Dermatology Practical & Conceptual

Comparative Efficacy and Safety of Tapinarof 0.5% and 1% Cream Regimens for Atopic Dermatitis: A Network Meta-Analysis

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ABSTRACT

Introduction: Atopic dermatitis (AD) is a chronic inflammatory skin disorder affecting quality of life. Tapinarof, a novel aryl hydrocarbon receptor (AhR) modulator, is a promising nonsteroidal treatment-but, optimal dosing regimens remain unclear.

Objectives: This network meta-analysis (NMA) compared the efficacy and safety of tapinarof 0.5%, 1% and 2% creams applied once or twice daily versus placebo in AD.

Methods: A systematic search of MEDLINE/PubMed, CENTRAL, Web of Science, ProQuest, and Scopus was conducted from inception to 31 March 2025. Randomized controlled trials (RCTs) evaluating tapinarof versus placebo were included. The frequentist NMA was conducted using STATA 18 software, , with efficacy measured through ≥75% improvement in Eczema Area and Severity Index (EASI-75) and Investigator's Global Assessment (IGA) response. Surface under the cumulative ranking (SUCRA) probabilities were used to rank treatments.

Results: Five RCTs (1,506 patients) were included. Tapinarof 1% twice daily showed the highest efficacy for EASI-75 (odds ratio (OR)=1.89, 95% confidence interval (CI): 1.17–2.62, P<0.001) and IGA response (OR=2.40, 95% CI: 1.30–3.95, P=0.002), ranking as the most effective regimen (SUCRA: 70.3%). Tapinarof 1% once daily and 0.5% twice daily showed moderate efficacy, while tapinarof 0.5% once daily and placebo were the least effective. Heterogeneity was low for EASI-75 (I^2=1.4%) but moderate for IGA response (I^2=67.14%). Adverse events were generally mild, with folliculitis and contact dermatitis being the most reported.

Conclusions: Tapinarof 1% twice daily is the most effective and well-tolerated regimen for AD, providing critical insights for clinical decision-making, although further head-to-head trials are needed.

Introduction

Atopic dermatitis (AD) is a common, chronic, itchy inflammatory skin disorder that is associated with erythema and recurrent flares and greatly impairs the quality of life of the patient population. While current treatment options, including topical corticosteroids, calcineurin inhibitors, and newer non-steroidal agents, can be effective, their prolonged use is often associated with adverse effects and tachyphylaxis [1]. In this context, tapinarof, a novel topical aryl hydrocarbon receptor (AhR) modulator, has emerged as a promising non-steroidal alternative for the treatment of AD. Clinical trials have evaluated tapinarof 0.5% and 1% topical cream applied once or twice daily, demonstrating favorable efficacy and tolerability. However, comparative data on the optimal concentration and dosing frequency remain limited [2].

To address this gap in comparative evidence, we conducted a network meta-analysis to determine the most effective and well-tolerated dosing regimen of tapinarof for AD.

Methods

This network meta-analysis was conducted in accordance with Cochrane methodology and reported following the PRISMA-NMA guidelines, with analyses performed using STATA 18 software [3].

The Research Question

What is the comparative effectiveness of tapinarof 0.5%, 1%, or 2% cream applied once or twice daily versus placebo in patients with atopic dermatitis, assessed using a network meta-analysis?

Research Aims

To evaluate the efficacy and safety of tapinarof 0.5% 1%, or 2% cream, applied once or twice daily, in comparison to placebo for the treatment of atopic dermatitis.

Research objectives: This study aimed to determine the most effective and well-tolerated dosing regimen for tapinarof in AD. The specific objectives were:

1. To compare the efficacy of different tapinarof dosing regimens (0.5 %, 1%, and 2% once daily or twice daily) versus placebo to improve atopic dermatitis severity.
2. To assess tapinarof's efficacy in reducing pruritus.
3. To use a network meta-analysis to rank several different treatment regimens according to their relative effect.

Types of Studies

This meta-analysis included randomized controlled studies that were published in English from 2012 to 29 March 2025.

