Efficacy and Safety of Topical Cyclosporine A in Moderate-To-Severe Dry Eye Disease: An Updated Systematic Review with Meta-Analysis

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Abstract

Background: The increasing prevalence of dry eye disease and its inflammatory nature have attracted interest for treatment. Cyclosporine A has been used to treat dry eye disease. This study aimed to provide the most recent and comprehensive evidence on the efficacy and safety of Cyclosporine A for treating moderate-to-severe dry eye disease.

Methods: A systematic search was conducted across three electronic databases and reference lists for randomized controlled trials (RCTs) comparing Cyclosporine A with artificial tears (ATs) in DED populations, following PRISMA guidelines. Primary outcomes included tear breakup time, Schirmer's test, fluorescein staining. Secondary outcomes include adverse events, ocular surface disease index, meibum expressibility, and goblet cell density. Meta-analysis was performed using the random effects method.

Results: Fifteen RCTs involving 1683 participants were analysed. Pooled analysis revealed better outcomes of CsA in tear breakup time (SMD0.85, 95%CI 0.35-1.34), Schirmer's test (SMD0.50, 95%CI 0.05-0.95), and fluorescein-staining (SMD0.74, 95%CI -1.14-0.34) indicating clinically relevant benefits. Although CsA exhibited a higher incidence of adverse events compared to Ats (Risk Ratio) 3.13, 95%CI 0.94-10.45), these were generally mild to moderate, with no severe adverse events were reported. Secondary outcomes, including the OSDI score (SMD -0.88, 95% CI -1.26 to -0.50), goblet cell density (SMD 1.06, 95% CI 0.04 to 2.08), and meibum expressibility (SMD 0.53, 95% CI -0.56 to 1.62), also favored CsA over ATs.

Conclusion: Evidence suggests that cyclosporine-A is more effective than artificial tears in improving key clinical outcomes in DED treatment. Further studies with improved control and extended follow-up are recommended to assess Cyclosporin A's role in delaying disease progression and optimizing treatment duration.

Keywords: Cyclosporine, Dry Eye Disease, efficacy, safety, meta-analysis

1.0 Introduction

Dry Eye Disease (DED) is a multifactorial chronic condition and a leading cause of ophthalmologist consultation. It is a complex condition of the ocular surface [1] and is caused by tear film instability [2], inflammation [3], and damage to the eye's surface. The incidence of DED varies notably across different age groups, with a significant prevalence among adults over 40 years of age, especially among women [4]. Globally, DED affects approximately 5–50% of the population, with some estimates peaking at 75%.

The symptoms of DED, such as headaches, visual disturbance, and fatigue, affect patients' quality of life [5]. As DED progresses, inflammation intensifies, damaging the nerves, surface epithelium, and goblet cells, thereby worsening the condition. This cycle of inflammation and tissue damage is self-perpetuating and contributes to the chronic nature of DED. Therefore, anti-inflammatory treatment is essential to break this cycle in patients with moderate-to-severe DED.

One treatment option that has been extensively studied is topical Cyclosporine A (CsA). CsA is known for its immunosuppressive properties and has shown efficacy in the treatment of various ocular conditions including dry eye syndrome (Perry, 2008). Studies have shown that treatment with topical CsA can result in an increase in goblet cell numbers and a decrease in epithelial turnover in patients with dry eye syndrome, indicating a positive impact on ocular surface health. Furthermore, the use of topical CsA has been associated with improvements in tear production, corneal staining, and blurred vision in patients with moderate-to-severe dry eye disease.

Cyclosporine A (CsA), as a common immunomodulator, effectively diminishes the manifestation of inflammatory markers within the conjunctiva of individuals diagnosed with DED [6, 7]. Its therapeutic action extends beyond mere regulation of inflammation, encompassing the prevention of apoptosis in conjunctival epithelial cells. CsA is the sole DED treatment officially approved by the United States Food and Drug Administration (FDA) for the management of DED [8], with multiple studies focusing on its safety and efficacy in the treatment of DED.

Although topical CsA has shown efficacy in treating dry eye disease and improving ocular surface health, it is crucial to consider individual patient factors and alternative treatment options, especially in cases of intolerance or lack of response to CsA. While the efficacy and safety of CsA have been studied extensively, new evidence continues to emerge. This review is, therefore, an updated and comprehensive synthesis of the latest evidence from randomized controlled trials (RCTs) published in the past decade, from 2014 to early 2024,

reflecting recent advancements in CsA therapy for DED. Unlike previous reviews, which are now outdated, this study consolidates findings from recent trials to offer a current evidence base that is critical for guiding clinical decision-making and evidence-based practice in moderate-to-severe DED management. The earlier results consistently showed high heterogeneity [9]. Furthermore, this review specifically addresses moderate-to-severe DED, a patient population that often requires a tailored approach to treatment and may experience different therapeutic outcomes from CsA compared to those with milder forms of the disease. Given the high heterogeneity observed in previous evidence and the advent of newer trials that may clarify the safety and efficacy profiles of CsA, this systematic review and meta-analysis aims to provide an updated and precise understanding of CsA's role. This synthesis will inform both future research and clinical practices, ensuring that the most relevant and recent evidence is readily accessible for healthcare providers managing moderate-to-severe DED.

2.0 Methodology

This systematic review was conducted by the team of authors, with each member contributing to tasks including article selection, quality assessment, bias assessment, and data analysis, adhering to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [10]. The study protocol was registered on PROSPERO (CRD42024524329).

