Therapeutic efficacy of tacrolimus in vernal keratoconjunctivitis: a meta-analysis of randomised controlled trials

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ABSTRACT

Background and objective Tacrolimus has been widely used in recent years for treating allergic conjunctivitis, but there is currently no available meta-analysis regarding its therapeutic efficacy. This study systematically evaluated the effectiveness of tacrolimus in the treatment of allergic conjunctivitis.

Methods Data obtained from literature searches of the PubMed, Cochrane Library, Embase, CNKI, and Wanfang databases were retrieved by combining medical subject words and free words. Literature was selected on the basis of established inclusion and exclusion criteria, and the extracted data were evaluated for risk of bias using RevMan 5.3 for meta-analysis.

Results A total of 177 articles were retrieved, of which 5 articles were eventually selected, all of which involved tacrolimus treatment for vernal keratoconjunctivitis. A total of 203 samples were analysed. Results of the meta-analysis showed that the tacrolimus treatment group had significantly lower ocular objective sign scores (SMD −1.39, 95% CI −2.50 to −0.27; p<0.05) and had a significantly lower subjective symptom evaluation score (SMD −0.92, 95% CI −1.59 to −0.24; p<0.05) than the control group.

Conclusion Current evidence shows that tacrolimus is effective in treating vernal keratoconjunctivitis.

INTRODUCTION

The conjunctiva is a thin and transparent membrane that covers the outer surface of the sclera and the inner surface of the eyelid. Inflammation or infection of the conjunctiva is called conjunctivitis and is characterised by a dilation of the conjunctival blood vessels, which leads to conjunctival hyperaemia and oedema, often accompanied by secretion.[1]

The prevalence of conjunctivitis varies according to its condition type. Allergic conjunctivitis is common, affecting 15–40% of the US population, and is more prevalent in the spring and autumn .[2] It is a recurrent inflammatory disease that can be stratified into mild forms—seasonal conjunctivitis, perennial conjunctivitis—and severe forms—vernal keratoconjunctivitis (VKC), atopic keratoconjunctivitis (AKC) and giant papillary conjunctivitis.[3] Its clinical manifestations include varying degrees of congestion, itching, tearing, burning, tingling, photophobia, increased secretion, and other associated symptoms and signs which are commonly controlled or alleviated by antihistamines, mast cell stabilisers, corticosteroids, non-steroidal anti-inflammatory drugs, and immunosuppressive agents.[4] Importantly, this disease occurs repeatedly, with a majority of patients having intermittent symptoms several times a year and nearly 30% exhibiting frequent episodes with intense symptoms.[5] For these reasons, the treatment of allergic conjunctivitis is challenging. Although local drug administration may control acute symptoms, there are currently no treatments for controlling the recurrence and sequelae of the disease.

Tacrolimus (TAC) is a macrolide immunosuppressant[6] that has been extensively used in tissue transplants. Its mechanism of action is similar to that of cyclosporine, targeting mainly CD4+ T lymphocytes, where it inhibits calcineurin, thereby suppressing interleukin 2 (IL-2) production and preventing the ensuing inflammatory cascade and eosinophil recruitment. In addition, TAC also acts as a membrane stabiliser for mast cells by inhibiting histamine release and prostaglandin production.[7] Studies have shown that TAC has a superior immunosuppressive effect to cyclosporine. Moreover, because TAC ointment has a higher efficacy and fewer side effects in comparison with corticosteroid ointment, it can also be used as a replacement therapy for corticosteroids.[8 9]

TAC has been extensively used in corneal transplantation, uveitis, and graft-versus-host disease.[8] Studies in recent years have also shown that topical TAC applications significantly alleviate the symptoms and signs of various forms of chronic allergic eye disease. In the treatment of most cases of allergic conjunctivitis, topical TAC is more effective than topical cyclosporine A.[3] TAC is currently used to treat allergic conjunctivitis at concentrations ranging from 0.005% to 0.1% and is an effective treatment method for steroid-resistant refractory VKC.[10] In addition, the effect of topical application of 0.02% TAC on giant papillae occurring in AKC and VKC is significantly better than cyclosporine A.[3] Therefore, TAC is gradually being used by an increasing number of clinicians for severe allergic conjunctivitis.