Participants

- Patients were diagnosed with atopic dermatitis (any age group).
- No restrictions on sex, ethnicity, or disease severity at baseline.

Interventions

This meta-analysis included randomized clinical trials that compared:

- Intervention: Tapinarof 0.5%, 1%, or 2% cream, applied once or twice daily.
- Control: placebo applied once or twice daily.

We excluded animal studies, retrospective studies, conference abstracts, duplicate records, case reports, reviews, commentaries, case series, and studies that lacked a control group.

Search Strategy

Electronic Searches

The following electronic databases were searched for eligible studies: MEDLINE/PubMed, Cochrane Central Register of Controlled Trials (CENTRAL), Web of Science, ProQuest, and Scopus. The search was set for all articles published in English from 2012 till 29 March 2025.

The following search terms were used: ((“Tapinarof OR GSK2894512 OR ARQ-151”AND cream AND 1% AND 0.5% AND 2%) AND ((atopic AND dermatitis) OR (atopic AND eczema))). Table S1 summarizes the used search terms for each database and the count of search results.

Other Resources

Reviewer 1 searched within the reference lists of obtained articles for other potentially relevant studies that were not retrieved by electronic search.

Selection of Studies

Reviewer 1 screened the retrieved reports for eligibility through title and abstract and full-text screening. Reviewer 2 checked the retrieved studies, and discrepancies were solved through discussion with a third reviewer.

Data Extraction

Reviewer 1 carried out data extraction from the included studies using a standardized data sheet which included: i) the study's characteristics (the author, year, the country, study design); ii) patients' characteristics (age at the time of treatment, sex, sample size); iii) intervention and control groups' details (active intervention, comparison arm, treatment period, follow-up duration, and adverse effects); iv)

the outcomes: proportion of subjects with >75% improvement over baseline in EASI and proportion of subjects who achieved an IGA of 0 or 1 with a minimum 2-point improvement over baseline in IGA. Reviewer 2 checked the collected data for consistency and clarity. Any disagreements were settled by refereeing the third reviewer.

Measured Outcomes (Event and Total)

Proportion of subjects with >75% improvement over baseline in EASI: The percentage of study participants who achieved at least a 75% reduction in their baseline Eczema Area and Severity Index (EASI) score after treatment.

Proportion of subjects who achieved an IGA of 0 or 1 and a minimum 2-point improvement over baseline in IGA. Investigator's Global Assessment (IGA) is a clinician-scored five-point scale that reflects the severity of AD (0 = Clear - no signs of AD, 1 = Almost clear - minimal signs of AD, 2 = Mild AD, 3 = Moderate AD, 4 = Severe AD). This metric is the percentage of participants showing an IGA score of 0 (clear) or 1 (almost clear) and an improvement of at least 2 points from baseline.

Assessment of the Risk of Bias in Included Studies

The risk of bias (ROB) in the included studies was assessed using the National Institute for Health and Care Excellence (NICE) checklists for randomized controlled clinical trials (RCTs) [4].

Data Synthesis

Initially, 219 records were retrieved from electronic database searches. After removing duplicates and excluded studies, 28 studies were finally eligible, of which five RCTs [5-9] (1506 patients) were included (Table S2). Concerning the 23 excluded clinical trials from the MA, they were irrelevant (N=6), duplicate (N=7), or a conference abstract (N=10); these studies are mentioned in Figure 1.

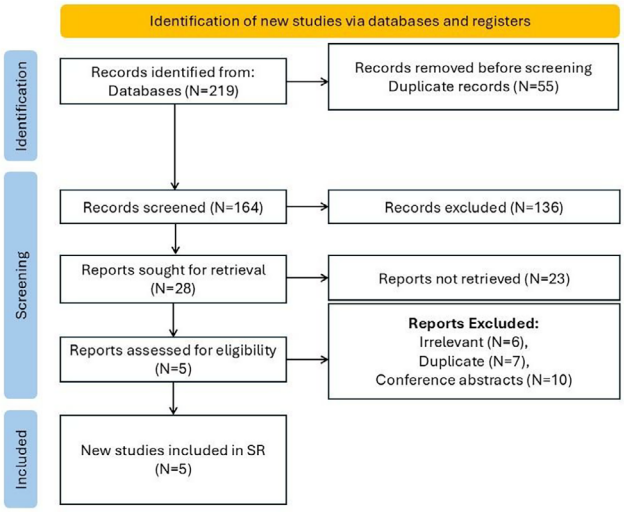

Figure 1. PRISMA flow diagram.