2.1 Data Sources and Search Strategy

PubMed, Web of Science, and Cochrane Library were searched using the following subheading, including explosions, and as well the test words: "Dry Eye Disease", "conjunctivitis sicca", "Cyclosporine", "artificial tear(s)", abbreviation of CsA and DED, and their synonyms and other related terms. Databases were searched with date restrictions for a certain period from January 2019 to December.2023. We conducted a thorough examination of the reference lists of all studies included in our analysis, as well as related systematic reviews, to identify and incorporate relevant studies. In addition, we performed a forward citation search to identify relevant studies.

2.2 Inclusion/Exclusion criteria

The inclusion criteria for this systematic review focus on selecting high-quality evidence from randomized controlled trials (RCTs) evaluating the efficacy and safety of topical Cyclosporine A (CsA) in the management of moderate-to-severe Dry Eye Disease (DED). As mentioned in the title, only studies that clearly define and classify Dry Eye Disease (DED) as moderate to severe were included. Eligible studies must be RCTs with a comparator group using artificial tears (ATs) or placebo, ensuring robust comparisons. Studies must include human participants

diagnosed with moderate-to-severe DED, regardless of age or gender. The primary intervention should be topical CsA, administered in standard dosages, with outcomes compared against ATs or placebo to determine the efficacy and safety of CsA. Studies are required to report on at least one clinically relevant outcome, such as tear break-up time (TBUT), Schirmer's test, Ocular Surface Disease Index (OSDI) score, adverse events, meibum expressibility, or goblet cell density. Only articles published between 2014 and 2024 are included to reflect current clinical evidence. No language restrictions are applied to capture a comprehensive range of studies.

The exclusion criteria are designed to omit studies that do not meet the methodological rigor or relevance for this review. Non-randomized studies, such as observational studies, case reports, reviews, and those lacking a control group, are excluded. Studies focusing on animal models, in vitro experiments, or involving only mild cases of DED are also excluded, as they do not directly inform treatment efficacy in the target population. Furthermore, studies comparing CsA with treatments other than ATs or placebo are excluded to prevent confounding results. Studies that do not report on clinically relevant outcomes related to DED or that rely solely on unvalidated or surrogate measures are excluded. Additionally, duplicate publications, conference abstracts, and preliminary findings lacking full peer review are not considered to ensure the integrity and comprehensiveness of the data included in the review.

2.3 Study Selection

Databases search was conducted on January 29,2024; and only articles published within the near 10 years were included. Only reports of randomised controlled trials (RCTs) were sought, and the language of the reports was not limited. These RCTs included data on the efficacy of CsA in comparison to ATs, involving DED patients. Furthermore, only studies that were carried out with humans were included. Exclusion criteria included comparing CsA with other interventions, not related to DED, and RCTs involving animal models.

2.4 Quality Assessment and Data Extraction

Two reviewers (ST and MK) were responsible for assessing whether a study met the inclusion criteria, evaluating its methodological validity in terms of confounding and bias, and extracting data using standardised forms. Any discrepancies were resolved by a third reviewer to identify potential methodological and underlying bias in the RCTs using the Cochrane risk-of-bias tool, which assesses seven specific criteria related to methodological factors. The factors considered include the randomness of sequence generation, concealment of allocation, masking of participants and personnel, masking of outcome evaluators, handling of incomplete outcome data, selective reporting, and other potential sources of bias. Data

extraction, using Microsoft Excel 2021 (Microsoft Corporation, Washington, United States) encompassed seven key outcome measures: tear break-up time (TBUT), Schirmer's test results, fluorescein-staining score, OSDI score, adverse events, meibum expressibility, and goblet cell density.

2.5 Data Analysis

The meta-analysis was conducted using the DerSimonian and Laird random-effects model. The metric outcomes were the standard mean difference (SMD) and 95% confidence intervals for all continuous outcomes. Odds ratio (OR) was used as an outcome measure for adverse effects which is a binary outcome. The study was conducted using Stata version 15.0, developed by Stata Corp in College Station, Texas, United States. Heterogeneity among trials was evaluated by analysing I^2 statistics. An I^2 estimate ≥ 50% was considered indicative of significant levels of heterogeneity. Publication bias was evaluated by employing a funnel plot. Subgroup analysis and Sensitivity analysis were performed to assess the robustness of data.

3.0 Results

From the three electronic databases, 147 references were initially identified. After removing duplicates and irrelevant references, 21 full-text articles were selected for review. Among these, four references from four RCTs [11-14] were included in this study for both qualitative and quantitative analyses. Additionally, 11 RCTs [15-25] that were included in previous reviews [9] were also discussed in this article. The evidence selection process is illustrated in **Figure 1**. However, two RCTs [16, 22] were excluded from the quantitative analysis due to the absence of mean and standard deviation.

