Topical Immunomodulators Improve Clinical Signs of Vernal Keratoconjunctivitis and Atopic Keratoconjunctivitis: A Meta-Analysis

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Topical Immunomodulators Improve Clinical Signs of Vernal Keratoconjunctivitis and Atopic Keratoconjunctivitis: A Meta-Analysis

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Running Header: Topical Immunomodulators and Keratoconjunctivitis

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Abstract

Objective: Topical immunomodulators cyclosporine A (CsA) and tacrolimus have been added in recent years to the armament to control severe chronic allergic ocular diseases such as atopic keratoconjunctivitis (AKC) and vernal keratoconjunctivitis (VKC). This meta-analysis summarizes the randomized controlled trials (RCTs) that utilized topical immunomodulators, to examine their effectiveness at decreasing clinical signs as assessed by clinicians in severe allergic eye disease.

Methods: A systematic search identified thirteen studies and a total of 445 patients for inclusion, making this the largest meta-analysis published on the subject.

Results: Thirteen RCTs were included. Eleven studies used Cyclosporine A as the treatment, and two used Tacrolimus. In total, 445 participants were included, 76.6% were male. The mean age of the participants was 14 years. All studies reported clinical signs as evaluated by an examining clinician. Signs were usually assessed by anatomical region, with the most common regions being the conjunctiva and the cornea, and the most common signs assessed were hyperemia and papillae. Three studies accounted for over 50% of the meta-analysis's weight. Effect size (d) ranged from -2.37 to -0.03, negative values favoring immunomodulators. Fixed Effect Meta-Analysis returned an SMD of -0.81 (95% CI: [-0.98, -0.65]). However, there was significant heterogeneity ($I^2=61\%$, $Q_w=30.76$) in the outcome measure ($P=0.0021$); therefore, a random-effect meta-analysis was also completed where the pooled SMD was -0.98 (95% CI: [-1.26, -0.69], $\tau^2 = 0.16$).

Conclusions: This study affirms that immunomodulators effectively treat clinical signs, including blepharitis, conjunctival hyperemia, edema, papillae, and corneal damage in severe ocular allergic disease.
Introduction

Allergic eye disease refers to various hypersensitivity disorders that affect the entire ocular surface, including the conjunctiva, lids, cornea, lacrimal glands, and tear film, with an estimated prevalence of 20% worldwide, and within the United States[1, 2]. An Israeli cross-sectional study of 10,057 children, aged 13-14 years old, reported 15.8% of allergic conjunctivitis symptoms[3]. The allergy process is a complex infrastructure that manifests slightly differently in the various disease categories but has a common genesis.

The external eye is exposed to a host of environmental, cosmetic, and pharmacological antigens[4]. Although individual responses may vary considerably[5-9], a spectrum of ocular surface allergic eye diseases have been classified which include seasonal allergic conjunctivitis (SAC) and perennial allergic conjunctivitis (PAC), the most common yet milder forms of allergic eye diseases, contact lens–associated conditions which include acute allergic conjunctivitis (AAC) and giant papillary conjunctivitis (GPC), and atopic keratoconjunctivitis (AKC) and vernal keratoconjunctivitis (VKC) which are considered chronic, severe forms. It is important to remember that this disease fluctuates, the majority of patients having intermittent symptoms which "flare up" throughout the year, challenging successful long-term treatment. Local administration may control acute symptoms, but currently no adequate treatments exist to quell disease recurrence.

Topical antihistamines effectively reduce clinical signs and symptoms of allergic eye disease by blocking the vasodilator effects of activated histamine receptors found in the conjunctival epithelium and goblet cells [8, 10-14] which generates the "early phase reaction" of the allergy cascade. However, they are also associated with dry eyes due to concomitant anticholinergic and muscarinic-binding action [8, 10-14]. Mast cell stabilizers inhibit the degranulation of mast cells, followed by the release of histamine[14, 15], and effectively reduce tryptase levels and decrease the recruitment of inflammatory cells[14, 15]. Their relatively slow activation period of three to five days has shifted treatment in recent years from their use as an isolated therapy to combining them with antihistamines, and found to be the treatment of choice for mild forms of allergic conjunctivitis; SAC and PAC affecting both the early and late phases of allergic
conjunctivitis signs and symptoms [14, 15]. This combined therapy was also the mainstay for moderate to severe allergic eye disease such as AKC and VKC, but it is frequently inadequate.