Statistical Analysis

The NMA was conducted using STATA 18, employing a frequentist approach. A fixed-effect model was applied due to the low heterogeneity observed between studies (Df=0 in most comparisons), while a random-effects model was used when warranted by the I^2 value. Treatment effects were estimated through multivariate meta-analysis using the mvmeta command, and indirect comparisons were performed within the network framework. We assessed agreement between direct and indirect estimates using a design-by-treatment interaction model, which confirmed no significant inconsistency. Surface under the cumulative ranking (SUCRA) method was used to obtain treatment rankings as probabilities of each intervention being the most effective. Heterogeneity between studies was assessed. Descriptive statistics using tau-squared (τ^2) indicated low variability. We conducted sensitivity analyses by removing studies with outlier values to test the robustness of our findings. We present the results as graphical summaries to aid interpretation (network plots, ranking probability distributions, and league tables).

Results

Proportion of Subjects with >75% Improvement over Baseline in EASI

The results indicate that tapinarof 1% twice daily had the greatest efficacy (odds ratio (OR)=1.89, 95% confidence interval (CI): 1.17–2.62, P<0.001), indicating statistically significant improvement over the reference treatment. Tapinarof 1% once daily (OR=1.60, P<0.001) and tapinarof 0.5% twice daily (OR=1.50, P=0.002) also demonstrated significant efficacy. In contrast, tapinarof 0.5% once daily (OR=0.91, P=0.179) and both placebo regimens (OR=0.06–0.08, P<0.001) were significantly less effective, showing limited improvement relative to the reference (Figures 2–3).

Between-study heterogeneity was minimal (I^2=1.4%), supporting the robustness of these findings. Ranking analysis

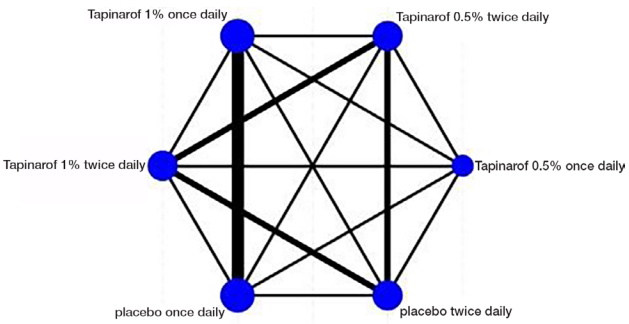

Figure 2. Network plot illustrating treatment effects based on the proportion of subjects achieving >75% improvement from baseline in EASI, comparing different doses and dosing frequencies of tapinarof.

