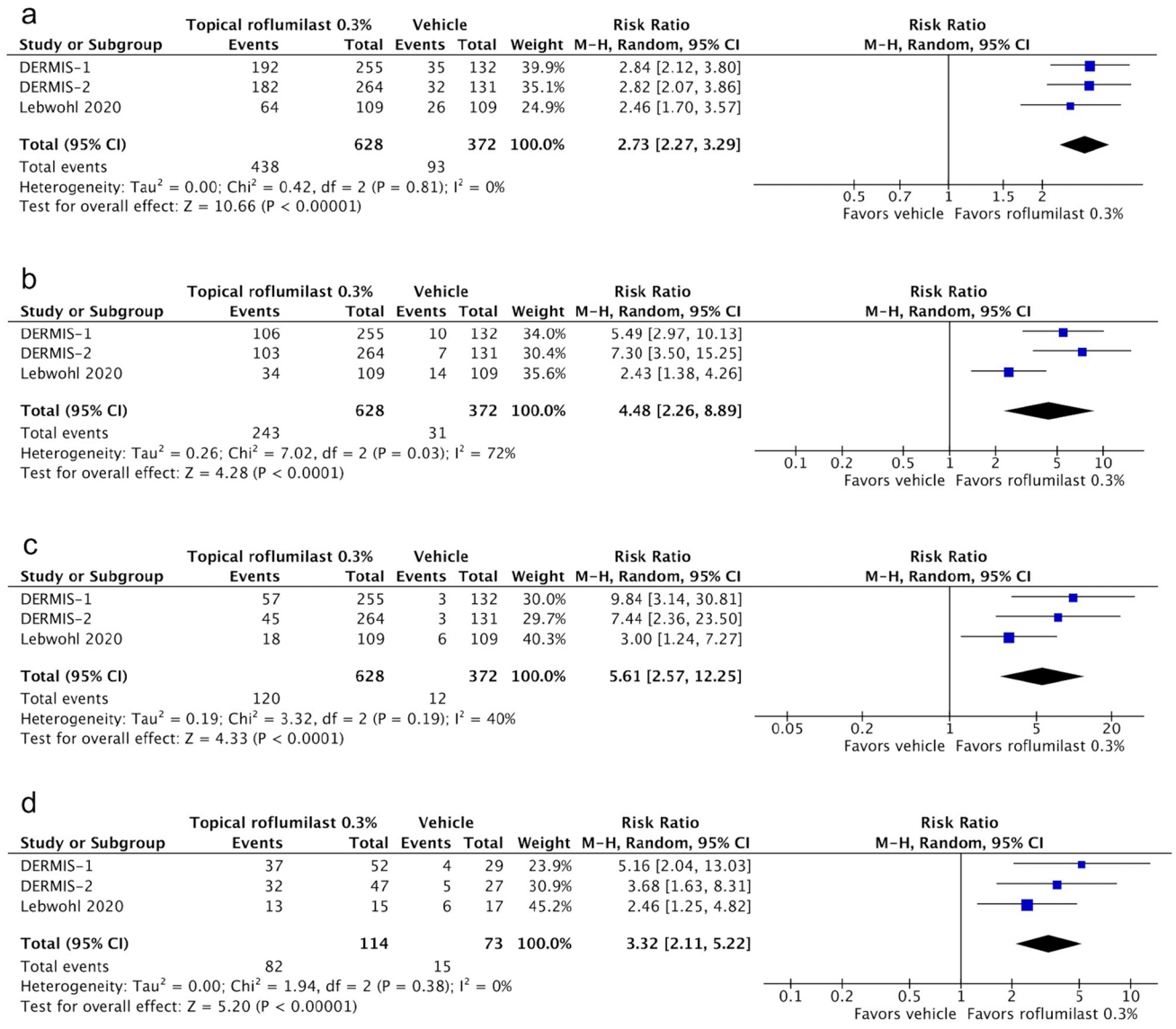

Fig. 3 Forest plot depicting the achievement of efficacy outcomes at week 8. **a** PASI-50; **b** PASI-75; **c** PASI-90; and **d** intertriginous-IGA success. *CI* confidence interval, *df* degrees of freedom, *M–H* Mantel–Haenszel, *PASI* Psoriasis Area and Severity Index