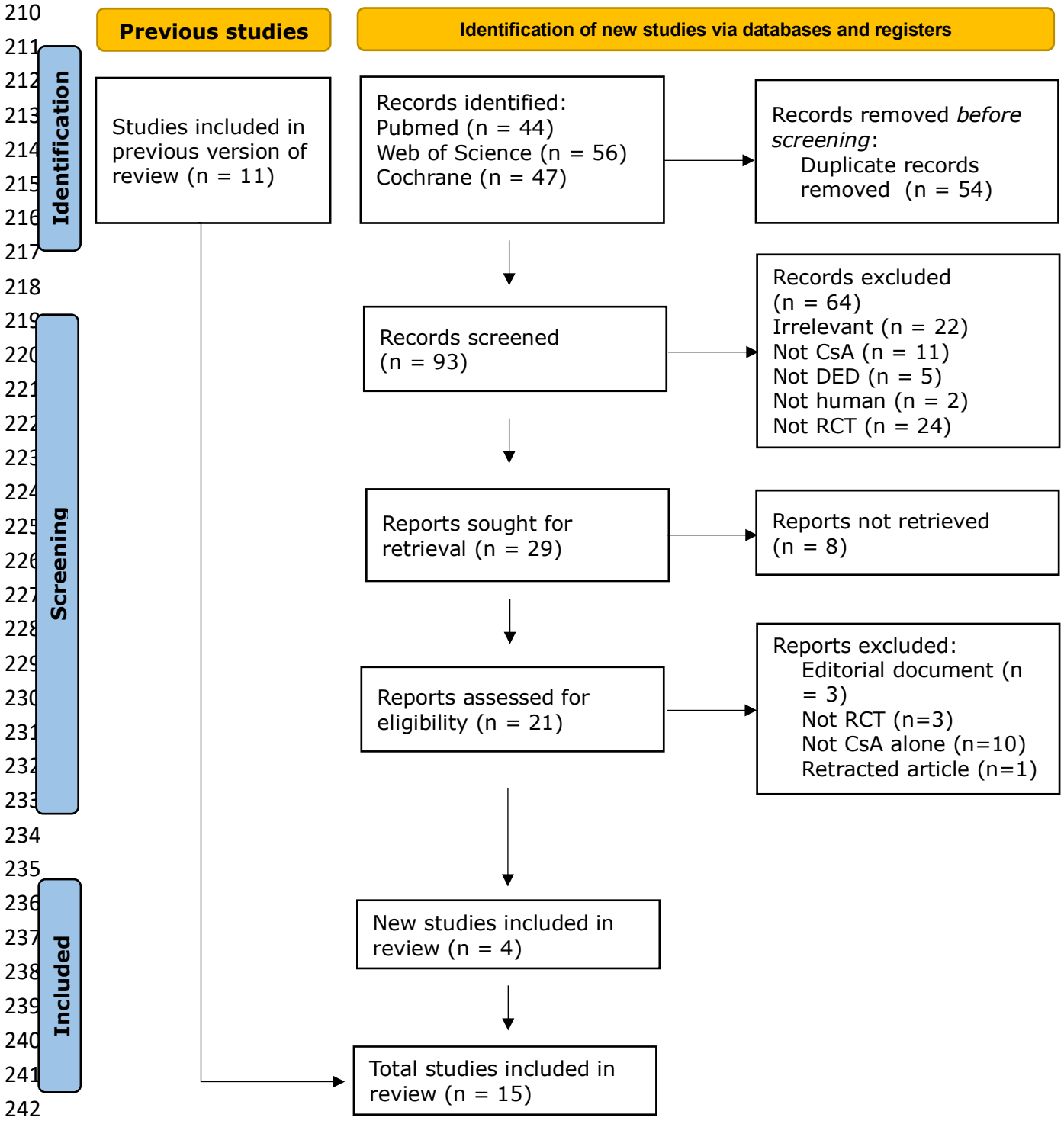

Figure 1: Flow diagram of evidence selection.

The flowchart above was adapted from the PRISMA 2020 statement [26] and amended for a better suit to the review. A flow diagram showing the number of articles included and visualising the process of evidence selection.

Abbreviations used: CsA (cyclosporine A), DED (dry eye disease), RCT (randomised controlled trial).

3.1 Study Characteristics and Quality

Thirteen RCTs were selected for inclusion, spanning from 2006 to 2023, involving patients with DED from various global locations. The treatment durations varied from one month to 12 months. In all trials, participants were administered the same dosage and frequency of CsA eye drops (0.05% CsA eye drops instilled twice daily). Additionally, most trials permitted patients in the CsA group to use ATs, leading to potential statistical heterogeneity owing to these conceptual differences. The overall quality of the RCTs is summarised in **Table 1**. The evaluation of the quality of RCTs encompassed various aspects, including the randomness of participant allocation, effectiveness of blinding, completeness of reported outcomes, potential for selective reporting, and other forms of bias.

Table 1: Risk of bias table of included studies.

Trial	Bias 1	Bias 2	Bias 3	Bias 4	Bias 5	Bias 6	Bias 7
[12]	Low	Low	Low	Low	High	Unclear	Low
[20]	Unclear	Unclear	Unclear	Low	Low	Low	Low
[22]	Unclear	Unclear	High	Low	Low	Unclear	Low
[13]	Low	Low	Low	Low	Low	Low	Unclear
[14]	Unclear	Unclear	Unclear	High	Low	Low	Low
[18]	Low	Low	High	High	High	Low	Low
[11]	Low	Low	Low	High	Unclear	Unclear	High
[15]	Low	Unclear	Low	Low	High	Low	Low
[24]	Low	Unclear	High	Low	Low	Low	Low
[21]	Low	Low	Low	Low	High	Low	Low
[23]	Unclear	Low	High	Low	Low	Low	Unclear
[16]	Low	Unclear	Low	Low	Low	Unclear	Low
[19]	Low	Low	Low	Low	Low	Unclear	Low
[17]	Unclear	Low	Low	Low	Low	Low	Low
[25]	Unclear	Unclear	High	High	Low	Unclear	Unclear

The risk of bias table was synthesised using the Cochrane risk-of-bias tool.

Indication of each bias representing: Bias 1, sequence generation; Bias 2, allocation concealment; Bias 3, blinding of participants and personnel; Bias 4, blinding of outcome assessment; Bias 5, incomplete outcome data; Bias 6, selective reporting; Bias 7, other source of bias.

3.2 Primary Outcomes

Synthesised evidence showed that CsA had better tear break-up time (TBUT) and Schimer's test scores, with a lower score for fluorescein-staining. A higher incidence of adverse events in the CsA group was also shown in the pooled results, while no severe adverse events were reported.

