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ORIGINAL RESEARCH

An Updated Systematic Review With Meta-Analysis Of Randomized Trials On Topical Cyclosporin A For Dry-Eye Disease

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Background/Aims: To evaluate the effects of topical cyclosporin A (CsA) and artificial tears (ATs) for treating patients with dry-eye disease (DED).

Methods: On January 25, 2019, five electronic databases and reference lists were searched for randomized clinical trials (RCTs) comparing CsA with ATs among patients with DED. The search strategy had no restriction on language or time. Two authors extracted surgery, mean age, anesthesia for Schirmer's test, tear-breakup time, Schirmer's test score, fluorescein-staining score, ocular surface–disease index, and adverse events. Mean differences (MDs) were calculated for continuous outcomes and Peto ORs for dichotomous data with zero cells. Results were analyzed with 95% CIs in a random-effect model.

Results: Eleven RCTs recruiting 1,085 cases with DED were included. Pooled results showed that CsA had better tear-breakup time (MD 0.94, 95% CI 0.08–1.80), fluorescein-staining score (standardized MD −0.72, 95% CI −1.28 to −0.16), and ocular surface–disease index (MD −4.75, 95% CI −6.31 to −3.18) when compared to ATs. Although CsA had more adverse events than ATs (Peto OR 7.70, 95% CI 3.17–18.68), no serious adverse events were reported.

Conclusion: Overall, CsA is an effective option for treating patients with DED, yet our evidence indicated decreasing effects when CsA was combined with ATs. CsA may be worth suggesting to relatively older patients with DED. We anticipate further RCTs to explore the effects of treatment duration, optimal dosage, and efficacy of CsA in different DED etiology.

Keywords: dry eye, cyclosporin A, meta-analysis

Introduction

Dry eye disease (DED; keratoconjunctivitis sicca), is one of the most common ophthalmological diseases, affecting 7%–33% of older population.[1–3] This multifactorial disease is commonly observed among females, and its prevalence increases with age.[4,5] DED causes many symptoms, including blurred vision, burning sensation, and photophobia. These symptoms impair daily life and lead to loss in productivity.[6] Therefore, appropriate management of DED is now an important issue around the world.

Multiple pathophysiology mechanisms induce DED, eg, dysfunction in lacrimal glands, inflammation of the ocular surface, and interconnecting neural pathways. These various mechanisms cause unstable tear film, hyperosmolar tears, and a damaged ocular surface,[7] resulting in a vicious cycle and making symptoms progress.[8] T cell–related inflammatory processes play an important

role in DED. Once an inflammatory cascade presents, T cells abort apoptosis of the epithelium on the ocular surface, increase cytokines secretion, and recruit more T cells to the ocular surface, remaining for about 110 days.[9] Therefore, immunomodulators are considered a promising treatment for DED.

The Tear Film and Ocular Surface Society International Dry Eye Workshop suggested DED management according to DED stage. Topical immunomodulatory agents, such as steroids and nonsteroid drugs, are recommended in stage two DED.[10] While topical steroids are beneficial in DED, they also result in various complications, including cataracts and glaucoma.[11] To avoid these compilations, clinical trials have investigated nonsteroid drugs, and a popular treatment in those trials has been cyclosporine A (CsA). A common immunomodulator, CsA decreases the number of activated T cells and the expression of inflammatory markers in the conjunctiva of patients with DED.[12,13] It not only regulates inflammation but also prevents apoptosis in epithelial cells of conjunctiva.[12,14] CsA was approved by the US Food and Drug Administration for treating patients with moderate–severe DED in 2013.[15]

Although synthesized evidence has reported efficacy of CsA in the past decade,[16–19] results have been highly heterogeneous.[18,19] For instance, the pooled results of ocular surface–disease index (OSDI; I^2=82%), tear-breakup time (TBUT; I^2=96%), and Schirmer's test (I^2=92%) in the last synthesized evidence in 2015 reflected vary high heterogeneity, which may have been due to age, treatment duration, and drug formulation. Our study aimed to figure out the real effect of CsA by gathering the newest evidence on this topic and exploring sources of heterogeneity.

