Short-term topical therapies in treating plaque psoriasis: An updated systematic review and network meta-analysis

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April 9, 2022

Abstract

Objective:To perform a network meta-analysis(NMA) of randomized controlled trials of topical therapies for plaque psoriasis, especially some new drugs for psoriasis.Our objective was to establish the effectiveness, tolerability and safety of topical treatments for people with chronic plaque psoriasis. Methods: We systematically searched PubMed, Cochrane Library and Embase databases to identify randomized controlled trials of topical therapies in adult patients with plaque psoriasis.Due to older literature were not able to included some novel topical therapies,we only searched the article that published between 01 January 2010 and 20 February 2022 in English. The primary efficacy assessment criteria were treatment success(the number of patients who achieved Physician's Global Assessment or Investigator's Global Assessment of a score of clear or nearly clear(PGA0/1,IGA0/1)) and the paitents who reported adverse events (AEs) at 4-12 weeks. Secondary criteria were the propotion of patients with 75 % reductions in Psoriasis Area and Severity Index (PASI 75) and the number of patients who reported drug withdrawal due to adverse events at 4-12 weeks.We combined with hierarchical cluster analyses to consider efficacy, safety and tolerability. Results: The review included 24 randomized controlled trials of topical treatments for plaque psoriasis with 9748 participants. This network meta-analysis showed that topical treatments were significantly more effective than placebo at 4-12weeks, in addition to tofacitinib ointment. hierarchical cluster analyses shows that topical calcipotriene and betamethasone dipropionate(Cal/BD),roflumilast,betamethasone,halobetasol-propionate and tazarotene(HP/TAZ), halobetasol were comparable with respect to high short-term efficacy, safety and tolerability, especially Cal/BD and roflumilast.

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Abstract :

Background: Plaque psoriasis is a relapsing immune-mediated skin disease and it characterised by redness, thickness and scaling. Topical therapies is the cornerstone for treating psoriasis.

Objective: To perform a network meta-analysis(NMA) of randomized controlled trials of topical therapies for plaque psoriasis, especially some new drugs for psoriasis.Our objective was to establish the effectiveness, tolerability and safety of topical treatments for people with chronic plaque psoriasis.

Methods: We systematically searched PubMed, Cochrane Library and Embase databases to identify randomized controlled trials of topical therapies in adult patients with plaque psoriasis.Due to older literature were not able to included some novel topical therapies,we only searched the article that published between 01 January 2010 and 20 February 2022 in English. The primary efficacy assessment criteria were treatment success(the number of patients who achieved physician's global assessment or Investigator's global assessment of a score of clear or nearly clear(PGA0/1,IGA0/1)) and the paitents who reported adverse events (AEs) at 4-12 weeks. Secondary criteria were the propotion of patients with 75 % reductions in Psoriasis Area and Severity Index (PASI 75) and the number of patients who reported drug withdrawal due to adverse events at 4-12 weeks.We combined with hierarchical cluster analysis to consider efficacy, safety and tolerability.

Results: The review included 24 randomized controlled trials of topical treatments for plaque psoriasis with 9748 participants. This network meta-analysis showed that topical treatments were significantly more effective than placebo at 4-12weeks, in addition to tofacitinib ointment. hierarchical cluster analyses shows that topical calcipotriene and betamethasone dipropionate(Cal/BD),roflumilast,betamethasone,halobetasol-propionate and tazarotene(HP/TAZ),

halobetasol were comparable with respect to high short-term efficacy, safety and tolerability, especially Cal/BD and roflumilast.

Limitations: limited direct comparisons and lack of long-term assessment.

Conclusions: Topical Cal/BD and Roflumilast had greater efficacy safety and tolerability than other topical drugs in 4-12weeks.

Keywords: plaque psoriasis; topical therapies; meta-analysis

What this study adds What is already known about this subject

To date, a number of randomized controlled trials have studied the efficacy and safety of some novel topical drugs.However, compared to traditional available topical therapies, the efficacy, safety and tolerability of these new drugs remain unclear.