To our knowledge, however, no meta-analysis of the therapeutic efficacy of TAC in allergic conjunctivitis has been reported. Hence, this study used meta-analysis methods to systematically evaluate the therapeutic efficacy of TAC in allergic conjunctivitis in order to provide a reference for future clinical applications of TAC in allergic conjunctivitis treatment.

RESEARCH METHODS

This meta-analysis followed the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement.[11]

Searching strategy

The medical subject words and free words, such as "tacrolimus or FK506", "conjunctivitis", and related synonymous terms were used to conduct searches in the PubMed, Cochrane Library, Embase, China National Knowledge Infrastructure (CNKI), and Wanfang databases and were combined using Boolean logic operations. The deadline for database searching was March 2020.

Criteria for literature selection
Inclusion criteria

Research articles for this meta-analysis were selected on the basis of the following criteria: (1) TAC treatment of allergic conjunctivitis published in English or Chinese; (2) randomised controlled trials (RCTs); (3) primary and secondary outcome indicators reported, where the primary outcome was classified by an objective sign score that included such signs as limbal conjunctival hypertrophy, conjunctival congestion, Trantas' dots, and punctate keratitis. A secondary outcome was classified according to a subjective symptom score that included symptoms such as itching, secretions, hyperaemia, tearing and pain due to foreign body sensation, and photophobia; (4) complete primary and secondary outcome indicator data; (5) a symptom score scale with the following stratification: score 0—none; score 1—mild (occasional symptoms); score 2—moderate (common symptoms); score 3—severe (sustained symptoms).

Exclusion criteria

The following criteria were used to exclude articles: (1) non-RCT, reviews, case reports, observational studies, editorial publications, and articles with only published abstracts; (2) articles written in non-Chinese or non-English languages; (3) studies of non-human trials; (4) reports without any primary or secondary outcome indicators; (5) studies with ambiguous data and/or incomplete information, having incomplete and/or invalid data; (6) previously reported publications.

Data extraction and management

Original studies were reviewed by two independent reviewers. Studies in which reviewer conclusions differed were either deliberated upon in order to arrive at a consensus or submitted to a third reviewer to obtain a confirming opinion. Each study included the following details: first author, year of publication, country of origin, patient age, sample size, interventions, and the chief outcome indicators obtained from the study.

Risk assessment of bias in the included studies

Studies were evaluated for risk of bias using the Cochrane risk-of-bias tool, which included random sequence screening, allocation concealment, blinding of patients and investigators, data completeness of results, selective reporting, and other biases. Each type of bias was classified as high, low, or unclear. Ambiguities in classification were re-evaluated and resolved through discussion.