Methods

Our team members are medical doctors in a department of ophthalmology and an experienced researcher in systematic reviews with meta-analysis.[20–23] We completed the evidence selection, quality assessment, and quantitative synthesis according to the PRISMA guidelines.[24] The study protocol was registered on PROSPERO (CRD42019117429): https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=117429.

Study Selection

To examine the effects of CsA and artificial tears (ATs) on DED, we defined eligible criteria for evidence selection beforehand. Inclusion criteria were randomized clinical trials (RCT), patients with DED, and comparing CsA to ATs. Two authors (HIT and SCC) selected evidence independently. The other author (YNK) made final judgments through discussion for any disagreement on evidence selection.

Data Sources And Search Strategy

We searched the Cochrane library (CENTRAL), Embase, PubMed, Scopus, and Web of Science for RCTs comparing effects of CsA and ATs among patients with DED. Our primary search strategy was built in PubMed using natural language, medical subject headings (MeSH in PubMed and Emtree in Embase), and abbreviations of relevant terms of CsA and DED. We did not put restrictions on language or publication date. Then, we adapted the search strategy to the other databases before January 25, 2019 (online supplementary file 1).

Quality Assessment And Data Extraction

Two authors (HIT and SCC) individually reviewed the included RCTs by using the Cochrane risk-of-bias tool. This tool consists of seven items for evaluating methodological bias. These authors also extracted relevant information about location, sample size, mean age, sex, treatment, treatment duration, anesthesia for Schirmer's test, and outcome data. Outcome data comprised TBUT, Schirmer's test, fluorescence-staining test, and OSDI score. Any disagreement on data definition was discussed by all authors.

Data Synthesis And Analysis

This study used pairwise meta-analyses for quantitative synthesis. Means and SDs were extracted for outcomes of TBUT, Schirmer's test, fluorescence-staining test, and OSDI score. Weighted mean differences (WMDs) with 95% CIs were calculated for outcomes with continuous data. Numbers of events were extracted for side-effect outcomes. Peto ORs with 95% CIs were calculated for the outcomes with binary data when any zero-cell value was reported. We pooled data in a random-effect model for all outcomes. When P<0.05, we judged the outcome statistically significant.

Because some potential factors may affect pooled results, we used subgroup analysis and metaregression for clarifying effects from treatment duration, combination therapy, mean age, and type of Schirmer's test in trials. Moreover, we examined heterogeneity and small-study

effects for pooled results. We further conducted sensitivity analyses for those highly heterogeneous results. To detect small-study effects, we drew funnel plots with Egger's test. When the Egger's regression intercept reached statistical significance, we judged that this a biased finding.

Results

We identified 642 references from five electronic databases. After duplicates and irrelevant references had been removed, we retrieved 23 full texts for review. Lastly, the eligible 12 references from eleven RCTs were included in this study for qualitative and quantitative synthesis.[25–36] The flow diagram of evidence selection is shown in Figure 1.

Characteristics And Quality Of Included Studies

The eleven eligible RCTs recruited 1,085 patients with DED from the US[28,30,32–34] and Asia during 2006–2016.[25–27,29,35,36] Available information showed that the mean age in each RCT was 39.45–73 years. A total of 164 (29.13%) males were included in the RCTs. Treatment duration was 2–12 months (Table 1). Overall, the quality of the included RCTs is shown in online supplementary file 2. Unfortunately, these trials provided patients different prescriptions with diverse dosage and frequency. Furthermore, some of those trials also allowed patients in the CsA group to use ATs. These conceptual heterogeneities may have resulted in statistical heterogeneity. There were no significant differences in TBUT, Schirmer's test score, fluorescein-staining score, or OSDI between CsA and ATs at baseline (online supplementary files 3 to 6).