A previous NMA have shown no difference between the combination of potent corticosteroid and vitamin D analogue and monotherapy,but some studies have shown that the efficacy of combination is superior to the monotherapy components.

What this study adds

Topical therapies is the cornerstone for treating psoriasis, aryl hydrocarbon receptor inhibitors have have high efficacy but lower safety and tolerability, roflumilast has higher efficacy,safety and tolerability.

INTRODUCTION

Psoriasis is a chronic relapsing immune-mediated disease affecting around 125 million people worldwide.[1]Plaque psoriasis is the commonest variant that accounts for 90% of psoriasis cases.[2] Clinically, Plaque psoriasis is characterized by sharply demarcated red, scaly lesions with desquamation.[1]With the further understanding of the pathogenesis of psoriasis, targeted biologics are more and more widely used as first-line agents in the treatment of moderate and severe psoriasis, and play a positive role in the treatment of refractory and special types of psoriasis. [3] [4]Howeve,topical medications is still the most commonly used treatment for mild to moderate psoriasis and all patients can benefit from extensive application of emollients.[3,5]Up to now,only a few meta-analysis studies have compared the efficacy of different topical therapies for plaque psoriasis.[6-10]To date, a large number of randomized controlled trials have studied the efficacy and safety of some novel topical drugs,such as aryl hydrocarbon receptor (AhR) inhibitors(tapinarof, benvitimod), phosphodiesterase type 4 (PDE-4) inhibitors(roflumilast) and janus kinase-signal transducer and activator of transcription(JAK-STAT) Inhibitors(tofacitinib, ruxolitinib) and proformed better efficacy.

For completeness,we report an overview of all randomized controlled trials of 10 topical medicine for the treatment of plaque psoriasis and updated the NMA and based on hierarchical cluster analyses to evaluate

the short-term topical teatment efficacy,safety and tolerability. It is hoped that, to some extent,these results can provide information for doctors when choosing therapeutic in clinic.

Methods

This multiple-treatments meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and network meta-analyses guidelines .[11]The primary design was registered on International Prospective Register of Systematic Reviews (PROSPERO #317865).

Inclusion and Exclusion Criteria

The eligibility criteria included(1)be a phase 2 or 3 clinical randomized controlled trials (RCTs) for trunk and limbs of adults plaque psoriasis and have at least 50 participants in each study;(2) topical interventions included were:tofacitinib, tapinarof, benvitimod, calcipotriol, roflumilast, Cal/BD, betamethasone, tacalcitol, halobetasol,HP/TAZ and vehicle(placebo);(3)studies reporting at least one of efficacy outcomes(PGA0/1,IGA0/1,PASI75) and safety outcomes (AEs,AEs leading to discontinuation of trial), all outcomes were extracted at 4–12weeks.The exclusion criteria included case reports, letters,retrospective studies, researches without data in outcomes and lack usable date.

Search strategy and date extraction

We searched for randomised controlled trials in the review, involving adult patients with plaque psoriasis of trunk and limbs. Only studies that included data from the most recent or comprehensive studies were included under multiple articles involving the same population and we investigated the efficacy, safety and tolerability of topical therapies compared with placebo for patients with plaque psoriasis,in particular some new drugs.An electronic search of the published literature using PubMed, Cochrane Library and Embase databases was conducted by two researchers independently who searched for publications on topical durgs in the treatment of plaque psoriasis and published between 01 January 2010 and 20 February 2022. References within the reviews literature on topical treatment of psoriasis and selected articles were reviewed to avoid missing relevant articles.The following information was extracted from the included first author's name,publishing date,clinical trial registration number,study country,blind evaluation,the number of participants, baseline patient characteristics (age, gender, PASI), treatment regimen, outcome assessment, and follow-up time.