The development of topical corticosteroids dramatically improved control over these severe forms of allergic eye disease [1, 16-19]. However, their use tends to be strictly limited and carefully monitored as long-term use may result in several significant side effects and complications, such as the formation of posterior sub-capsular cataract[20], glaucoma[21], and secondary infections such as bacterial or fungal infections[22-26]. Corticosteroids, mainly transported in the blood complex to corticosteroid-binding globulin and albumin[26-28], bind to the glucocorticoid receptor alpha[29, 30], which inhibits many inflammatory gene transcriptions in the cell nucleus [31, 32]. In addition to the genomic mechanism, corticosteroids act through rapid, nongenomic processes, including nitric oxide-dependent vasorelaxation and inhibition of the release of pro-inflammatory prostaglandin[29, 30, 33, 34], which then controls inflammation by upregulating the expression of anti-inflammatory genes and suppressing the expression of pro-inflammatory genes[30, 33, 34]. Other anti-inflammatory effects of corticosteroids include vasodilation suppression, macrophage, and neutrophil migration inhibition, reduction of inflammatory T cells and B cells, and stabilization of intracellular and extracellular membranes[33, 34].

Treatment options for chronic and severe allergic eye disease have markedly expanded in recent years, the primary focus on topical applications[6-8, 15]. Immunomodulatory agents such as cyclosporine A (CsA) and tacrolimus have been shown to control allergic eye disease as an alternative to corticosteroids[35, 36]. While they do not display the rapid effect of corticosteroids, they seem to carry fewer risks and are safe for long-term use[16, 37-44].

CsA is a lipophilic molecule isolated from the fungus Beauveria Nivea which was initially used to prevent rejection of transplanted organs and later for the treatment of atopic dermatitis and autoimmune disease[45-48]. It is an immunosuppressive and immunomodulatory drug adapted for ophthalmic use as an emulsion (0.05%). It has been a prescription drug in the United States since 2003 to treat dry eye[46, 47, 49, 50]. CsA is
an immunomodulator that specifically inhibits CD4 T lymphocyte proliferation via inhibition of IL-2 receptor expression[5-9]. It also has direct inhibitory effects on eosinophil and mast cell activation and release of mediators, which seem to be important in its role in the treatment of allergic inflammation[51-53].

Tacrolimus is a macrolide immunomodulatory agent previously known as FK506[54-58]. Its' functional mechanism is similar to CsA, namely to disrupt the signaling events mediated by the calcium-dependent calcineurin(CaN)-calmodulin(CaM) complex in T lymphocytes, which activates the nuclear factor of activated T cells (NFAT) [54-58]. This suppresses the formation of various cytokines[59-64]. Transcription factors of the NFAT family are essential for antigen-specific T cell activation and differentiation[59-64].

Whilst the mechanism of action of immunomodulators is well understood, this meta-analysis aims to examine through randomized controlled trials (RCTs) whether the scientific literature supports that topical immunomodulators improve VKC and AKC clinical signs.

**Methods**

**Data Extraction**

Two independent reviewers (DBEN, NE) conducted searches and assessed the methodological quality and abstracted data. The searches were carried out using the electronic professional literature Medline (National Library of Medicine, Bethesda, Maryland, USA), LILACS, SCIELO, Scopus (Elsevier Inc; Amsterdam, Netherlands), and Thomson Reuters Web of Science (WoS) databases and search engines. The terms employed in the search included "Vernal Keratoconjunctivitis", "Atopic Keratoconjunctivitis", "Allergic", "Seasonal", "Immunomodulators", "Calcineurin", "Cyclosporine", "Restasis", "FK-506", "Tacrolimus", "Placebo", and "Control". The meta-analysis was performed following the preferred reporting items for systematic reviews and meta-analysis guidelines(PRISMA)[65].
**Inclusion and Exclusion Criteria**

The titles and abstracts of studies were considered eligible if they met the following inclusion criteria: non-duplicates, random control trials (RCT); patients with pathology on the allergic eye disease spectrum (VKC, AKC, SAC, PAC, AAC, GPC) inclusion; comparing an immunomodulator (cyclosporine A or tacrolimus) versus a placebo; assessing at the clinical signs as an outcome measure. Studies generally displayed some version of a composite sign score, which was calculated as the sum of at least one of the clinical sign scores given by an ophthalmologist for the following signs on the conjunctiva- hyperemia, papillae, giant papillae, edema; or corneal involvement. Studies presenting non-quantifiable data were excluded.