Primary Outcomes

TBUT data for quantitative synthesis were available from six of the eleven trials.[25,28–30,34,36] Based on the data of 333 cases, CsA led to significantly higher TBUT scores than ATs (WMD 0.94, 95% CI 0.08–1.80) with high heterogeneity (I^2=85%, Figure 2A). In subgroup analysis, however, significance was observed only for treatment duration >3 months (WMD 1.21, 95% CI 0.36–2.05, online supplementary file 7) and comparison of CsA alone with ATs alone (WMD 1.74, 95% CI 1.17–2.32). Interestingly, comparison of CsA alone and ATs alone showed a bigger effect size with reduced heterogeneity (I^2=64%) than overall pooling (online supplementary file 8). Results of meta-regression showed that mean age was not significantly associated with MD in TBUT scores between CsA and ATs and showed a positive trend (point estimate 0.03, P=0.58, online supplementary file 9). To confirm the effect of CsA on TBUT score, we also applied sensitivity analysis, and the overall pooled trend was not significantly affected by any single trial (online supplementary file 10). No small-study bias (Egger's test, t =−0.52, P = 0.72) was detected in the pooled result of TBUT (online supplementary file 11).

Five RCTs recruiting 269 cases with DED provided usable data on Schirmer's test scores,[25,28,30,34,36] and pooled results showed no significant difference between the two groups, but a favorable trend for CsA over ATs (WMD 0.45, 95% CI −2.25 to 3.15). Because this was a highly heterogeneous result (I^2=86%, Figure 2B), we conducted further analyses. Then, we observed significant results at the first and second months, but an insignificant difference after the third month (online supplementary file 12). Moreover, we also found a better outcome from CsA in the anesthesia subgroup using Schirmer's test, but this result was based on only one trial. There were no significant differences between the two treatments using Schirmer's test II (online supplementary file 13). Interestingly, CsA alone showed a significantly better score on Schirmer's test than ATs alone (WMD 2.18, 95% CI 1.62–2.74) with very low heterogeneity (I^2=0). On the other hand, we observed no significance and very high heterogeneity for CsA plus ATs vs ATs alone (I^2=95%, online supplementary file 14). Furthermore, mean age was positively associated with MD in Schirmer's test score between CsA and ATs (point estimate 0.67, P<0.001, online supplementary file 15). There was noo evidence of small-study bias (Egger's test, t=−1.57, P=0.38) in the pooled results of Schirmer's test scores (online supplementary file 16).

Secondary Outcomes

Data for fluorescein staining were reported by only three RCTs (152 cases),[28,30,36] and pooled results showed that CsA had significantly lower scores than ATs (standardized MD −0.72, 95% CI −1.28 to −0.16) with a relatively higher heterogeneity (I^2=61%, Figure 3A). Appropriate OSDI-score data for quantitative synthesis were available from only two RCTs (102 DED cases).[30,34] Pooled results showed significantly lower OSDI scores for CsA than ATs (WMD −4.75, 95% CI −6.31 to −3.18, Figure 3B) with very low heterogeneity (I^2=0). Adverse-event data were