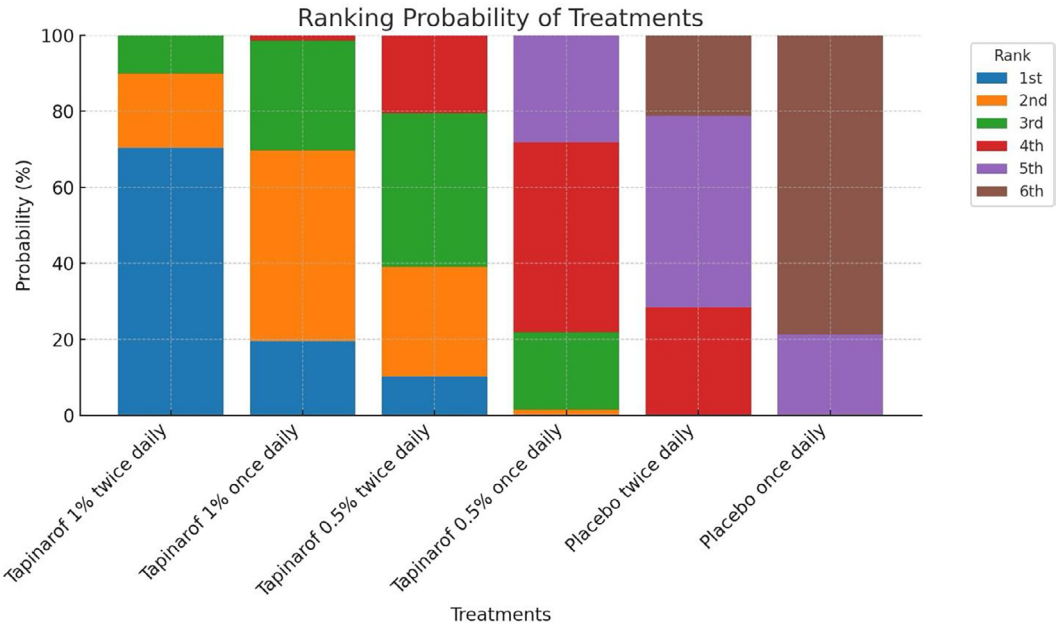

Figure 3. Ranking probability of treatments for achieving >75% improvement from baseline in EASI, comparing different doses and dosing frequencies of tapinarof.

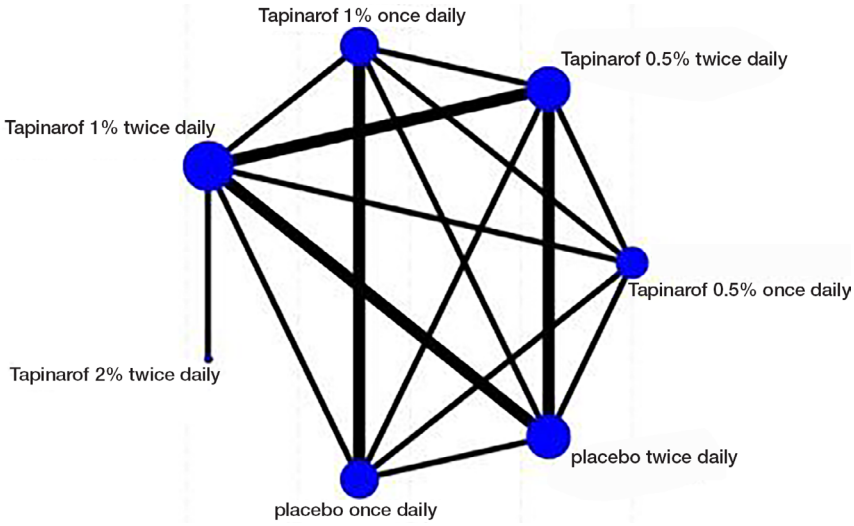

Figure 4. Network plot illustrating treatment effects based on Investigator's Global Assessment (IGA) of 0 or 1, with a minimum 2-point improvement from baseline, comparing different doses and dosing frequencies of tapinarof.

showed that tapinarof 1% twice daily had the highest probability of being the most effective treatment (70.3%), followed by tapinarof 1% once daily (19.5%) and tapinarof 0.5% twice daily (10.1%). Tapinarof 1% once daily most frequently ranked second (50.2%), while tapinarof 0.5% twice daily often ranked third (40.5%). Tapinarof 0.5% once daily had the highest probability (50.0%) of ranking fourth. In contrast, placebo twice daily (50.4%) and placebo once daily (78.8%) had the greatest probabilities of being among the least effective, with placebo once daily ranking last most often (Table S3).