3.2.2.3 PASI-75 At week 8, patients treated with topical roflumilast 0.3% once daily achieved a higher rate of PASI-75 compared with vehicle (38.7% versus 8.3%; RR 4.48; 95% CI 2.26–8.89; $p < 0.01$; $I^2 = 72\%$; Fig.3b). Similar results were observed at week 2 (5.1% versus 1.3%; RR 3.45; 95% CI 1.33–8.96; $p = 0.01$; $I^2 = 0\%$), week 4 (17.9% versus 5.3%; RR 3.33; 95% CI 1.10–10.04; $p = 0.03$; $I^2 = 79\%$), and week 6 (28.9% versus 5.3%; RR 5.33; 95% CI 2.31–12.27; $p < 0.01$; $I^2 = 69\%$; ESM Fig. 3).

3.2.2.4 PASI-90 At week 8, patients in the topical roflumilast 0.3% group achieved PASI-90 at a higher rate compared with those in the vehicle group (19.1% versus 3.2%; RR 5.61; 95% CI 2.57–12.25; $p < 0.01$; $I^2 = 40\%$; Fig. 3c). Similarly, positive findings were observed at week 4 (5.8% versus 0.8%; RR 5.42; 95% CI 1.74–16.87; $p < 0.01$; $I^2 = 0\%$) and week 6 (11.5% versus 1.3%; RR 7.20; 95% CI 3.01–17.25; $p < 0.01$; $I^2 = 0\%$). Nevertheless, data on PASI-90 at week 2 were only available in two trials (DERMIS-1 and DERMIS-2) [15], and no significant difference was observed (1.5% versus 0.3%; RR 3.03; 95% CI 0.54–17.05; $p = 0.21$; $I^2 = 0\%$; ESM Fig. 4).

3.2.2.5 Intertriginous-IGA Success At week 8, a significantly higher percentage of patients treated with topical roflumilast 0.3% once daily achieved intertriginous-IGA success compared with those receiving vehicle (71.9% versus 20.5%; RR 3.32; 95% CI 2.11–5.22; $p < 0.01$; $I^2 = 0\%$; Fig. 3d). Similar findings were observed at earlier time points: at week 2 (34.4% versus 9.0%; RR 3.54; 95% CI 1.68–7.46; $p < 0.01$; $I^2 = 0\%$), week 4 (47.0% versus 21.6%; RR 2.07; 95% CI 1.28–3.34; $p < 0.01$; $I^2 = 0\%$), and week 6 (59.3% versus 20.5%; RR 2.86; 95% CI 1.79–4.59; $p < 0.01$; $I^2 = 0\%$; ESM Fig. 5).

3.3 Safety Endpoints

The analysis revealed a higher proportion of overall AEs in patients treated with topical roflumilast 0.3% once daily compared with the vehicle group (26.6% versus 22.5%; RR 1.23; 95% CI 1.01–1.49; $p = 0.04$, $I^2 = 0\%$; Fig. 4a). However, there was no statistically significant difference between groups in terms of treatment-related AEs (4.3% versus 5.2%; RR 0.84; 95% CI 0.52–1.37; $p = 0.49$, $I^2 = 0\%$; Fig. 4b), serious AEs (0.5% versus 0.8%; RR 0.65; 95% CI 0.17–2.50; $p = 0.53$, $I^2 = 0\%$; Fig. 4c), and AEs leading to study discontinuation (1.4% versus 1.7%; RR 0.81; 95% CI 0.32–2.07; $p = 0.66$, $I^2 = 0\%$; Fig. 4d). Some of the most common AEs in the topical roflumilast group were diarrhea, hypertension, upper respiratory tract infection, and headache. All reported AEs can be found in ESM Table 1.