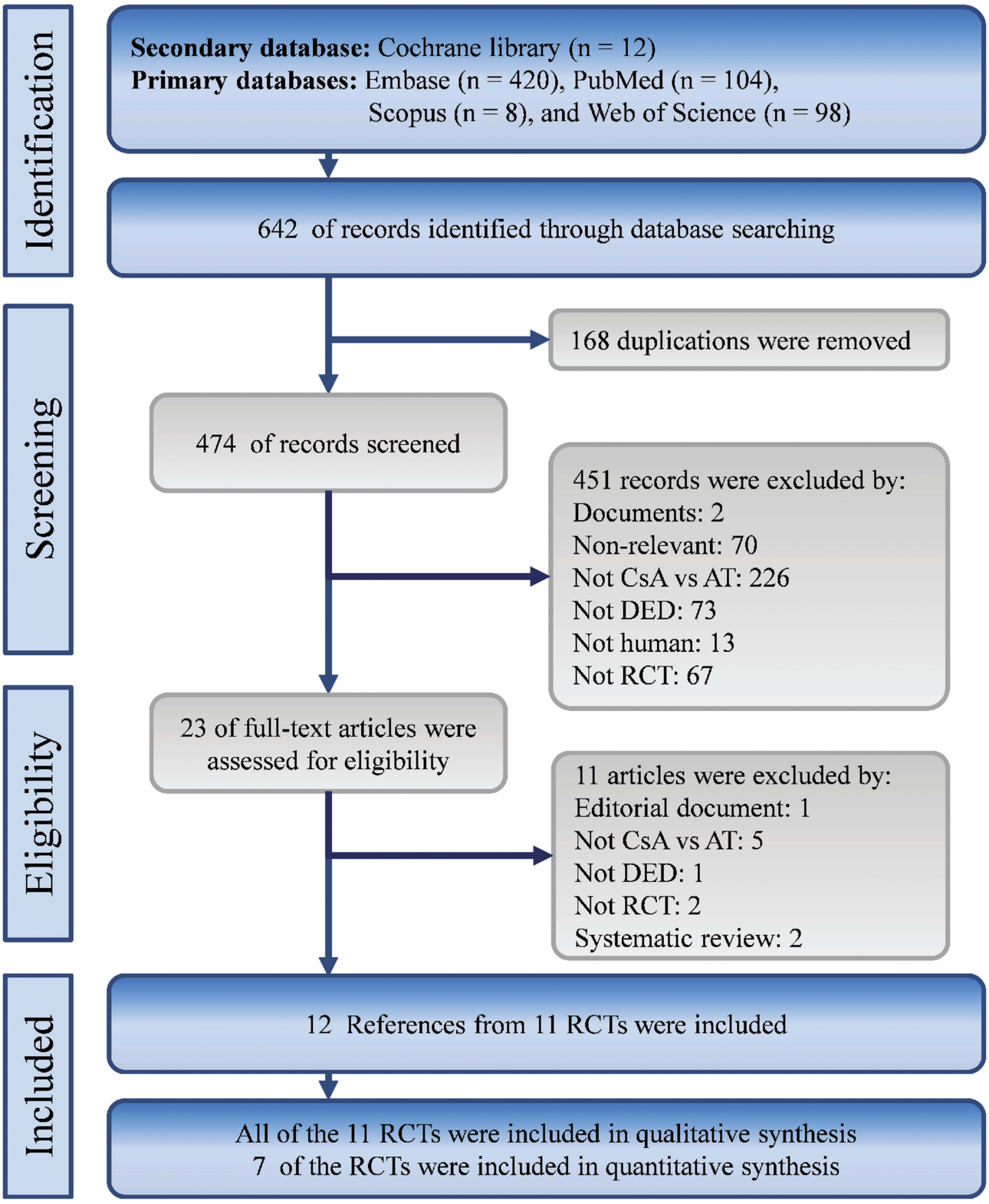

Figure 1 Flow diagram of evidence selection.

available from four trials (203 cases).[25,27–29] Pooled results showed that CsA had a significantly lower adverse-event rate than ATs (Peto OR 7.70, 95% CI 3.17–18.68) with low heterogeneity (I^2=0, Figure 3C).

Table 1 Characteristics of included studies

	Location	Sample Size (Eyes)		Mean Age, Years	Sex (Male/ Female)	Blinding	Treatment Group	Treatment Duration	Anesthesia For Schirmer's Test
		CsA	ATs						
IAltiparmak et al, 2009[25]	Turkey	25	48	41.6	6/31	NR	CsA + ATs	6 months	Yes
Demiryay et al, 2011[26]	Turkey	44	40	45.50	2/40	Partially masked	CsA + ATs	4 months	No
Kim et al, 2009[27]	Korea	100	100	39.45	40/60	Not masked	CsA + ATs	3 months	No
Perry et al, 2006[28]	USA	32	34	NR	NR	Double-masked	CsA alone	3 months	Yes
Prabhasawat et al, 2012[29]	Thailand	36	34	51.45	13/57	Double-masked	CsA alone	3 months	No
Rao et al, 2010[30,31]	USA	82	66	47.81	17/41	Investigator-masked	CsA alone	12 months	Yes
Salib et al, 2006[32]	USA	22	20	47	2/19	Double-masked	CsA alone	4 months	Yes
Schechter et al, 2009[33]	USA	42	32	73	24/13	Double-masked	CsA alone	3 months	Yes
Willen et al, 2008[34]	USA	44	44	43.1	7/37	Double-masked	CsA alone	3 months	Yes
Wu et al, 2009[35]	China	52	52	51	23/29	NR	CsA + ATs	3 months	No
Yang et al, 2016[36]	China	68	68	51.33	30/72	NR	CsA + ATs	2 months	No

Abbreviations: ATs, artificial tears; CsA, cyclosporin A; NR, not reported.