Proportion of Subjects who Achieved an IGA of 0 or 1 and a Minimum 2-point Improvement over Baseline in IGA [5,6,8,9]

In the network meta-analysis comparing six treatment regimens (Figure 4), a random-effects model was applied due to moderate heterogeneity (I^2=67.14%), indicating variability across study results. Tapinarof 1% twice daily again showed the highest efficacy (OR=2.40, 95% CI: 1.30–3.95, *P*=0.002). Tapinarof 1% once daily (OR=1.89, 95% CI: 1.02–3.25, *P*=0.041), and tapinarof 2% twice daily (OR=1.65, 95% CI: 0.91–3.01, *P*=0.094) also showed favorable outcomes,

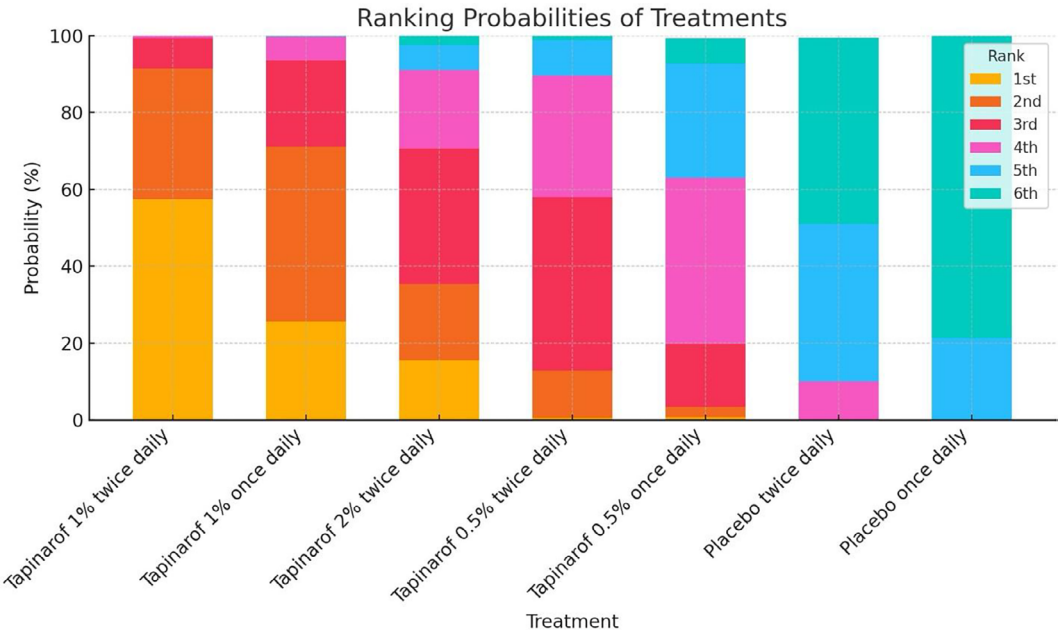

Figure 5. Ranking probability of treatments based on Investigator's Global Assessment (IGA) of 0 or 1, with a minimum 2-point improvement from baseline, comparing various doses and dosing frequencies of tapinarof to determine the most effective regimen.

although the latter did not reach statistical significance and was not a primary focus of this analysis.

Tapinarof 0.5% twice daily (OR=1.22, 95% CI: 0.75–2.10, *P*=0.321) and tapinarof 0.5% once daily (OR=0.91, 95% CI: 0.50–1.71, *P*=0.779) were less effective. Both placebo regimens were the least effective: placebo twice daily (OR=0.35, 95% CI: 0.18–0.67, *P*<0.001) and placebo once daily (OR=0.28, 95% CI: 0.14–0.54, *P*<0.001) (Figure 5, Table S4).

Ranking analysis showed that tapinarof 1% twice daily had the highest probability of being the most effective treatment (57.4%), followed by tapinarof 1% once daily (25.7%) and tapinarof 2% twice daily (15.5%). Placebo twice daily had a 48.4% probability of being the worst treatment, while placebo once daily was most likely to rank last (78.8%).

Risk of Bias

Based on the ROB assessment, the overall risk of bias for the included studies was low to moderate. While the majority of studies exhibited a low risk of bias across all domains, Bissonnette R., et al. [6] introduced notable concerns due to its open-label design (high risk of performance bias) and potential industry funding (unclear risk of other bias). Despite this, the remaining studies demonstrated robust methodology with minimal bias, ensuring confidence in the overall findings of the network meta-analysis. Therefore, while some caution is warranted, particularly regarding potential sponsor bias in one study, the overall risk of bias does not significantly undermine the validity of the results (Figures S1 and S2).