3.4 Sensitivity Analysis

Given the high heterogeneity found for some outcomes (PASI-50 at weeks 2 and 4; PASI-75 at weeks 4, 6, and 8; and PASI-90 at week 8), a leave-one-out sensitivity analysis was performed. Removal of Lebwohl et al. [14] reduced all $I^2 > 25\%$ to 0, and the results continued to favor topical roflumilast 0.3% over vehicle (ESM Fig. 6).

3.5 Quality Assessment

The risk of bias assessment for each RCT included in this meta-analysis was conducted using the RoB-2 tool, and all studies were categorized as low risk of bias (Fig. 5).

4 Discussion

This systematic review and meta-analysis of four RCTs, including 1403 patients, compared topical roflumilast 0.3% with vehicle for plaque psoriasis. The main findings were: (1) topical roflumilast 0.3% significantly increased the proportion of patients achieving IGA or body-IGA success, PASI-50, PASI-75, PASI-90, and intertriginous-IGA success, compared with those receiving vehicle and (2) a significantly higher incidence of overall AEs was found in patients treated with topical roflumilast 0.3% compared with vehicle, with no difference between groups in terms of treatment-related AEs, serious AEs, and AEs leading to study discontinuation.

Roflumilast is a selective and highly potent inhibitor of PDE-4 [19]. PDE-4 is an intracellular enzyme that degrades cyclic adenosine monophosphate (cAMP) to adenosine monophosphate (AMP) [12, 13, 20, 21]. Decreased intracellular levels of cAMP up-regulate the expression of pro-inflammatory mediators such as tumor necrosis factor α, IFN-γ, IL-2, IL-12, and IL-23 [7, 22, 23]. Since individuals with psoriasis exhibit increased expression of PDE-4 compared with healthy controls [7], inhibiting PDE-4 with roflumilast can be effective in modulating the production of anti-inflammatory cytokines and suppressing T helper, Th17, and type 1 interferon pathways [22, 24].

Roflumilast cream 0.3% (Zoryve®) has been approved by the US FDA for the topical treatment of plaque psoriasis in patients aged 6 years and older [25], and by Health Canada for patients aged 12 years and older [26]. It is recommended to be applied once daily to affected skin, including intertriginous areas, and is intended for topical use only, not for ophthalmic, oral, or intravaginal use [25, 26]. Although areas such as the face and genitals are not directly mentioned in the prospectus, roflumilast 0.3% cream has demonstrated efficacy and tolerability in these areas [27]. This medication is contraindicated in patients