Discussion

Key Findings

As we know, cytokine-driven and immunomediated inflammation will occur within the lacrimal functional unit, leading toward an alteration in tear quantity and composition. Our evidence confirmed the benefits of topical CsA drops on DED. The benefits were observed in not only subjective outcomes but also objective clinical parameters, including TBUT, fluorescence-staining tests and OSDI scores. These findings echo previous evidence of the weak association between subjective symptoms and objective parameters.[37] Actually, it is important that CsA not only had benefits on objective parameters but also improved patients' subjective response. However, the benefits of CsA may be affected by treatment duration, combination therapy, and mean age at trial level.

Unfortunately, the data in this study cannot give a clear answer to the question of how treatment duration affects the effects of CsA on patients with DED. Our outcomes showed some inconsistent trends. For instance, TBUT showed that the effects of CsA became more evident with longer treatment duration (>3 months). In contrast, Schirmer's test scores revealed that CsA had no more benefit for DED after a relatively longer period (>3 months). These puzzling and uncertain results might have been due to a single-study effect and lack of data at the first- and second-month visits. Also, the mechanism of CsA on DED may have contributed to the inconsistency among outcomes. To clarify the effect of combination therapy of CsA and preservative-free ATs through subgroup analysis, interestinglycombination therapy did not have more benefit than ATs alone on either TBUT or Schirmer's test scores. These findings go against some previous studies.[17,38,39] The mechanism of the interaction between CsA and ATs should be investigated in future.

Mean age at trial level may be another interesting factor affecting the efficacy of CsA. The current findings indicate that MDs in Schirmer's test scores between CsA and ATs were significantly associated with mean age. Although this phenomenon was not significant in the outcome of TBUT, a similar trend was observed. All these trends showed that topical CsA is probably more effective on DED in a relatively older population. A possible reason for these trends is that systemic use of Cs has a fast clearance rate in younger populations. Unfortunately, the current results only point to topical CsA yielding much better outcomes than ATs among relatively older patients with DED. We anticipate further study to investigate how age affects topical Cs pharmacokinetics among patients with DED.

Comparing Recent Evidence And Argument

Before our study, there had been several syntheses. In the last meta-analysis, CsA was compared to ATs, vehicle, or no topical treatment. The results were highly heterogeneous for OSDI, TBUT, Schirmer's test, and corneal fluorescein staining. Most studies have not declared the composition of their vehicles. The different formulation of the vehicle in each study may cause heterogeneity, though most patients with DED receive ATs in real-