**Data Extraction**

The following variables were collected from the included studies; main author, year of publication, sample size, group design, mean age, pathology, follow-up duration, treatment regimen, intervention and placebo substances, intervention substance active ingredient concentration, intervention solution substance, and outcome measure. Extracted outcomes relied on data from double-blinded placebo-controlled (DBPC) phases exclusively. Outcome changes from baseline (BL) were extracted and analyzed in all but one study (Daniell et al.) in which the standard deviation (SD) for change from BL was unavailable and non-imputable. This was done because a change from BL takes the starting point and initial differences between the control and intervention into consideration, thus better representing the efficacy. Moreover, some studies have presented outcome measures that naturally represent a change from BL[66, 67]. These cannot be broken down into two distinct outcomes at BL and end. However, studies that present data for BL and end separately can usually be used to calculate and analyze a change-from-baseline outcome. In one study, obtaining SDs for means of change from BL was unavailable. Moreover, imputing SDs was not possible as the authors did not report their scaling method[19]. To overcome that – mean changes from BL were used, coupled with SDs of final follow-up means, to calculate a standardized mean difference.
and pooled variance. A ruleset was established to unify the direction of all of the studies in the analysis, whereby larger values translated to worse outcomes (i.e., the more negative the difference, the better the outcome); change from BL was calculated as subtracting the outcome at BL from the outcome in the final follow-up; the between-group mean difference for the analysis was calculated as Intervention Mean minus Control Mean (i.e., the more negative the comparison, the better the intervention). In cases where a predefined scale was set in a study, the entire scale was multiplied by (-1) to adjust to the direction of the analysis. Where necessary, SDs were calculated from standard errors, P-values, or manually calculated with Excel. Common assumptions were made regarding the equality of variances between the two arms when required. Numerical data was interpolated from figures using a ruler in case it was not reported elsewhere. All data extractions, assumptions, and imputations were prepared according to the methods described in the Cochrane Handbook for Systemic Reviews of Interventions.

Statistical Analysis

The Meta-Analysis was done using Microsoft Excel. The change from BL to final follow-up in composite sign scores was analyzed as a continuous variable. Due to the different scales of measurement of the sign score and variability in the combination of different signs to compute the total score, Hedges’d was calculated as the standardized mean difference (SMD) to achieve an effect size and pool the results together. Therefore, it is important to interpret the analysis’s results only in light of the confidence intervals (CIs) and P-values. The fixed-effect and the random-effect models were calculated to reflect 95% CIs. A Chi-Square test calculated I² assessed the between-study heterogeneity and pointed out the appropriate model for the analysis.

Results

The search yielded 381 peer-reviewed articles, and from the references of those articles, another 147 articles related directly to the subject were identified.

As per inclusion criteria, 229 articles were discarded as duplicates. An additional 169 were discarded as non-eligible. One hundred and thirty articles were obtained for full-text review. One hundred and seven were then excluded for not being RCTs. Nine were
excluded for disqualifying interventions. One was excluded for disqualifying outcome measures. The characteristics of the thirteen RCTs ultimately included in this meta-analysis are shown in Table 1, Table 2, and Figure 1.

Eleven studies were conducted using CsA, and two used tacrolimus. Three studies treated one eye of every patient with an immunomodulator and the other eye with a placebo. The remainder divided the groups by patients and applied the same treatment to each patient's eyes. The combined studies included 445 patients, 76.6% were male (one study included nine patients and did not report gender distribution). The combined mean age of the studies was 14 years, three studies had a mean age of patients above 18. Cohort sizes ranged from 8 to 58. Two studies included only patients with AKC, nine included only VKC, and two included both pathologies.

Effect size (d) ranged from -2.37 to -0.03, negative values indicating favorable treatment with immunomodulators over placebo. Three studies (two papers) accounted for more than 50% of the meta-analysis's weight. All included studies except one showed significant improvement of outcomes in the treatment arm compared to the control. This was also backed in the Fixed Effect Meta-Analysis, which returned an SMD of -0.81 (95% CI: [-0.98, -0.65]). However, the Homogeneity test indicated statistically significant heterogeneity ($I^2=61\%$, $Q_w=30.76$) in the outcome measure of change from baseline in composite sign score ($P=0.0021$); therefore, a random-effect meta-analysis was also completed (Figure 2).