Data analysis

Data analysis was performed using a random-effects model within a frequentist method in Stata version 14.0 using the network meta-analysis.[12]Multiarmtrials were divied into two groups for comparisons and network meta-analyses to combine direct and indirect evidence.[13] Because our outcomes are categorical data,so we estimated the pooled odds ratios (ORs) and 95% confidence interval(CI) of clinical efficacy and safety parameters,if the CI for the ORs did not involve one,the comparisions were thought to be with statistical sighificance.We evaluated the heterogeneity of all control groups was assumed to be equal and the correlation of multi-arm studies was considered and use node-splitting method using visual inspection of the forest plots assess local inconsistency .[14]If the treatments form a closed circle,loop inconsistency should also be tested by using χ^2-test and inconsistency factors (IFs).[14,15] We calculated the probabilities of ranks and surface under the cumulative ranking (SUCRA) of the treatments. The higher the treatment's SUCRA value,value ranges from 0 to 1, the higher the likelihood that the treatment was better the curative effect. [16]Under the circumstances,hierarchical cluster analyses is the better choice to achieve compare short-term topical teatment efficacy,safety and tolerability of these topical treatments.[17]Besides,we assessed publication bias using comparsion-adjusted funnel plot.

Results

Search results and study characteristics

18 articles reporting the results of 24 RCTs including 9748 patients with plaque psoriasis met the inclusion criteria.[18-35](Figure 1).Due to insufficient data,so we excluded tazarotene data from one of the articles.[31]

Study characteristics is presented in Supplemental table 1.

Quality assessment

In selected RCTs quality was assessed by the Cochrane Collaboration Risk-of-Bias Instrument.[36] Quality assessment was performed by two independent authors and any disagreements were discussed and resolved by a third reviewer.A majority of RCTs were double-blind and were conducted across multiple centers, we rated 3 out of 24 RCTs as "high risk" because they had blinding of bias[24 27,30].The more details on quality assessment results are shown in Supplemental figure 2a–b.

Primery efficacy oftopical therapies at 4–12 weeks

All RCTs that reported the number of patients who achieved PGA0/1 or IGA0/1 were included in the network.NAM showed that all treatments were significantly more effective than vehicle,expect tofacitinib cream(OR1.39,95%CI0.88 to 2.19).(Table 1)According to the SUCRA, Cumulative ranking probabilities for treatment success showed that Cal/BD performed best(SUCRA 97.2),followed by tapinarof cream(SUCRA 85.7) and betamethasone(SUCRA 75.6) (Supplemental table 4). Compared with vehicle, Cal/BD had the highest treatment success rate(OR 10.35,95%CI7.40 to 14.48) followed by tapinarof cream(OR 8.28,95%CI 5.35 to 12.82)(Supplemental figure 3a).No evidence of inconsisitency was showed for primery efficacy.(P= 0.405)

Most effective treatment is Cal/BD,formulation fall mainly into five categories: PAD^{TM}Technology cream(PAD-cream),topical suspension(TS),ointment, aerosol foam(AF),gel. The subgroup analysis according to drug formulation, according to the SUCRA, aerosol foam(96.3) was ranked the best among the five formulation. (Supplemental table 5).

PASI75 at 4-12weeks

12 articles reporting 14 RCTs comparing 9 treatment arms,including vehicle, tofacitinib, tapinarof, benvitimod, calcipotriol, roflumilast, Cal/BD, betamethasone, tacalcitol, halobetasol.The NMA showed that all treatments except tofacitinib performed significantly better than vehicle(Fig.2 and Supplemental table 2).We found that Cal/BD and tapinarof had higher rank probabilities (SUCRA 91.5and 84.1 respectively) in terms of PASI75,followed by roflumilast, betamethasone and benvitimod.

Safety oftopical therapies at 4–12 weeks

13 RCTs comparing among 11 treatments(including vehicle),according to the SUCRA, tofacitinib had lower AEs than Cal/BD(SUCRA 85 and 43.8 respectively), the highest probability for AEs was found with tapinarof(SUCRA 1.2),followed by benvitimod and HP/TAZ(Supplemental Table 4).Compared with vehicle,the highest odds of AEs were tapinarof(OR 3.50 95%CI2.71 to 4.52),benvitimod(OR 2.68 95%CI1.91 to 3.77) and HP/TAZ(OR 1.92 95%CI1.29 to 2.87), the lowest odds of AEs were tofacitinib(OR 0.85 95%CI0.57 to 1.27) and betamethasone(OR 0.89 95%CI0.62 to 1.29). (Table 1 and supplemental figure 3b).