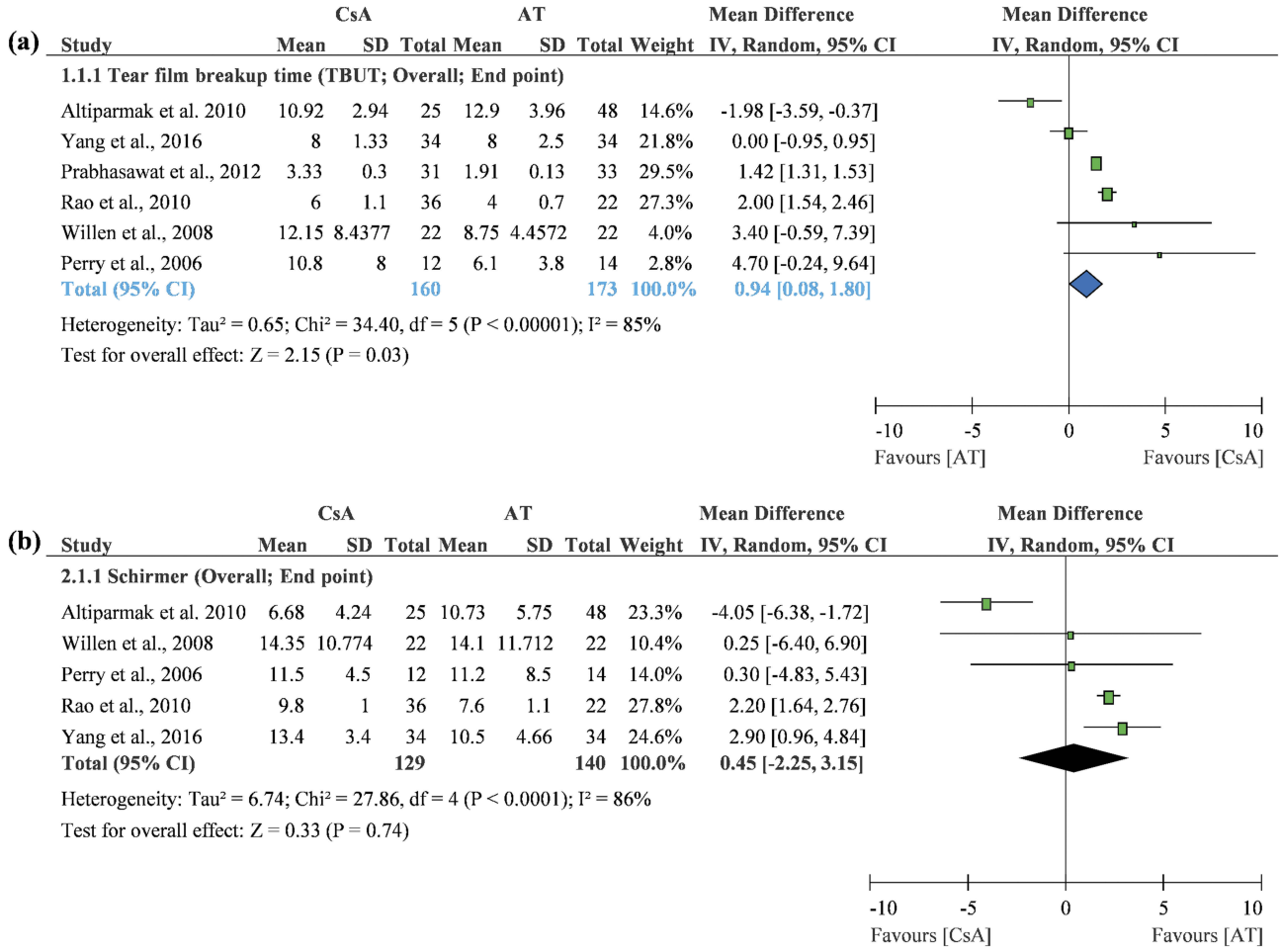

Figure 2 Forest plots of primary outcomes. (**A**) Tear film–breakup time. (**B**) Schirmer's test score.

world clinical practice. Therefore, to reflect real-world practice, our study focused only on those studies using ATs in a control group. We got pooled results with relatively lower heterogeneity than previous meta-analyses through subset analysis, and thus our results provide some insights for clinicians in clinical practice.

Our study also responds to a reflection on the effectiveness of CsA for DED through analyzing spending and prescriptions in the US.[40] That article indicated that CsA was not effective for DED, but rather brought tears to eyes by burning billions in the US. Actually, the economic burden and controversial effect of CsA should be reconsidered in the real-world context and updated synthesized evidence, especially in this visual displayed era.[41] In recent years, visual displayed terminal–related ocular symptoms have been increasing, and the prevalence of visual displayed–terminal DED (49.5%) was higher than in the common population in recent year.[42] Therefore, an appropriate interpretation for the increased spending on and prescriptions for CsA should be that spending on and prescriptions for CsA may be increased with the increasing prevalence of DED. Furthermore, a report indicated that definite DED leads to US$799 work-productivity loss.[43] It will be a huge loss when DED is not treated properly.