3.2.1 Tear Break-Up Time (TBUT)

Quantitative synthesis of TBUT data was extracted from nine of the 13 trials [11, 13, 15, 17-21, 23, 25], involving 627 cases. The results indicated that CsA significantly improved TBUT scores compared to ATs (SMD 0.85, 95% CIs 0.35 to 1.34, **Figure 2**), although with high heterogeneity (I^2=88.2%). Pooled results of TBUT showed the existence of small-study bias (*t*= -1.91, P= 0.024, **Supplementary File 3 and Supplementary File 4**).

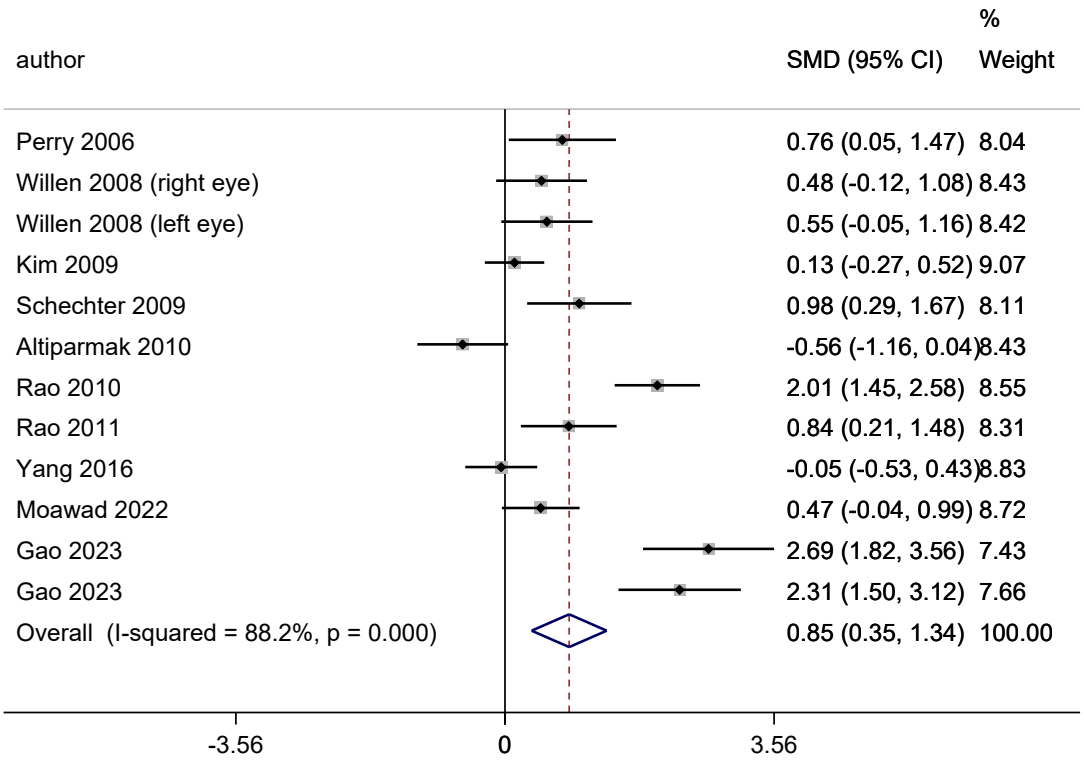

Figure 2: Forest plot of tear film-breakup time (TBUT).

3.2.2 Schirmer's Test

Ten RCTs [11, 13, 15, 17-21, 23, 25] involving 649 cases provided data on Schirmer's test scores, showing a significantly higher score for CsA than ATs (SMD 0.50, 95% CI 0.05 to 0.95, **Figure 3**) with high heterogeneity (I^2=86.7). However, the analysis did not reveal any signs of small-study bias in the pooled results of Schirmer's test scores, as indicated by a t-score of -0.73 and a p-value of 0.292, as shown in **Supplementary File 6 and Supplementary File 7**.