Statistical analysis

Review Manager Software (version 5.3, Cochrane Community, UK) was used for data analysis. Although some differences between outcome indicators were observed, most of the outcome indicators included in this meta-analysis were continuous variables. Quantitative analyses included the mean, standard deviation (SD), and sample size of each result. Results from comparable evaluation scales were re-analysed using the weighted mean difference (WMD) and 95% confidence interval (95% CI) to assess the degree of similarity. When the assessment scales differed greatly, standard mean differences (SMD)
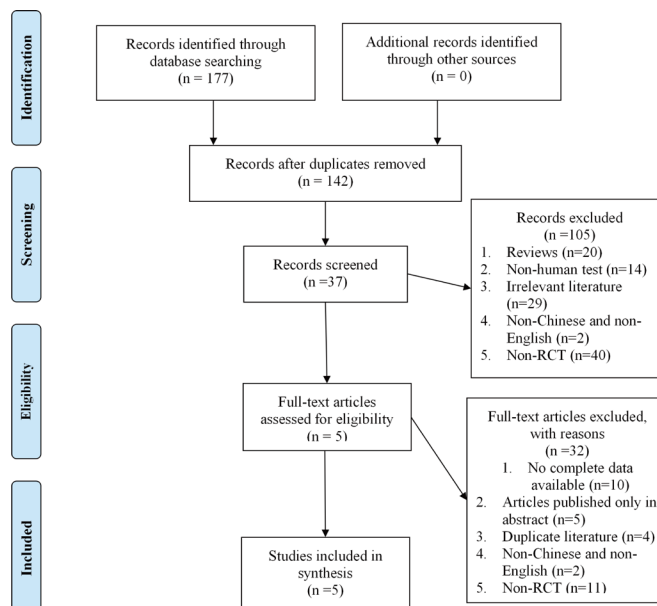
Figure 1 PRISMA diagram of literature screening. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RCT, randomised controlled trial.

and 95% CI were used. The heterogeneity between the included trials was evaluated by I^2 test statistics. When the heterogeneity was clear and $I^2 > 50\%$, a random effect model was used; otherwise, a fixed effect model was used. A value of $p < 0.05$ was considered significant. When the numbers of included studies exceeded 10, a funnel plot was used to analyse publication bias. Sensitivity analysis was performed by excluding individual studies one by one to assess the impact of individual studies on aggregate estimates.

RESULTS
Search results

A total of 177 articles were retrieved from the database through the aforementioned search strategy, including 107 articles from PubMed, 17 articles from the Cochrane Library, 22 articles from Embase, 9 articles from CNKI, and 22 articles from Wanfang Data. Five articles were eventually included after the screening based on the established inclusion and exclusion criteria.[12–16] Figure 1 shows the flow chart of literature screening from this meta-analysis.

Basic features of included literature

All five articles included in this study investigated TAC treatment of VKC. Three articles were sourced from English language publications and two from Chinese publications. Overall, the combined patient sample size was 203. The general features of the included literature are shown in table 1.

Risk assessment of bias in the included studies

Figures 2 and 3 summarise the methodological quality parameters and author conclusions regarding risk of bias for each study.

Results of meta-analysis
Ocular objective sign score

All five articles evaluated the objective sign score of the eye after completing treatment. Significant heterogeneity was observed between articles ($I^2 = 91\%$), so the random effect model was used. The results of meta-analysis showed that the ocular objective sign scores of the TAC test group at the end of the treatment

Table 1 Characteristics of included literature

Author/year/ref	Country	Sample size (T/C)	Age (T/C)	Drug concentration (T/C)	Frequency of administration (T/C)	Intervention measure (T/C)	Intervention duration	Objective sign baseline (mean±SD, T/C)	Subjective symptom baseline (mean±SD, T/C)	Outcome measures
Zhang X/ 2014[12]	China	8/8	12.56±8.97	0.1%	One drop/time, twice daily	Tacrolimus/ placebo	4 W	17.3750±5.31507/ 19.0000±5.57375	8.3750±2.24722/ 8.3125±2.21265	Signs, symptoms
Pucci N/ 2015[13]	Italy	30/30	9.05±2.12	0.1%/1%	One drop/time, 3 times daily	Tacrolimus/ cyclosporine A	3 W	6.016±1.133/ 6.000±1.121	6.3±3.415/ 6.566±3.349	Signs, symptoms, side effects, quality of life score,
Zanjani H/ 2017[14]	Iran	20/20	10.9±3.4/ 11.3±5.4	0.005%/ 1000000 IU/mL	Two drops/time	Tacrolimus +placebo/ interferon α-2b+placebo	NA	7.7±1.2/ 8.9±1.2	9.6±0.8/ 9.7±0.9	Signs, symptoms, side effects
Kumari R/ 2017[15]	India	16/16	8.06±1.94/ 7.12±1.66	0.03%/0.05%	Twice daily+4 times daily/ 4 times daily+twice daily	Tacrolimus +placebo/ cyclosporine +placebo	6 W	4.88±1.5/ 4.5±1.15	7.06±2.59/ 7.75±2.90	Signs, symptoms, side effects, recurrence rate
Xiang Q/ 2018[16]	China	28/27	10.86±2.98/ 10.93±3.51	NA/NA	One drop/time, twice daily/1 drop/time, 4 times daily	Tacrolimus/ tobramycin dexamethasone	1 W	15.25±1.69/ 15.19±1.57	11.21±2.25/ 11±2.20	Signs, symptoms,