We agree with the criticism of insufficient evidence for the effectiveness of CsA in the previous systematic review by Schwartz and Woloshin.[17,40] As such, we updated the synthesis with a meta-analysis for this issue. Our work provides direct evidence showing a better outcome for CsA than ATs in patients with DED, and the evidence overcame the criticism of single-group analysis by Schwartz and Woloshin.[17,40] Although our study tried to provide stronger evidence through synthesizing trials with better study design and reducing conceptual heterogeneity from different comparators, evidence for different types of CsA needs to be discussed to gain better understanding on this topic.

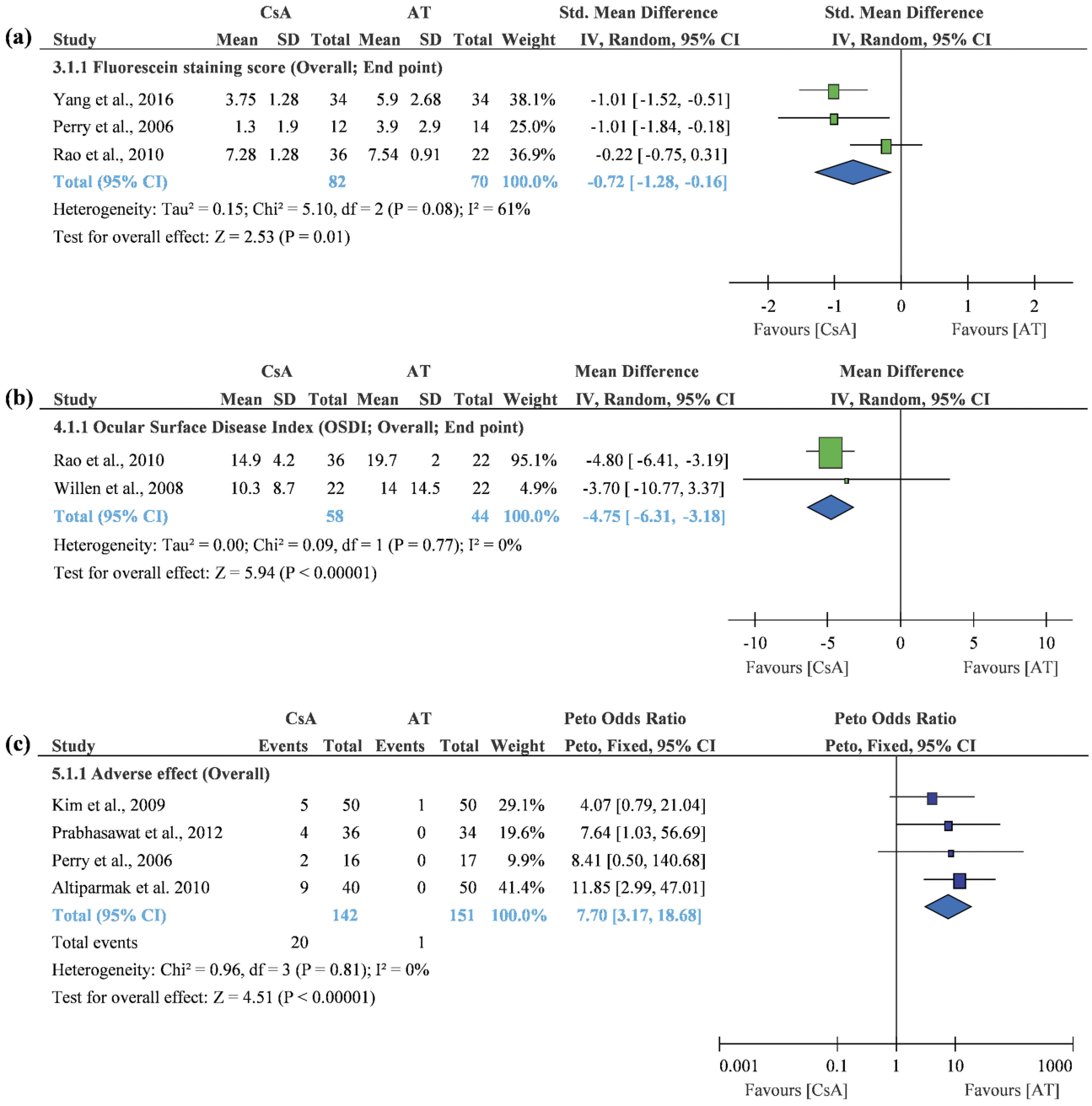

Figure 3 Forest plots of secondary outcomes. (**A**) Fluorescein-staining score. (**B**) Ocular surface disease–index score. (**C**) Adverse events.