Tolerability of topical therapies at 4–12 weeks

We measured tolerability of drugs from withdrawal data due to adverse events.15 RCTs reported the tolerability by comparing 10 treatments. The highest odds of withdrawal were with tapinarof(OR 3.97 95%CI1.14 to 13.89) and benvitimod(OR 3.23 95%CI1.33 to 7.82) that compared with vehicle. (Supplemental Table 3).According to the SUCRA,the betamethasone and roflumilast had highest tolerability(SUCRA 86.3 and 83.3 respectively). (Supplemental Table 4)

Hierarchical cluster analysis

Simultaneous ranking of the interventions in terms of efficacy(PGA0/1 or IGA0/1) and safety(AEs) were summarized using a clustered–ranking plot(Figure 3a).Cal/BD,betamethasone, roflumilast and halobetasol formed a large cluster of topical therapies with higher efficacy and safety. Tapinarof shows high efficacy but lowest safety than other treatments. Tofacitinib shows lower efficacy but highest safety than other agents. Clustered ranking was applied to efficacy(PGA0/1 or IGA0/1) and tolerability(Figure 3b)

.Cal/BD,betamethasone, roflumilast and HP/TAZ presented in the top–right corner,were higher efficacy and tolerability than orther agents.

Publication bias and inconsistency

General view, no significant inconsistency was identified.The comparison-adjusted funnel plots appeared symmetrical,indicated no obvious evidence of publication bias.(Supplemental Fig 4(a)-(d))

DISCUSSION

This network meta-analysis synthesized efficacy, safety and tolerability data from 24 RCTs comparing traditional and new topical medicines in adults with plaque psoriasis. The findings of our review suggest that Cal/BD are more effective than some new topical drugs,such as tofacitinib, tapinarof and benvitimod. More improtantly We provide new evidence that Cal/BD aerosol foam formulation had the highest efficacy than other formulations. Furthermore, we considered both efficacy safety and tolerability outcomes together in hierarchical cluster analyses,suggesting that Cal/BD, roflumilast and betamethasone demonstrate higher short-term efficacy,safety and tolerability.These results have potential clinical implications for clinicians to consider when choosing treatment options.

Topical agents is the preferred therapy for patients with mild and moderate psoriasis,however,patients can benefit from topical treatments,regardless of disease severity.[5] Extensive forms of psoriasis may require a combination of systemic and topical treatments to achieve complete regression of skin lesions.[37]Plaque psoriasis usually requires a long course of treatment,adherence to treatment is associated with better efficacy,which is affected by frequency of application, and the properties of the formulation and vehicle.[38,39]Most frequently topical treatment is a fixed dose combination of calcipotriene and betamethasone dipropionate(Cal/BD) and various clinical trials have demonstrated the efficacy and safety of Cal/BD.[40] Halobetasol propionate 0.01% and tazarotene 0.045% lotion(HP/TAZ) has been shown to be more effective than tazarotene alone, and was consistently effective in reducing the psoriasis symptoms of erythema, plaque hypertrophy and scaling.[31]However,it also have some concerns and limitations,for instance, betamethasone has been associated with skin atrophy,telangiectasia and striae that limit the long-term use, particularly sensitive areas like face and intertriginous areas.Thus,due to these unmet needs for topical treatment of psoriasis,new therapeutic durgs are emerging.

Some new topical treatments for psoriasis,such as tapinarof,has completed a phase III study and showed good efficacy results and the most common adverse reactions are folliculitis, contact dermatitis, and headache ,but the most adverse reactions are mild-to-moderate.[19]Benvitimod needs two daily applications,it has the same active ingredients as tapinarof containing different escipients,and it can be used alternately and sequentially with other topical drugs.Topical roflumilast,one of the phosphodiesterase type 4 (PDE-4) inhibitors,showed high efficacy,safety and tolerability in our conclusions,.A 24-week extention study is currently underway to assess its long-term safety.[41]Tofacitinib is a small molecule Janus kinase (JAK) inhibitor and selectively JAK1 and JAK3.[42]In our conclusion, tofacitinib is well tolerated and has a high safety profile,consistent with the findings of Ports WC,[43]but it showed only a modest improvement and not significantly different from vehicle,some research on this drugs was abandoned.[44] Brepocitinib, a Tyrosine kinase 2 (TYK2) /JAK 1 inhibitor, is the latest option in this class of drugs and also undergoing a phase IIb clinical trial in patients with mild and moderate psoriasis.[45]