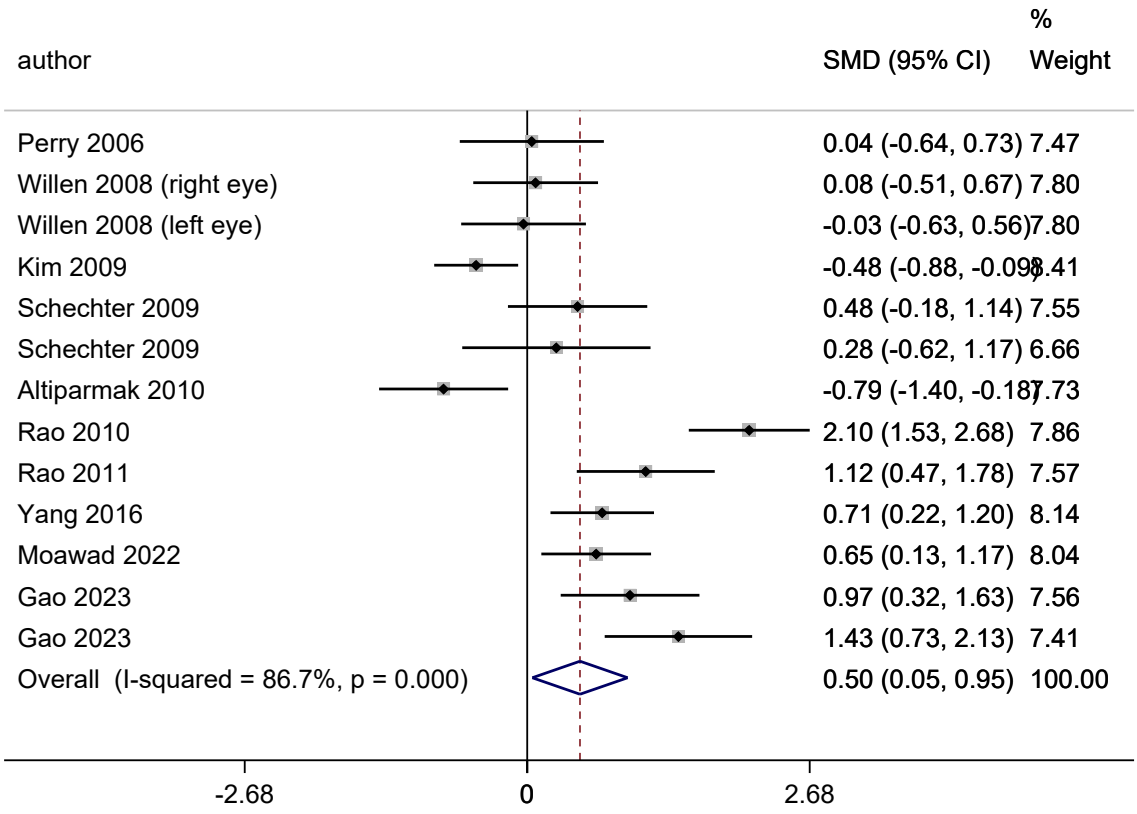

Figure 3: Forest plot of Schirmer's test.

3.2.3 Fluorescein-Staining and Adverse Events

Fluorescein-staining data were reported by seven RCTs [13, 15, 17-19, 21, 25], with a total of 458 cases, where CsA showed notably lower scores than ATs (SMD -0.74, 95% CI -1.14 to -0.34, **Figure 4**) with moderate heterogeneity (I^2=74.2%). Adverse event data were collected from twelve RCTs [12-25], consisting 1503 cases, indicating a higher adverse event rate in CsA group (RR 3.13, 95% CI 0.94 to 10.45) with relatively low heterogeneity (I^2=44.2%). The forest plot in **Figure 5** represents a meta-analysis of adverse events across multiple studies comparing the use of Cyclosporine A (CsA) to a comparator, such as artificial tears (ATs).However, the pooled results did not show a significant difference between the two groups, with a trend favouring ATs. Small-study bias analysis for fluorescein staining also

revealed evidence of a small-study effect (*t*= 1.50, P=0.047; **Supplementary File 9 and Supplementary File 10**).

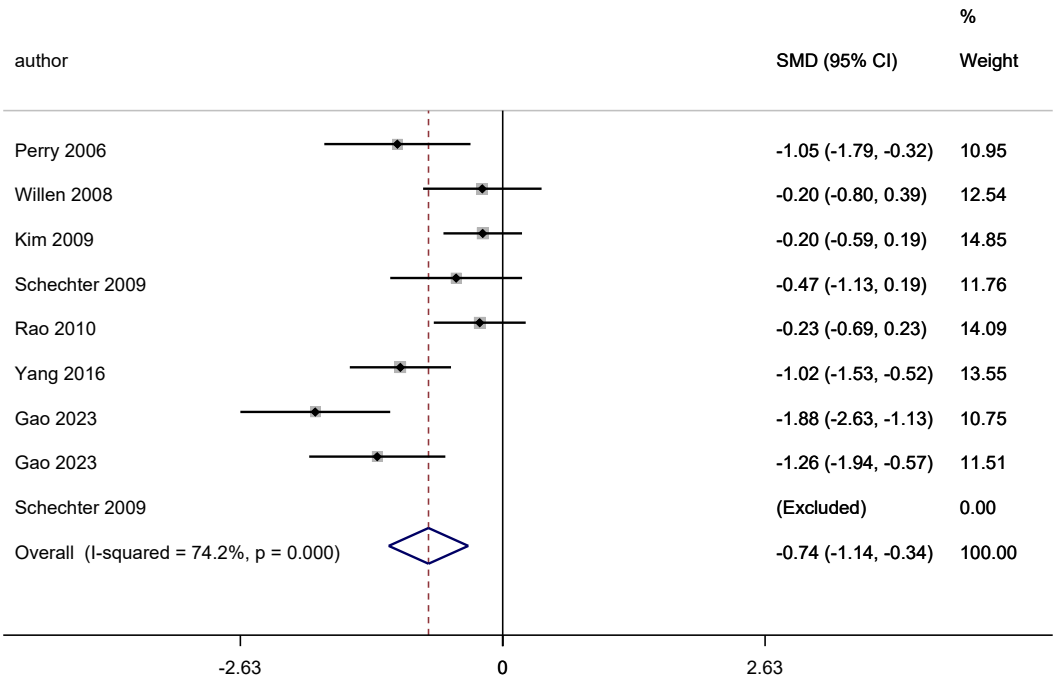

Figure 4: Forest plot of fluorescein-staining scores.