Topical treatment with immunomodulatory agents was associated with a greater reduction in sign scores from BL of allergic eye disease compared to placebo. The pooled SMD was -0.98 (95% CI: [-1.26, -0.69], $\tau^2 = 0.16$).

All studies reported clinical signs as evaluated by an examining clinician. Signs were usually assessed by anatomical region, with the most common regions being the conjunctiva and the cornea. The conjunctiva was evaluated in eleven studies (84.6%), albeit not in an identical method. The studies generally checked for hyperemia and papillae, and were occasionally divided into two separate anatomical locations: the palpebral conjunctiva and the bulbar conjunctiva (Table 3). All studies evaluated the
cornea (100%), and included an epithelial evaluation such as punctate keratitis or vascularization. One study specifically mentioned Corneal Fluorescein Staining (CFS). Other anatomical assessments included the lids, which were commonly assessed for blepharitis; Trantas' dots at the limbus, which were either evaluated as an isolated parameter or combined with other measurements of corneal evaluation. One study incorporated initiation of rescue medication therapy into the clinical score, as it was believed that requiring such treatment indicated a degradation in clinical status.

The occurrence of treatment-related adverse events (AE) was not analyzed for Odds Ratio due to several studies' improper or incoherent reporting. However, all studies reported similar safety between the active treatment with immunomodulators and the placebo. No serious AEs were reported throughout the studies in any arm.

**Discussion**

The current meta-analysis strengthens the premise that immunomodulators effectively diminish clinical signs of AKC and VKC, specifically those evaluated by clinically by a specialist. These included hyperemia and edema and notable objective pathological changes such as papillae and architectural damage to different tissues (Table 3).

Several studies also investigated the effect of topical immunomodulators on the symptoms of allergic eye disease, such as itching, burning, foreign body (FB) sensation, and photophobia. However, this analysis incorporated the more objective clinical signs rather than subjectively reported symptoms. Clinical signs are essentially the cause of the symptoms, or they indirectly indicate their presence; thus, the analysis of clinical signs has a more substantial impact (e.g., corneal ulceration is a clinical sign and the underlying reason for the symptoms such as burning, or FB sensation, and redness of the eye).

AKC has complex immune dysregulation pathogenesis combining genetic, environmental, and psychological factors. It is categorized as a chronic disease with symptoms lasting year-round in variable degrees, yet 30% of patients report a seasonal influence[53]. Histopathologic examinations of conjunctival biopsies will present goblet cell proliferation, epithelial pseudotubular formation, and a pronounced epithelium
invasion by degranulating eosinophils and mast cells. Management is often challenging, and devastating corneal complications of AKC progress in up to 60% to 70% of patients, including neovascularization, subepithelial haze, pannus, and pseudopterygium formation. Approximately a third of patients ultimately require a corneal transplant for visual or structural objectives[51, 52].

The pathogenesis of VKC is likewise multifactorial, though approximately half of the patients with VKC have no familial or personal history of atopy. Research has demonstrated the possible involvement of neural factors such as substance P, sex hormones, as suggested by overexpression of estrogen and progesterone receptors in the conjunctiva of VKC patients, and conjunctival histaminase deficiency participating in the pathogenesis of the disease[51, 52].

The VKC process appears to be a Th2-driven mechanism. Th2 lymphocytes are responsible for the hyperproduction of cytokines such as IL-4, IL-5, IL-13, growth factors and enzymes, the ensuing production of IgE, the differentiation and activation of mast cells, and eosinophils. Increased levels of CD4+ T lymphocytes have been found in conjunctival specimens or tears of patients with VKC, suggesting they play a key role in the pathogenesis of the disease. Specifically, IL-3, IL-4, IL-5, IL-6, IL-13, and granulocyte-macrophage colony-stimulating factors are increasingly expressed in conjunctival eosinophils of VKC patients, and levels of tear IL-5 and eosinophil cationic protein are also elevated[51, 52].