Many topical corticosteroids used to treat psoriasis are available in different formulations,development of new high-efficiency vehicle formulations could improve patient compliance and efficacy of treatment.[46]This systmetic review,we concluded that Cal/BD aerosol foam, followed by PAD-cream,appears to be more efficacy than the combination onitement,gel and topical suspension.

The purpose of this NMA was to compare the evidence of efficacy, safety and tolerability of these topical therapies. A previous NMA showed the combination of potent corticosteroid and vitamin D analogue, administered once daily in a single two-compound formulation or alone, were the most effective interventions, with no significant difference between them,[10]but some studies have shown that the efficacy of Cal/BD is

superior to the monotherapy components.[4]We performed a updated NMA,in order to resolve controversial issues and incorporate recently topical treatments.Our study suggested that compared with vehicle,the efficacy and safety of Cal/BD was superior to the monotherapy components,and there is significant difference between them. In terms of new topical drugs,the hierarchical cluster analyses demonstrated that topical AhR inhibitors have have high efficacy but lower safety and tolerability, roflumilast has higher efficacy,safety and tolerability.However,tofacitinib has poor efficacy but higher safety and tolerability.

This study had several limitations. First,because of short-term observation,we cannot measure the difference in the long-term efficacy and safety of these drugs. Second,in the included studies,the severity of some patients psoriasis was recorded as moderate to severe and our study did not involve a comparison of the frequency of drug administration. Third, due to regional and racial differences, results of NMA may not generalize to real-world patient populations.Fourth, Other new drugs not included in some studies which results were not reported. Therefore, the interpretation and implementation of the results of this NMA should mainly consider short-term treatment and require long-term follow-up treatment studies.

CONCLUSION

In conclusion,this study provided evidence that Cal/BD, roflumilast and betamethasone presented higher short-term efficacy,safety and tolerability for treating plaque psoriasis and Cal/BD aerosol foam formulation had the highest efficacy than other formulations.,However, the long-term analysis was hampered by a lack of comparative studies.Because of larger and longer prospective studies future,NMAs will provide increasingly precise relative efficacy and safety comparisons.

Conflict of interest .All other authors have no conflicts of interest.

Funding. This article is not funded.

Supplementary Information

The Supplementary information can be found online of this article.