C, Control group; T, Trial group; W, weeks.
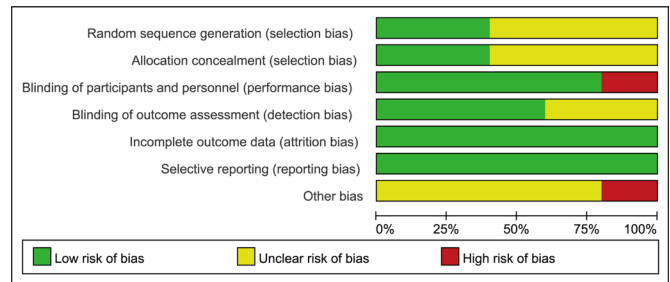
Figure 2 Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

were significantly lower than those of the control group (SMD −1.39, 95% CI −2.50 to −0.27; p<0.05) (figure 4).

Subjective patient symptom score

All five articles reported the subjective patient symptom score at the end of treatment. Because statistically significant heterogeneity between articles was observed (I^2=79%), the random effect model was used. The results of meta-analysis showed that the subjective symptom scores of the patients in the TAC trial group at the end of the treatment were significantly lower than those of the control group (SMD −0.92, 95% CI −1.59 to −0.24; p<0.05) (figure 5).

Publishing bias and sensitivity analysis

A funnel plot was not prepared due to the small number of articles (only five) included in this study and the low-test reliability of the funnel plot. Consecutive exclusion of individual studies was followed by meta-analysis on the remaining studies in order to assess result consistency. Combined effect values were found to be stable following the exclusion of single studies one by one, indicating that the results of the meta-analysis were relatively stable.