The potential efficacy of CsA was first reported for the treatment of VKC in 1986 [45] and later evaluated as a low-concentration topical CsA (0.1%) aqueous ophthalmic solution in 594 patients with severe VKC and AKC. It was described there as effective and safe[68]. It effectively controls ocular inflammation, blocking Th2 lymphocyte proliferation and IL-2 production. It also inhibits histamine release from mast cells and basophils, and through a reduction of IL-5 production, it may reduce the recruitment and the effects of eosinophils on the conjunctiva[51-53]. Moreover, the therapeutic efficacy of CsA in VKC, a conjunctival hyperproliferative disorder, seems to be related to the drug's efficacy in reducing conjunctival fibroblast proliferation rate and IL-1b production[51-53]. Multiple studies have reported a beneficial effect of topical
cyclosporine in relieving symptoms of VKC in patients with different severity grades of the disease[51-53]. In a recent study, both topical treatments of 0.1% FK-506 ophthalmic ointment and 2% CsA eye drops have been reported to be effective for VKC. They also reported that FK-506 ophthalmic ointment twice daily improved symptoms of VKC similar to that of CsA eye drop four times daily. In ophthalmology, topically applied CsA in various oil-based solvents was first used to inhibit experimental corneal allograft reaction in the early 1980s[51-53].

Various studies evaluated CsA at a low concentration of 0.05%. They proved it beneficial, safe, and effective compared to placebo or artificial tears to manage severe VKC and AKC[36, 68-71]. However, other studies stated contradictory results, including a randomized placebo-controlled study, where using the same agent did not exhibit any benefit over placebo[36, 68-71]. A prospective, randomized cross-over study conducted in VKC patients using 0.5% topical CsA showed that the drug reduced symptoms and signs at a more moderate pace than preservative-free 0.5% ketorolac tromethamine[49]. Concentrations of 1% and 1.25% of CsA investigated in 22 patients with severe VKC in a double-blind, placebo-controlled study[50] decreased the mean objective signs and symptoms, suggesting that 1% is probably the minimum concentration to treat severe forms of VKC effectively [50]. Several studies evaluated CsA using a relatively high concentration of 2%, which was found very effective at treating severe forms of VKC and AKC[47, 66], sometimes as quickly as one week of treatment. It was found to be safe and effective in the short term. This 2% concentration does not seem to cause significant side effects other than a mild transient burning sensation upon administration which also occurs at the 1% and 1.25% concentrations[50, 70-73]. The lower concentrations of 0.05% and 0.1% reported no adverse reactions[16, 68, 70, 74].

Prolonged use of topical 2% preparations has been reported, and the only serious side effects reported are lid maceration (which developed in one patient in this trial) and corneal epitheliopathy, both of which resolve on cessation of treatment and which do not necessarily preclude further use of CsA[52]. However, drug-related symptoms of blurring (vehicle-related), which may last up to 3 hours and may prevent driving, and of intense stinging (CsA-related), which may sometimes cause severe blepharospasm for some time.
after instillation, make this drop difficult to tolerate and sometimes almost impossible to instill four times daily if the patient is active[51-53, 75].

Topical tacrolimus 0.1%, the most common concentration for treating allergic eye diseases, is available in cream, solution, emulsion, and gel formulations[76]. It has been widely reported as an efficacious alternative in cases resistant to conventional therapies such as topical CsA or topical corticosteroids[39, 44, 70, 77-80]. It is worth mentioning that concentrations of 0.003%, 0.005%, 0.01%, 0.02%, and 0.03% of topical tacrolimus have also become accepted treatments over the past few years[41, 81-88], as studies have proven that these low concentrations are effective and control the clinical signs in patients with severe VKC compared with conventional treatments[41, 81, 82, 84-88].

Topical tacrolimus has been reported to provide significant relief from symptoms including photophobia, redness, itching, ocular discomfort, foreign body sensation, and discharge[38, 39, 76, 89]. Importantly, it provides considerable improvements in clinical signs of VKC and AKC, such as conjunctival hyperemia, Trantas dots, limbal infiltration, conjunctival papillary hypertrophy, and superficial punctate keratopathy[38, 39, 76, 89]. Topical tacrolimus 0.1% is efficacious for treating chronic allergic eye disease with and without atopic dermatitis as well as demonstrating corticosteroid-sparing effects[39, 44, 70, 80, 90]. It has further shown an ability to resolve giant papillae comparably to topical corticosteroids, and is better tolerated than CsA[39, 44, 70, 80, 90].