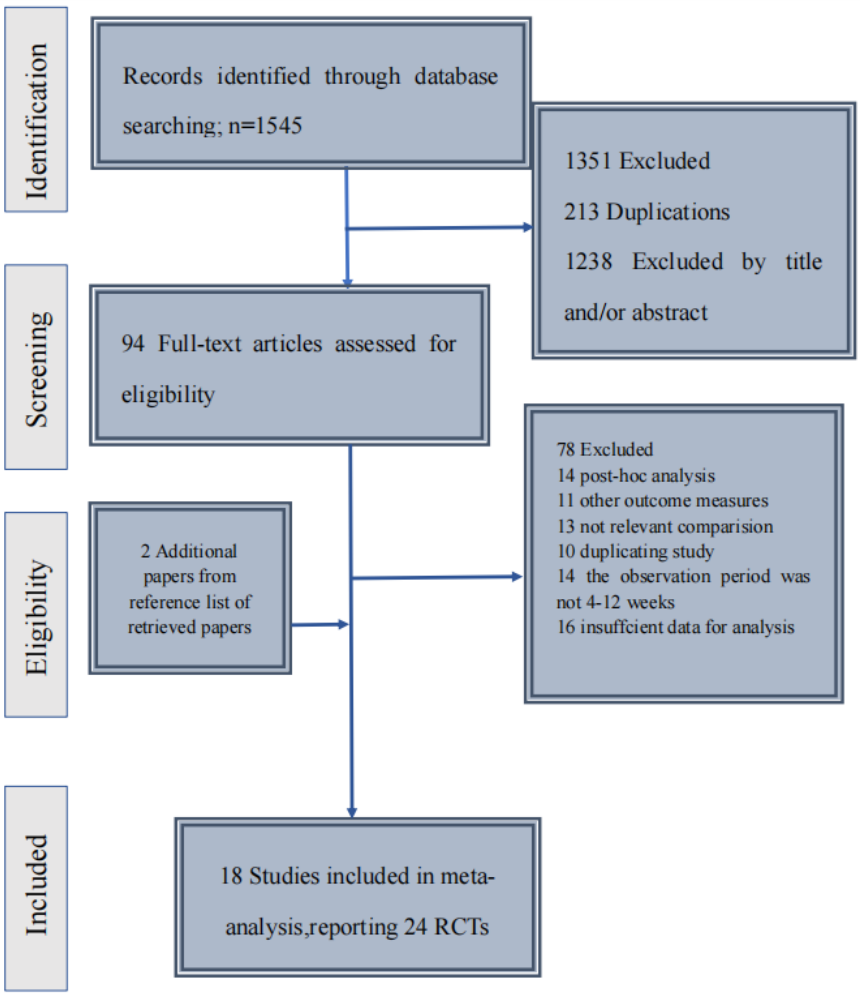


Figure 1 Flowchart of study selection. RCT, randomized controlled trial.

Table 1 Efficacy and safety of the ten drugs (OR 95 % CI). Drugs are ranked in effectiveness order. Significant results are in bold. (Abbr.:Cal/BD,calcipotriene and betamethasone dipropionate;HP/TAZ, halobetasol-propionate and tazarotene;PGA, Physician's Global Assessment;IGA, Investigator's Global Assessment)