DISCUSSION

Allergic conjunctivitis, also known as eye allergy, is a common allergic disease. Considering that 20% of people suffer from allergic diseases, and that half of these individuals experience eye allergies, it is estimated that up to 10% of the global population suffers from allergic conjunctivitis,[5] with the quality of life of up to 30% of these patients being seriously affected.[17] Allergic conjunctivitis also incurs additional burdens associated
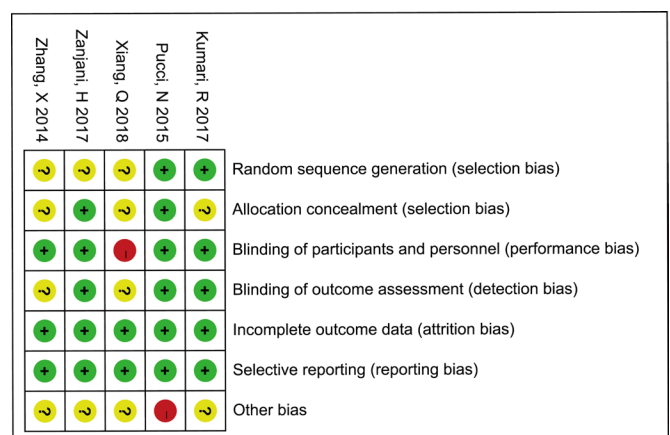
Figure 3 Risk of bias summary: review authors' judgements about each risk of bias item for each included study.
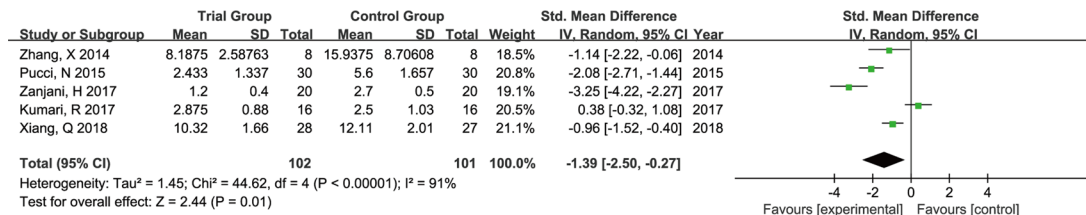
Study or Subgroup	Trial Group Mean	SD	Total	Control Group Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI	Year
Zhang, X 2014	8.1875	2.58763	8	15.9375	8.70608	8	18.5%	-1.14 [-2.22, -0.06]	2014
Pucci, N 2015	2.433	1.337	30	5.6	1.657	30	20.8%	-2.08 [-2.71, -1.44]	2015
Zanjani, H 2017	1.2	0.4	20	2.7	0.5	20	19.1%	-3.25 [-4.22, -2.27]	2017
Kumari, R 2017	2.875	0.88	16	2.5	1.03	16	20.5%	0.38 [-0.32, 1.08]	2017
Xiang, Q 2018	10.32	1.66	28	12.11	2.01	27	21.1%	-0.96 [-1.52, -0.40]	2018
Total (95% CI)			102			101	100.0%	-1.39 [-2.50, -0.27]	

Heterogeneity: Tau² = 1.45; Chi² = 44.62, df = 4 (P < 0.00001); I² = 91%
Test for overall effect: Z = 2.44 (P = 0.01)

Figure 4 Forest plot of objective sign scores at the end of treatment.

with direct medical costs as well as indirect economic effects that are associated with the illness, such as the inability to work, attend school, or work efficiently.[18]

TAC is mainly used clinically for treating various chronic allergic conjunctivitis conditions, including VKC, AKC, and giant papillary conjunctivitis.[19] Several studies have shown that TAC plays an important role in the treatment of chronic allergic conjunctivitis, based on TAC's effect in substantially reducing the symptom score by approximately 50%.[20–26] In addition, the safety of long-term TAC application in the treatment of allergic conjunctivitis has also been verified. A study by Al-Amri et al,[27] using 0.1% topically applied TAC for treatment of AKC over 48 months, demonstrated the control and remission of the disease in the absence of other medications. Beyond a mild burning sensation, no other adverse reactions were observed. A study by Müller et al,[7] with continuously applied 0.03% TAC over a period of 41 months, showed no serious side effects in the treatment of VKC, highlighting the safety of long-term application. In brief, the data and results of these studies indicated that TAC was a safe and effective treatment for allergic conjunctivitis and an efficacious replacement for steroid therapy designed to control disease activity.

Consistent with previous research reports, the results of this meta-analysis showed that the clinical application of TAC in the treatment of VKC in allergic conjunctivitis was therapeutically effective, greatly improving ocular objective signs, as well as reducing itching, congestion, tearing, foreign body sensation, and other subjective patient symptoms. Additionally, most of the reported adverse reactions were limited to eye burning,[12 13] with no other adverse reactions reported.