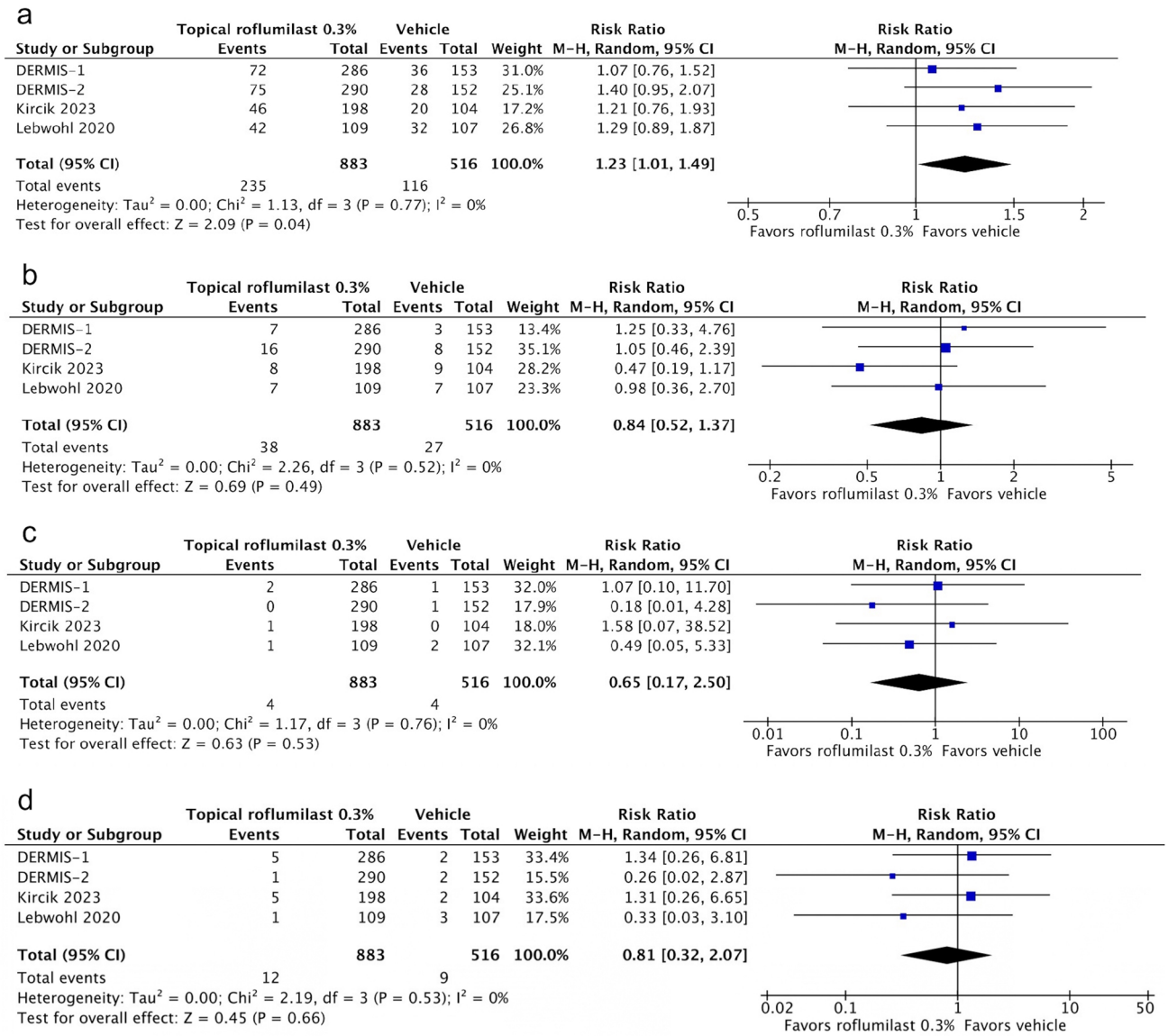

Fig. 4 **a** Forest plot of overall AEs; **b** forest plot of treatment-related AEs; **c** forest plot of serious AEs; and **d** forest plot of AEs leading to study discontinuation. *CI* confidence interval, *df* degrees of freedom, *M–H* Mantel–Haenszel, *AE* adverse event

with moderate to severe liver impairment (Child−Pugh B or C) [25, 26]. There is no reported restriction on the maximum body area for application, except for in women who are breastfeeding, who are advised to use the smallest area of skin possible for the shortest duration necessary and to avoid applying the cream directly to the nipple or areola [25, 26]. There are insufficient data available on the use of roflumilast 0.3% cream in pregnant women [25, 26]. Additionally, the roflumilast 0.3% foam formulation (Zoryve®) has been approved by the US FDA only for the treatment of seborrheic dermatitis in patients aged 9 years and older [28].