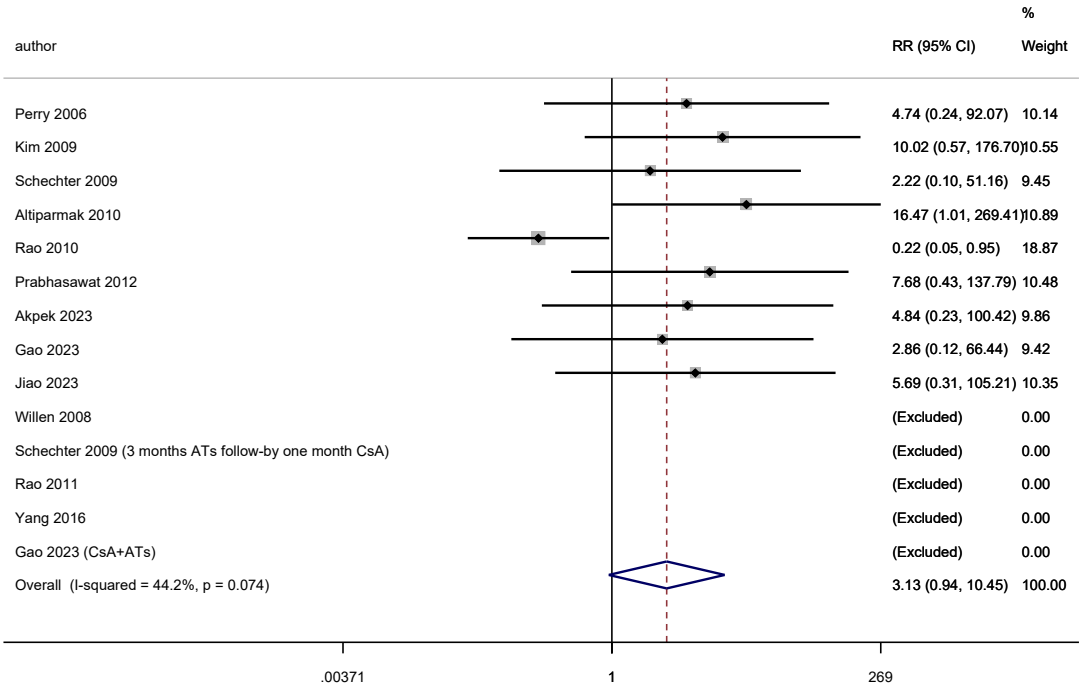

Figure 5: Forest plot of adverse events.

3.3 Secondary Outcomes

3.3.1 Ocular Surface Disease Index (OSDI)

Five trials [13, 17, 19, 21, 23] provided valid Ocular Surface Disease Index (OSDI) score data for quantitative synthesis, involving 299 cases. The combined findings showed that CsA resulted in significantly lower OSDI scores compared to ATs (SMD -0.88, 95% CI -1.26 to -0.50 **Supplementary File 11**), with low heterogeneity (I^2= 57.8%), indicating the reduction of symptoms reported by the subjects after CsA application. No small study effects were observed (*t*=-1.62, P=0.393; **Supplementary File 12 and Supplementary File 13**).

3.3.2 Goblet Cell Density

Data on goblet cell density were reported by three RCTs [18, 21, 23], totalling 216 cases, showing significant results favouring CsA over ATs (SMD 1.06, 95% CI 0.04 to 2.08, **Supplementary File 16**) with high heterogeneity (I^2=91.2%). The positive SMD showed improvement in goblet cell density in the CsA-treated DED population.

3.3.3 Meibum Expressibility

Only two RCTs (97 cases) [11, 19] reported appropriate meibum expressibility data, with pooled results revealing no statistically significant difference between the two groups yet exhibiting a preferential trend favouring CsA over ATs. (SMD 0.53, 95% CI -0.56 to 1.62, **Supplementary File 15**) with high heterogeneity (I^2=84.3%).

3.4 Other Outcomes

3.4.1 Cytologic Analysis Grade

Two trials [11, 15] involving 130 cases reported on the cytologic analysis grade, demonstrating a statistically significant disparity between the CsA and ATs groups (P<0.05). Studies by Perry et al.. and Moawad et al. [15, 11] focused on the meibomian gland, particularly examining meibomian gland inclusion and meibum gland quality. Perry et al. observed a notable reduction (P=0.001) in the meibomian gland inclusion value by over 50% in the CsA group compared to the placebo group. Conversely, Moawad et al. [11] found no statistically significant difference (P=0.763) between the two groups regarding meibomian gland inclusion and quality.

3.4.2 DED Symptoms

Studies by Kim et al. and Gao et al. [18, 13] documented various symptoms of dry eye, including blurred vision, ocular dryness, photophobia, foreign body sensation, burning, conjunctive congestion score, and tear meniscus height (TMH). Kim et al. [18] identified significant differences in photophobia and blurred vision between the CsA and control groups (P<0.05), while Gao et al. [13] reported that the control group exhibited significantly higher

levels of ocular dryness (P<0.001), foreign body sensation (P<0.001), photophobia (P=0.001), and burning (P=0.007) than the CsA group. However, only the CsA group showed notable changes in the conjunctive score (P<0.001) and TMH (P=0.048), with no significant alterations observed in the control group. In addition to the OSDI, the Total Ocular Symptom Score (TOSS) was documented by Perry et al., noting a notable decrease in the CsA group, although it was not statistically significant (P=0.21).

3.4.3 Ocular Staining, NIBUT, and FBUT

In a study conducted by Prabhasawat et al. [24], it was observed that both the non-invasive breakup time (NIBUT) and the invasive fluorescein breakup time (FBUT) in subjects treated with CsA were significantly increased compared to those in the control group. This increase was statistically significant (P<0.001), with a high degree of correlation noted between the NIBUT and FBUT values at each measurement point. Data concerning ocular staining, such as lissamine Green, SICCA score, and van Bijsterveldt score, were similarly reported by Perry et al. and Moawad et al. In a study conducted by Perry et al. [15], the application of lissamine green staining revealed an improvement in the group treated with CsA compared to the control group. However, the observed improvement did not reach statistical significance (p = 0.19). Conversely, Moawad et al.'s findings revealed significant changes when comparing the two groups for both SICCA and van Bijsterveldt scores (P=0.002 for all) [11].