The high heterogeneity in this study may be due to several causes. (1) The control was not uniform, as some research control groups received only placebo,[12] while other research control groups received cyclosporine,[13 15] interferon α-2b,[14] or tobramycin dexamethasone.[16] (2) The drug concentration and frequency of TAC administration varied across different studies. TAC concentrations in the included studies, for example, were 0.1%, 0.005%, and 0.03%. The number of daily TAC administrations given to the patients also varied in different studies. (3) The TAC treatment duration varied across different studies as well. For instance, one study treated the patients with TAC for up to 6 weeks,[15] while another study treated the patients for just 1 week.[16] (4) The baseline scores of objective signs and baseline

scores of subjective symptoms between the five included studies were also different. For example, the average scores of objective signs were higher than 15 points in two studies,[12 16] lower than 9 points in another two studies,[13 14] and even lower than 5 points in the remaining study.[15]

This study had some limitations: (1) the number of included studies was small, thus requiring caution in the interpretation of results; (2) the sample size involved in the included studies was also small, which was prone to bias; (3) the analysis of patient objective signs and subjective symptoms after TAC treatment showed high heterogeneity in the merged literature data, thereby reducing the reliability of the analysis—accordingly, further research will be needed to verify the findings of this study; (4) given the small amount of literature included in the present study, no subgroup analysis of the causes of high heterogeneity was performed.

In addition, it is worth noting that the five studies included in this meta-analysis are all TAC treatments for VKC, with differences in the concentration, dose, frequency of administration, intervention duration, follow-up time, intervention measures, and scoring indications in each study. These differences increase the difficulty of organising and analysing existing research data and reduce the credibility of the meta-analysis. Therefore, we hope that investigators can use appropriate and consistent TAC concentrations, doses, frequency of administration, intervention duration, intervention measures, and scoring indications in clinical studies of allergic conjunctivitis in the future. In addition, future studies should increase the sample size to improve reliability, to better assess the clinical use of TAC in treating allergic conjunctivitis.

CONCLUSION

The existing evidence showed that TAC was effective in the treatment of VKC in allergic conjunctivitis, and significantly improved and controlled the ocular objective signs and subjective symptoms of patients, with few reports of adverse reactions. Since there are currently few clinical studies of TAC in the treatment of allergic conjunctivitis, meta-analysis of the efficacy of TAC in allergic conjunctivitis has not been previously reported. This meta-analysis was limited by the quantity and quality of the studies currently available for review, and will require further validation of the results in future, high-quality studies.
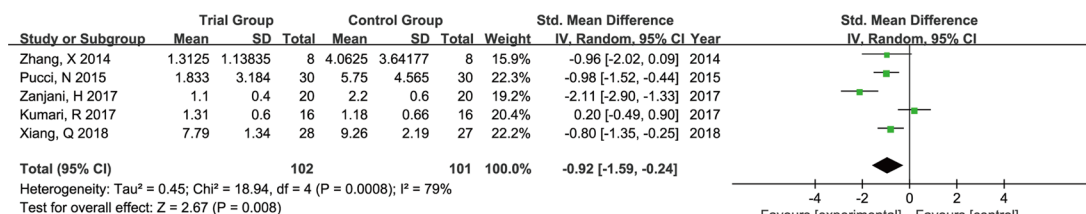

Study or Subgroup	Trial Group Mean	SD	Total	Control Group Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI	Year
Zhang, X 2014	1.3125	1.13835	8	4.0625	3.64177	8	15.9%	-0.96 [-2.02, 0.09]	2014
Pucci, N 2015	1.833	3.184	30	5.75	4.565	30	22.3%	-0.98 [-1.52, -0.44]	2015
Zanjani, H 2017	1.1	0.4	20	2.2	0.6	20	19.2%	-2.11 [-2.90, -1.33]	2017
Kumari, R 2017	1.31	0.6	16	1.18	0.66	16	20.4%	0.20 [-0.49, 0.90]	2017
Xiang, Q 2018	7.79	1.34	28	9.26	2.19	27	22.2%	-0.80 [-1.35, -0.25]	2018
Total (95% CI)			102			101	100.0%	-0.92 [-1.59, -0.24]	

Heterogeneity: Tau² = 0.45; Chi² = 18.94, df = 4 (P = 0.0008); I² = 79%
Test for overall effect: Z = 2.67 (P = 0.008)

Figure 5 Forest plot of patient's subjective symptom score at the end of treatment.

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