Discussion

Atopic dermatitis is a chronic inflammatory skin disease that significantly impacts patients' quality of life. While topical corticosteroids and calcineurin inhibitors have traditionally been the mainstay of treatment, newer nonsteroidal agents such as tapinarof offer promising efficacy with a favorable safety profile. However, the availability of multiple formulations and dosing frequencies underscores the need for comparative evidence to guide optimal treatment selection [10]. Standard pairwise meta-analyses provide results for direct comparisons but are limited when multiple options exist. In contrast, network meta-analysis (NMA) allows both direct and indirect comparisons by pooling evidence from overlapping trials, enabling treatment ranking and offering a more comprehensive perspective.

This NMA found tapinarof 1% twice daily to be the most effective regimen for both Investigator's Global Assessment (IGA) response and ≥75% improvement in Eczema Area and Severity Index (EASI) (Figures 2–5), in agreement with Gold et al. [7]. Ranking analysis showed it had the highest probability of being the most effective (70.3% for IGA; 57.4% for EASI-75) (Tables S3 and S4), suggesting a dose-response relationship where both concentration and application frequency influence outcomes. Tapinarof 1% once daily ranked second, showing good efficacy but lower likelihood of treatment success compared with twice-daily use. Tapinarof 2% twice daily showed a non-significant trend toward better IGA improvement, differing from the results of Silverberg JI et al. [11], possibly due to variations in study design or

patient characteristics. Lower-dose regimens (0.5% once or twice daily) were consistently less effective, suggesting insufficient anti-inflammatory activity, although Igarashi et al. [8] reported no notable difference across concentrations. Placebo arms performed poorly, confirming tapinarof's superiority over inactive treatment trials [5-9].

Heterogeneity patterns differed between outcomes. EASI-75 had minimal heterogeneity (I^2=1.4%), indicating consistent effects and robust treatment ranking (Figures 2–3, Table S3). In contrast, IGA outcomes showed moderate heterogeneity (I^2=67.14%; Figures 4–5, Table S4), likely reflecting variability in baseline disease severity, treatment duration, and study populations. The inclusion of Bissonnette et al. [6], which lacked a well-connected comparator, may have contributed to this variability. Nonetheless, the overall evidence consistently favored tapinarof 1% twice daily across both measures.

Safety outcomes indicated that tapinarof was generally well tolerated. The most common adverse events were folliculitis, acne, contact dermatitis, and headaches, with low rates of application site irritation [11]. Most events were mild to moderate, and no serious adverse events occurred in the majority of cases. However, three participants in the 2% cohort discontinued treatment due to systemic adverse events [6]. Overall, the 1% twice-daily regimen appeared to provide the most favorable balance between efficacy and tolerability.

Limitations

This network meta-analysis offers valuable insights into tapinarof's efficacy but has limitations. One study, Bissonnette R. et al. [6], had a high risk of performance bias due to its open-label design and industry funding. While heterogeneity was low in some comparisons (I^2=1.4%), moderate heterogeneity (I^2=67.14%) suggests variability in study populations and methods. Indirect comparisons in network meta-analysis, though statistically robust, may introduce uncertainty compared to direct trials. Despite tapinarof 1% twice daily ranking highest, overlapping confidence intervals emphasize the need for further large-scale, high-quality trials to confirm their superiority and long-term safety.

Conclusions

In conclusion, this analysis identifies tapinarof 1% twice daily (OR=2.40, 95% CI: 1.30–3.95, *P*=0.002) as the most effective treatment, with significant improvement over the reference. Tapinarof 1% once daily (OR=1.89, 95% CI: 1.02t–3.25, *P*=0.041) also showed favorable results, while tapinarof 2% twice daily (OR=1.65, 95% CI: 0.91–3.01, *P*=0.094) did not reach significance. Tapinarof 0.5% once daily and placebo were the least effective. Findings were robust, with low heterogeneity and bias. Future research should prioritize direct comparisons and long-term safety evaluations to optimize tapinarof's clinical use.

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