In this meta-analysis, superior results for all efficacy outcomes at week 8 (achievement of IGA or body-IGA success, PASI-50, PASI-75, PASI-90, and intertriginous-IGA) were observed in the topical roflumilast group compared with vehicle. Statistically significant differences were observed as early as week 2 in the pooled data for IGA or body-IGA success, as well as for PASI-50, PASI-75, and intertriginous-IGA. By week 4, more than half of the patients receiving roflumilast had achieved PASI-50. Emphasizing the rapid onset of response to roflumilast is essential, as early treatment response is known to promote adherence and strengthen patients' commitment to ongoing therapy [29].

This meta-analysis revealed positive results for intertriginous affection treated with topical roflumilast 0.3% compared with vehicle, demonstrating its effectiveness in areas traditionally challenging to treat. Although individual

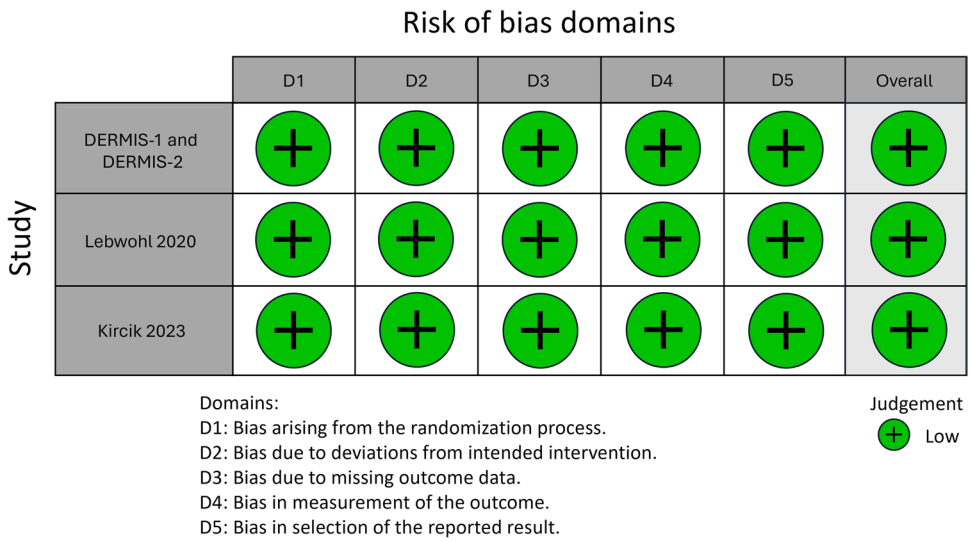

Fig. 5 Risk of bias assessment of included studies according to RoB2 tool

studies such as DERMIS-1 [15] and Lebwohl et al. [14] did not show differences in the achievement of intertriginous-IGA success at weeks 2 and 4, pooled data consistently demonstrated favorable results for roflumilast at all evaluated time points. The scalp is another challenging location. Kircik et al. [16] reported significantly improved rates of scalp-IGA success in patients treated with roflumilast 0.3% foam compared with those receiving vehicle at weeks 2 (17.4% versus 3.1%), 4 (41.3% versus 5.6%), and 8 (59.1% versus 11.4%). Given that involvement in these special body zones is well known to be associated with a lower quality of life and greater resistance to topical treatments [30, 31], it is important to highlight roflumilast's potential as an effective therapy for these challenging-to-treat areas, addressing an unmet need in the topical management of psoriasis.

In the individual studies, there was no significant difference in overall AEs. However, a significant difference was observed in the pooled data, with more AEs reported among patients treated with roflumilast compared with those receiving vehicle, although it does not appear to be clinically relevant. No differences were found in AEs related to treatment, serious AEs, and AEs that led to discontinuation of the study, indicating favorable safety data for roflumilast. Diarrhea, ranging from 1.5% in Kircik et al. [16] to 3.5% in DERMIS-1 [15], was the most frequently associated AE. Application site symptoms were infrequently reported, indicating that roflumilast was well tolerated in both cream and foam formulations. Both good tolerability and a swift response are important factors for better medication adherence, which, in turn, improves outcomes in patients with psoriasis receiving topical therapy [29].