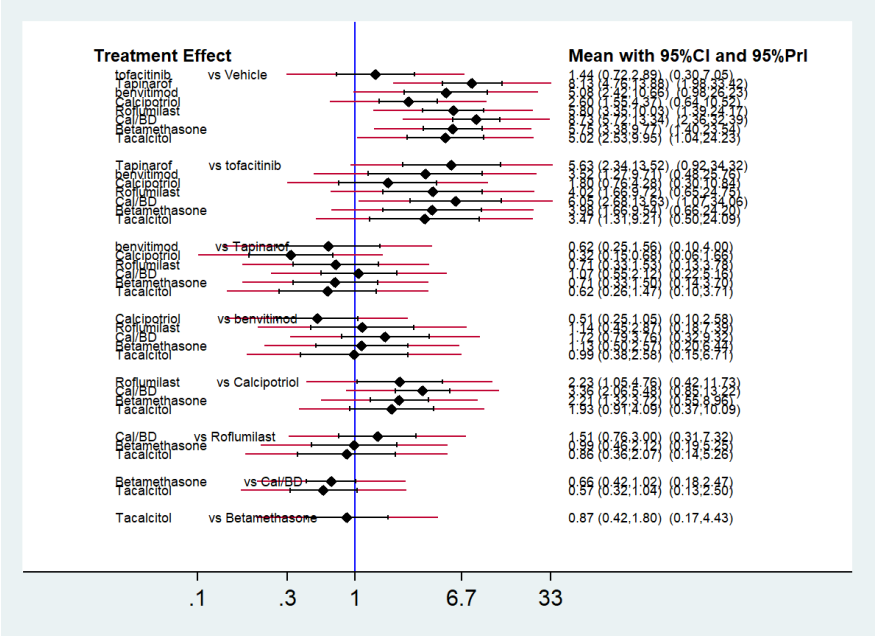
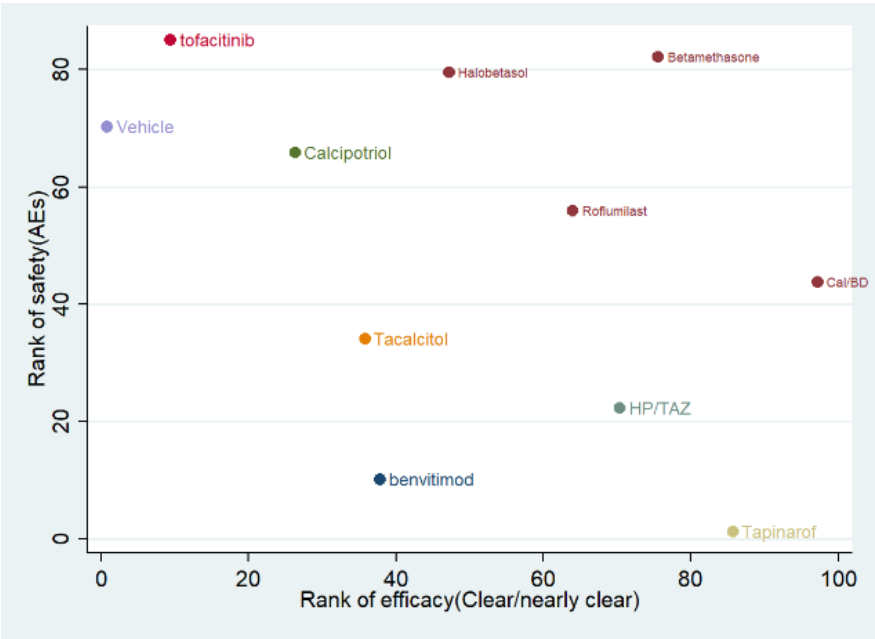
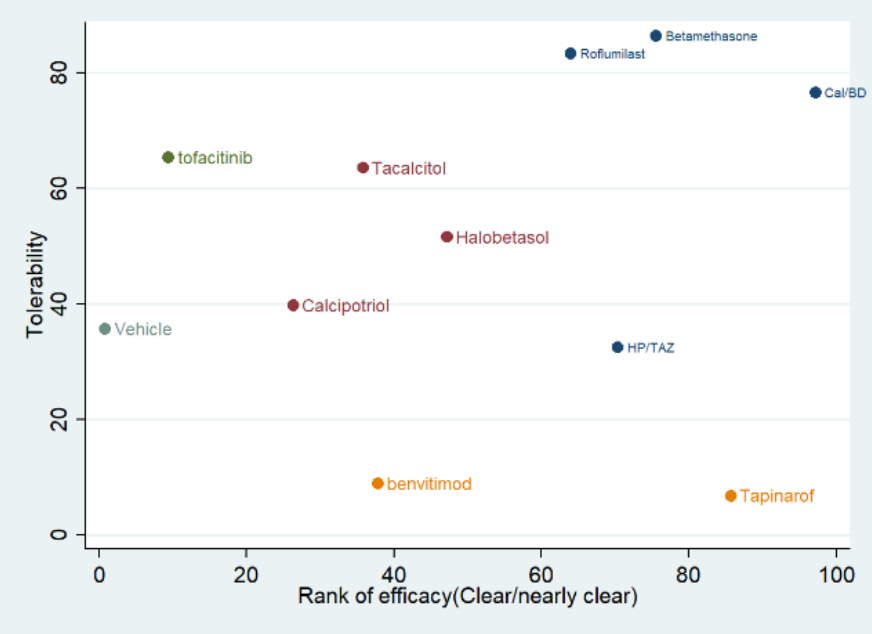


Figure 2 NMA summary plots. PASI75 [OR (95% CI) (95% PrI)] The diamond in each line represents the aggregate summary odds ratios of each comparison. The black lines represent the (95%) confidence intervals for pooled odds ratios for each comparison and the red lines represent the respective (95%) prediction intervals.(Abbr.:Cal/BD,calcipotriene and betamethasone dipropionate;HP/TAZ, halobetasol-propionate and tazarotene.)





3a 3b

Figure 3a Ranking of topical drugs according to efficacy and safety. Figure 3b Ranking of topical drugs according to efficacy and tolerability. (Abbr.:Cal/BD,calcipotriene and betamethasone dipropionate;HP/TAZ, halobetasol-propionate and tazarotene. AEs, adverse events.)

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