3.5 Subgroup and Sensitivity Analysis

Sensitivity analysis was performed for all major outcomes by subgrouping the trials based on population and duration of trial. For TBUT, only studies from the US population, when pooled, were statistically significant (Supplementary File 16). Further, the trials conducted over 3 months and 12 months were significant. However, 6 months remained insignificant. (Supplementary File 18) For the Shirmer test, data from both China and the US population remained significant (Supplementary File 19). Only the 12-month trial data remained significant, indicating that the 3-month and 6-month treatments were inadequate for this outcome (Supplementary File 20). For the fluorescence staining test and OSDI, data from both China and the US population remained significant (Supplementary File 21 and 23). For the fluorescence staining test, only 3-month trials could be pooled as most of the trials measured this data at 3 months, and it remained significant (Supplementary File 22), whereas for OSDI outcomes, 3 months and 12 months remained significant (Supplementary File 24). Adverse events remained statistically significant mainly at 3 months (Supplementary file 25). All studies were either high-risk or unclear risk, hence sensitivity analysis were not performed based on exclusion of high-risk trials.

4.0 Discussion

The evidence from the systematic review showed that the administration of CsA eye drops, applied twice daily, leads to a substantial enhancement in several parameters of DED: Schirmer's test, TBUT, goblet cell density, fluorescein-staining, meibum expressibility, and OSDI scores. In addition, the results from the systematic review suggest that CsA may delay the progression of DED.

Goblet cells contribute mucins to the tear film, essential for tear film stability and ocular surface health. Higher goblet cell density is preferable, as it reflects a healthier ocular surface. A considerable decline in goblet cell numbers induced by CsA indicates the onset of ocular diseases [27]. These cells produce TGF-b2, a molecule with a variety of immune-regulatory functions, including inhibition of T-cell proliferation. This might be part of the immune-mediated processes of DED. Furthermore, goblet cells secrete mucin; therefore, increased goblet cell count might explain improvements in ocular surface condition and tear film stability [28]. This score assesses ocular surface damage by applying fluorescein dye to the eye and observing staining patterns. Higher scores indicate more severe damage to the corneal and conjunctival surfaces, so lower scores are preferable. The use of fluorescein staining to measure corneal health and barrier function has been widely established. In CsA-treated patients, fluorescein-staining was significantly reduced. Activation of ocular surface T-cells in DED results in reduced corneal sensitivity [29] and leads to a reduction in reflex tearing and lacrimal responses to ocular surface trauma.

TBUT is a diagnostic examination for evaporative dry eye and targets the tear film's lipid layer. The TBUT measure assesses the stability of the tear film, indicating how long it takes for the tear film to break up on the ocular surface after a blink. Longer TBUT values reflect more stable tear films, with higher scores signifying improvement in tear film stability and thus a favorable outcome. A higher goblet cell density is thought to be the primary reason for better TBUT, as goblet cells increase mucin production and enhance tear film stability. Schirmer's test result indicates tear production status. Higher scores indicate increased tear production, a desirable result in patients with DED. The significant improvement in Schirmer's test indicates that better tearing is due to reduced T-cell activation in CsA-treated DED. A significant difference in TBUT was observed between the CsA and control groups, indicating increased tear film stability. The enhancement of TBUT might be attributable to the direct influence of CsA's on meibomian glands, and not its indirect effect on Schirmer's test score. Sullivan *et al*. (2014) reported various degrees of connection between TBUT and Schirmer test scores among DED populations [30], highlighting the complexities of these relations.

The OSDI is a patient-reported outcome measure used to assess DED symptoms and their impact on vision-related quality of life. It scores symptom frequency and severity, with higher scores indicating more severe symptoms and a greater impact on quality of life; therefore, lower scores are better. Enhancements in objective signs aid in the overall improvement of subjective symptoms, as seen in the decrease in OSDI scores, and in reducing the impact of DED symptoms on daily life. Nevertheless, there is often a weak correlation between symptom severity and clinical signs, with many patients showing inconsistent signs and symptoms [31]. In the early stages of DED, increased pain sensitivity can lead to discomfort, even without visible corneal damage, whereas in advanced cases, decreased corneal sensitivity may alleviate symptoms.

While the treatment of moderate-to-severe Dry Eye Disease (DED) with topical Cyclosporine A (CsA) has demonstrated efficacy, its associated adverse events (AEs) can pose challenges that may affect patient adherence and long-term treatment outcomes. Although our analysis found that adverse events in the CsA group were generally mild to moderate, their impact on patient experience should not be overlooked. The most commonly reported AEs—burning, stinging, and foreign body sensation—typically occurred immediately after CsA application. These sensations, although transient and resolving upon treatment discontinuation, can contribute to patient discomfort and discourage continued use, particularly given the need for prolonged treatment in managing chronic DED. Adverse events in the included studies were typically reported as specific symptoms associated with Cyclosporine A (CsA) use, such as burning sensation, stinging, and foreign body sensation. These events were generally classified as mild-to-moderate and were described as transient, resolving either spontaneously or upon discontinuation of treatment. Each study provided its own reporting criteria for adverse events, often noting both the frequency and type of events observed during follow-up periods.

The overall RR of 3.13 with a 95% CI of 0.94–10.45 implies that, while the point estimate suggests CsA is associated with a higher risk of adverse events compared to the comparator, the confidence interval is wide and includes the value of 1. This indicates that the result is not statistically significant, and caution should be exercised when interpreting these findings. The variability in individual study results suggests differences in study designs, sample sizes, and follow-up durations. Future studies with more consistent reporting and larger sample sizes would help refine these estimates and confirm the findings.

The clinical significance of these adverse events lies in their potential to reduce adherence to CsA therapy. Persistent discomfort, even if non-severe, can lead patients to discontinue or inconsistently apply the medication, ultimately reducing its therapeutic efficacy.

Studies included in this review indicate that even mild symptoms can affect patients' quality of life and daily activities, emphasizing the need for clinicians to address these symptoms proactively. To manage AEs effectively, clinicians might consider gradually introducing CsA or co-prescribing artificial tears to alleviate discomfort.