**Limitations**

Though this is the largest meta-analysis to date, this study has limitations, including the small number of studies. The studies included compared immunomodulators to a placebo. Ideally, studies comparing immunomodulators to other treatments, such as corticosteroids, would have added validity to the conclusions. Unfortunately, appropriate studies were not found in a sufficient amount to statistically justify a meta-analysis. Pooling was done in this case for the treatment arm, and so pooling different control arm regimens would mean a radical deviation from accepted limitations and was thus not performed. Furthermore, while the analysis successfully assessed the effect of immunomodulators on the clinical signs of allergic eye disease as a group, only two
studies used tacrolimus as the treatment. Though they had displayed results that concurred with the analysis, they had been responsible for only 12% of its weight. Hence significant conclusions drawn specifically regarding tacrolimus should be done with caution.

The epidemiological prevalence of allergic eye diseases is mainly in young male patients, and approximately three-quarters of the subjects in the included studies were male adolescents. This can raise a possible uncertainty regarding the potential comparable benefit for additional populations.

The study analyzed the effect of immunomodulators on the clinical signs of allergic eye disease, and although these are considered the more objective of the two, it is the symptoms of the patients (e.g., itching, burning sensation) that aggravate quality of life and motivate them to seek medical treatment. Likewise, the analysis does not address the critical issues of side effects and adverse events, which could affect patient compliance, due to a lack of uniform reporting between studies.

A meta-analysis aims to strengthen conclusions, and though variability in result reporting can be an obstacle and cause slight deviations in pooled results, measures widely accepted by the Cochrane community have been utilized to overcome this. A possible bias to consider is the different measuring scale types used in studies. One study did not report its measuring method and merely stated that clinical signs were analyzed.

The outcomes that quantified the treatment efficacy are somewhat subjective as the examining ophthalmologists graded the signs. However, as previously discussed, they are relatively more objective than self-reported symptoms and are commonly used to make clinical decisions and patient management. Additionally, although only two studies in this analysis demonstrated the effect of topical Tacrolimus, the substance has a similar mechanism of action to CsA and is thus reasonable to be pooled together for this purpose.

Hence, it is plausible to regard these methodologies as acceptable for evaluating outcomes and conclude that patients treated with topical immunomodulators, regardless of the dose, active ingredient, and treatment regimen, demonstrated significantly greater improvement in the clinics of allergic eye disease compared with placebo.
To the best of our knowledge, this is the most extensive analysis to date on the effectivity of immunomodulators on ocular clinical signs and the only one that assesses the outcome of change from the BL (as opposed to prior analyses, which assessed the outcome without addressing the improvement compared to the BL), presenting more robust conclusions than previous publications. That, potentially, potently strengthens their favorability to clinicians among other available treatments. Future studies comparing immunomodulators to other treatments in diverse age groups and genders would further ascertain the role of immunomodulators in severe allergic eye disease.

**Conclusions**

The main topical immunomodulators currently utilized to treat allergic eye disease are cyclosporine A and tacrolimus. The analysis presented here supports that these effectively alleviated VKC and AKC clinical signs of blepharitis, conjunctival hyperemia, edema, papillae, and corneal damage, encouraging patient compliance. Moreover, the analysis of pooled studies significantly strengthens the assertion that immunomodulators are an effective and safe treatment for VKC and AKC. The analysis's limitations emphasize the need for developing an accepted, validated assessment method for signs and symptoms of allergic eye disease to more efficiently track patients' status and allow dependable comparison between different treatment regimens.

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**Author contributions**

- NE, DBEN, SN contributed to the study's conception and/or design
- Data collection was performed by DBEN, NL, DL, IL
- Analysis was performed by NE, DBEN
- The first draft of the manuscript was written by NL, AS
- Critical revision by SN, YM

All authors commented on versions of the manuscript, read and approved the final manuscript
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Figure titles and legends

Figure 1. Flow chart

Figure 2. Graph showing the effect of topical immunomodulators versus placebo as the change from baseline in a composite score of signs.

CI: Confidence Interval, SMD: Standardized Mean Difference
Figures

Articles identified through search (n=528)

Included (n=299)

Included (n=130)

Included (n=22)

Included (n=14)

RCT studies included n=13

Articles excluded- duplicates (n=229)

Non-eligible (n=169)

Excluded because non-RCT (n=107)

Disqualifying interventions (n=9)

Disqualifying outcome measures (n=1)

Figure 1

Flow chart
Figure 2

Graph showing the effect of topical immunomodulators versus placebo as the change from baseline in a composite score of signs.

CI: Confidence Interval, SMD: Standardized Mean Difference