Consequently, topical roflumilast could be an important tool in the treatment algorithm for psoriasis, serving as a first-line option for mild-to-moderate plaque psoriasis and as a complementary treatment in conjunction with systemic therapies for more severe cases, especially when sensitive areas such as the intertriginous zones, face, and genitals are involved. This novel agent could streamline treatment regimens by reducing the need for multiple treatments to address different body areas, minimizing the necessity to switch to weaker steroids or calcineurin inhibitors for sensitive regions, and eliminating the need to cycle off steroids to prevent atrophy [32].

Cost remains a significant limitation for the widespread use of topical roflumilast. In the USA, Zoryve® 0.3% cream costs approximately US$900 for a 60-g supply (price without discounts or insurance) and about CAN$275 in Canada [33]. Moreover, another significant barrier to the broader adoption of topical roflumilast is the uncertainty surrounding the timeline for its evaluation and potential approval by the European Medicines Agency (EMA). The unavailability of this steroid-free topical treatment in Europe and other parts of the globe exacerbates inequality in access to a therapeutic option that could fulfill an unmet need in the topical treatment of psoriasis.

This meta-analysis has certain limitations. Firstly, including only a small number of studies with patients from a limited number of countries may affect the generalization of the results. Secondly, high heterogeneity was observed in some of the outcomes. Notably, a leave-one-out analysis showed that excluding Lebwohl et al. [14] reduced all I^2 values greater than 25% to 0, while the results still favored topical roflumilast. This could be attributed to differences in study methodologies. For instance, the study by Lebwohl et al. [14] is a phase 2b trial that included only adults, whereas DERMIS-1 and DERMIS-2 [15] are two identical phase 3 trials that enrolled patients aged 2 years or older. Thirdly, there was a slight variation in one of the efficacy measures among the studies: three trials reported IGA results, while

Kircik et al. [16] presented body-IGA outcomes, a similar scale that excludes the scalp, palms, and soles. These scales can be considered sufficiently comparable for analyzing results, and the low heterogeneity observed in the pooled analysis for outcomes involving these scales supports this hypothesis. Finally, long-term efficacy and safety of topical roflumilast could not be assessed, as outcomes were evaluated for a maximum of 8 weeks in three trials [15, 16] and 12 weeks in one study [14]. However, an open-label single-arm study evaluating the long-term safety of roflumilast 0.3% cream in patients with chronic plaque psoriasis demonstrated sustained efficacy. Of the patients who achieved an IGA of clear or almost clear, 50% maintained this status for more than 10 months. The study also reported low rates of treatment-related AEs (2.7%), with no new safety signals [34].

Future studies that compare topical roflumilast 0.3% with existing topical therapies are crucial to ascertain its role in the topical management of plaque psoriasis. Furthermore, real-world data will be invaluable in understanding its effectiveness and safety profile beyond the controlled setting of clinical trials. Additionally, clinical trials focused on evaluating the efficacy of this treatment in non-plaque psoriasis phenotypes would be particularly interesting.

5 Conclusion

In patients with plaque psoriasis, topical roflumilast 0.3% led to higher achievement of clinical milestones compared with vehicle, including increased rates of IGA or body-IGA success, intertriginous-IGA success, and significant improvements in PASI, with a favorable safety profile. These findings suggest it could emerge as a valuable asset for the topical management of psoriasis.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s40261-024-01368-w.

Declarations

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Conflict of Interest Rafaela de Moraes-Souza, Regina Chahine Chater, Izabela Pera Calvi, Yasmin Mesquita, Rubiana Sarto, Izadora Lapenda, Lívia Figueiredo Pereira, Luana Moury, and Pedro Herranz-Pinto have no conflicts of interest that are directly relevant to the content of this article.

Ethical Approval Not applicable.

Informed Consent Not applicable.

Consent for Publication Not applicable.

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