Regarding the severity and duration of adverse events, studies report that these symptoms tend to peak shortly after application and gradually lessen as patients continue CsA therapy. However, the duration varies, with some patients experiencing symptoms for several weeks. Long-term monitoring, as noted in follow-up periods ranging from 2 weeks to 6 months across studies, is essential to assess tolerance and manage patient expectations. Clinicians should be aware that while CsA's side effects are generally not serious, their persistence can compromise adherence, potentially impacting long-term treatment success. By counseling patients on the typical course of these adverse events and offering strategies to mitigate discomfort, clinicians can improve adherence, thereby enhancing the likelihood of achieving desired therapeutic outcomes.

While on the other hand, recent clinical trials have demonstrated good tolerance of CsA eye drops over a three-year period [32, 33]. In a phase 3 trial where 0.1% CsA eye drops were applied twice daily for three years, stinging and ocular burning were the primary reported adverse events, although most participants did not encounter such discomfort. All participants expressed willingness to persist with CsA eye drops and suggested them to other patients with DED, highlighting the overall positive clinical outcomes compared to the minimal discomfort experienced.

Publication bias, particularly in meta-analyses that include small studies, can skew the results, often leading to an overestimation of treatment effects. Smaller studies, which sometimes report greater efficacy than large trails [34], may contribute to an exaggerated view of CsA's performance, as they are more likely to be published if they yield positive or significant outcomes. . This "small-study effect" can amplify perceived benefits in parameters like TBUT and fluorescein-staining scores, as these studies tend to emphasize more favorable results than larger, potentially less biased studies. In this meta-analysis, asymmetry observed in the funnel plot analysis further suggests the possibility of publication bias, which has been noted to influence pooled estimates by disproportionately including studies with positive results while potentially underrepresenting studies with null or negative findings. The impact of this publication bias on our findings could mean that the apparent alignment of subjective and objective improvements with CsA treatment may not fully reflect the true therapeutic effect across diverse patient populations. It is plausible that selective reporting has led to an overrepresentation of studies showing significant benefits, which could distort the perceived

efficacy and clinical relevance of CsA. This skew in the literature may thus yield an overly optimistic view of CsA's performance, especially in subjective measures such as OSID, which might vary considerably in real-world application. Therefore, while our results suggest beneficial effects of CsA across multiple clinical outcomes, it is essential to interpret these findings with caution, recognizing the potential for publication bias [10]. Future research should prioritize large, rigorously designed studies with transparent reporting of both positive and negative results to mitigate publication bias. A more balanced distribution of study sizes and a comprehensive report of all outcomes would allow for a clearer, less biased understanding of CsA's efficacy in DED treatment.

Thus, the available data from this review show that the use of CsA in DED is beneficial for both subjective and objective parameters. It is crucial to interpret these findings with caution, acknowledging the potential for small study effects on both TBUT and fluorescein-staining scores. This caution is warranted because of the observed asymmetry in the funnel plot analysis, as described by Debray et al.,(2018) [34], which could indicate the presence of publication bias. Future research directions must not only reduce these biases through rigorous study design and transparent reporting but should also include a wide range of study sizes and outcomes to provide more accurate bias-free data about CsA in the treatment of DED.

Despite the established advantages of CsA eye drops for DED from previous studies, these conclusions are affected by methodological, clinical, and statistical differences among the studies included. First, the classification of patients in these studies into different DED types, such as aqueous-deficient dry eye and evaporative dry eye, introduces a potential source of clinical variation. However, it is important to note that both types share a common underlying cause: a T cell-mediated inflammatory process. Therefore, combining such studies is justified and should minimally affect the results.

Variations in outcomes are influenced by several factors, including disease severity. CsA therapy appears to show promising results, particularly in the initial stages of diseases, by potentially delaying inflammation. Regardless of the duration of follow-up in different studies, statistical improvements were evident as early as two weeks after initiating CsA therapy, as seen in studies by Akpek et al., (2023), Gao et al., (2023), and Jiao et al. (2023) [12-14]. Thus, it is reasonable to combine the results based on the latest follow-up, as this time period (4 weeks to 12 months) typically allows for the manifestation of benefits. However, future trials could benefit from longer and more consistent follow-up periods to better understand the sustained effects of CsA therapy. While pooled results with varying follow-up durations did produce some data heterogeneity, given the lack of evidence suggesting CsA

tachyphylaxis over time, this approach remains justifiable. Further all studies were graded with unclear or high risk which highlights the need of more trials with high quality data.

The findings from this study align with the current knowledge of the pathophysiological mechanism involved in DED [35]. CsA has shown effectiveness across several types of DED, including evaporative and aqueous-deficiency dry eye. Notably, CsA is the sole treatment approved by the Food and FDA for the management of DED. Therefore, it is recommended for patients who do not benefit from standard symptomatic treatment. Although patients treated with CsA experienced notable improvements in both objective measures and subjective symptoms, it remains unclear if these benefits persist over the long term. Thus, lengthier clinical trials are necessary to clarify this uncertainty.

5.0 Conclusion

The findings from this systematic review contribute to evidence bolstering the superiority of CsA over ATs in improving both objective and subjective outcomes. However, it is crucial to exercise caution in assessing the overall efficacy and safety of CsA owing to the variability in methodological, clinical, and statistical approaches across the studies included. There is a need for more rigorous trials with extended durations and follow-up periods to further explore the potential of CsA in halting disease progression and determining the ideal timing for CsA therapy.

6.0 Author Contributions

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7.0 Disclosure

The authors declare that they have nothing to disclose regarding the funding and conflicts of interest with respect to this work.

8.0 Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work the author used ChatGPT in order to enhance the overall readability and clarity. After using this tool/service, the author reviewed and edited the content as needed and takes full responsibility for the content of the published article.

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