For instance, an important type of CsA is worth taking into consideration, as we mentioned with regard to the effects of CsA on DED. Due to poor water solubility, the bioavailability and tolerability of typical oil-based CsA-delivery systems is an challenging issue.[44] The novel cationic emulsion formulation was developed in the past decade, and several trials in Europe reported that CsA cationic emulsion was superior to vehicle in improving TBUT, Schirmer's test score, OSDI score, corneal fluorescein staining, and reduction in inflammatory markers. Though some ocular adverse effects were noted, systemic adverse events were not observed.[8,45] As we mentioned before, we did not include these studies comparing CsA to vehicle because of the potential risk of causing heterogeneity. However, these trials using CsA with novel formulations provide further options in treating DED. Relevant information for the remarkable trials on this type of CsA was presented in Table 2.

As we know, it is important to treat patients with DED appropriately, because DED symptoms impair daily activities and workperformance. Increasing spending on and

Table 2 Characteristics of pivotal studies of CsA CE

	Location	Sample Size (Eyes)		Mean Age, Years	Sex (Male/ Female)	Blinding	Treatment Group	Treatment Duration	Anesthesia For Schirmer's Test
		CsA	Vehicle						
Leonardi et al, 2016[45]	Italy	308	182	61.3	36/209	Double-masked	CsA alone	6 months	No
Baudouin et al, 2017[8]	France	482	496	58.2	76/413	Double-masked	CsA alone	6 months	No

Abbreviation: CsA, cyclosporin A.

prescription of CsA are a reality, but these trends cannot represent the failure of CsA. Although we agree that "standardised diagnostic criteria to assess the efficacy of topical CsA are recommended to improve the design of future RCTs in DED",[17] we cannot deny that CsA may bring tears to DED patients' eyes.

Limitations

Though our study has many advantages, it also has some limitations. Firstly, we could not control for the influence from DED etiology, though we know that etiology might relate to disease progression. The RCTs included did not differentiate etiology, and our results might thus have been affected. Secondly, timing of interventions could not be well controlled. Because of various categorizations for timing of intervention in the RCTs, we cannot exclude this variation. Thirdly, the RCTs accommodated different DED severity, dosage, treatment frequency, and combinations (target treatment). Our study could not control for these potential factors contributing to heterogeneity, though we tried to reduce heterogeneity through excluding studies comparing CsA with vehicle. However, these limitations were not well controlled in previous systematic reviews either.

Conclusion

Overall, CsA is an effective option for treating patients with DED, yet our evidence showed attenuated treatment effects when CsA was combined with ATs. That result contradicts current clinical practice, and should be interpreted in clinical practice carefully. The combination effect of CsA with ATs needs to be clarified in future by three-arm RCTs. CsA may also be worth suggesting to relatively older patients with DED. Though the current evidence adds some new practical knowledge for clinicians in treating patients with DED, we still anticipate further RCTs to explore the effects of treatment duration, optimal dosage of CsA, and efficacy of CsA on different DED etiology.

Abbreviations

CsA, cyclosporin A; DED, dry-eye disease; WMD, weighted mean difference; OSDI, ocular surface–disease index; RCT, randomized clinical trial; TBUT, tear-breakup time.

Author Contributions

HIT systematically identified evidence, critically appraised the included articles, acquired data, managed data, and drafted the first version of the manuscript. SCC supervised the research and critically revised the manuscript. YNK designed the study, systematically identified evidence, analyzed the data, interpreted the results, and drafted the first version of the manuscript. All authors contributed to data analysis and drafting and revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Disclosure

Dr Kang's current affiliations are at the Evidence-Based Medicine Center, Wan Fang Hospital, Taipei Medical University and Institute of Health Policy and Management, College of Public Health, National Taiwan University, Taiwan. The authors declare that they have nothing to disclose regarding funding or conflicts of interest with respect to this work.

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