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Siklosporin Topikal Pada Konjungtivitis Alergi Anak Respon Minimal Terhadap Dexamethasone Topikal*: Laporan Kasus Berbasis Bukti*

Topical Cyclosporine in Allergic Conjunctivitis in Children with Minimal Response to Topical Dexamethasone: An Evidence-based Case Report

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Abstrak

Efektivitas siklosporin dan kortikosteroid untuk penanganan konjungtivitis alergi pada anak termasuk vernal keratokonjungtivitis dan keratokonjungtivitis atopic, baik dalam bentuk kombinasi atau secara terpisah mampu mengurangi gejala yang dialami pasien. Tujuan laporan kasus berbasis bukti ini adalah membandingkan efikasi antara kortikosteroid dan siklsoporin pada kasus konjungtivitis alergi. Urgensi masalah ini terletak pada kebutuhan untuk mengidentifikasi pengobatan yang paling efektif dan aman untuk mengelola gejala parah pada pasien anak-anak. Sebagai ilustrasi kasus seorang anak laki-laki berusia 8 tahun dengan kedua mata merah dan bengkak, serta penurunan visus, dicurigai akibat paparan allergen. Pasien didiagnosis sebagai keratokonjungtivitis alergi dan diberikan Dexamethasone 1 mg tetes mata, namun setelah 2 minggu penggunaan hanya dijumpai perbaikan minimal. Obat tetes mata digantikan dengan Siklosporin tetes mata dengan pertimbangan mencegah efek samping penggunaan tetes mata steroid yang berkepanjangan. Laporan kasus ini memasukkan analisis literatur yang membandingkan efikasi siklosporin dan kortikosteroid topikal sebagai pengobatan konjungtivitis alergi parah. Setelah melakukan analisis literatur sistematis mengikuti pedoman PRISMA, analisis teks penuh dilakukan pada dua uji klinis dengan menilai validitas dan aplikabilitas sesuai kriteria Oxford CEBM. Hasil penelusuran literatur menunjukkan bahwa tetes mata siklosporin yang diberikan kepada pasien dengan vernal keratoconjunctivitis parah dapat mengurangi tanda dan gejala. Apabila dibandingkan dengan kortikostreoid, tidak ditemukan perbedaan signifikan efikasi pada kasus konjungitivits alergi.
***Kata Kunci**: siklosporin; kortikosteroid; konjungtivitis alergi berat; .*

Abstract

The effectiveness of cyclosporine and corticosteroids in treating allergic conjunctivitis in children, including vernal keratoconjunctivitis and atopic keratoconjunctivitis, whether in combination or separately, has been shown to reduce patient symptoms. The aim of this evidence-based case report is to compare the efficacy of corticosteroids and cyclosporine in cases of allergic conjunctivitis. The urgency of this issue lies in the need to identify the most effective and safe treatment for managing severe symptoms in pediatric patients to improve their symptoms. As an illustration, a case of an 8-year-old boy with red, swollen eyes and reduced vision, suspected to be due to allergen exposure. The patient was diagnosed with allergic keratoconjunctivitis and initially treated with Dexamethasone 1 mg eye drops. However, after two weeks of use, only minimal improvement was observed. The eye drops were then replaced with Cyclosporine eye drops to prevent the side effects associated with prolonged use of steroid eye drops. This

case report includes a literature analysis comparing the efficacy of topical cyclosporine and corticosteroids in treating severe allergic conjunctivitis. Following a systematic literature review in accordance with PRISMA guidelines, a full-text analysis was conducted on two clinical trials, assessing their validity and applicability based on Oxford CEBM criteria. The literature search results indicate that cyclosporine eye drops administered to patients with severe vernal keratoconjunctivitis can reduce signs and symptoms. When compared with corticosteroids, no significant difference in efficacy was found in cases of allergic conjunctivitis.

Keywords: Cyclosporine; corticosteroid; severe allergic conjunctivitis.

Introduction

Allergic conjunctivitis is an inflammation of the eye, more specifically conjunctiva, causing an allergic reaction such as ocular itching, swelling, redness, foreign body sensation, soreness, and watery discharge. Some of the substances are pollen, dust, spores, animal skin or secretion, contact lens, and chemical scents. It is a multifactorial condition contributed also by individual susceptibility or genetics. Globally, it is one of the most common ocular diseases worldwide. Allergic conjunctivitis is more commonly found in a tropical or subtropical region or countries such as Middle East, Africa, South America, and Asia. This condition may affect people of all ages, but they are more common in children (La Rosa et al., 2013; Leonardi et al., 2008).

Topical corticosteroids are the treatment of choice for allergic conjunctivitis. Other topical agents such as antihistamines, mast cell stabilizers, non-steroidal anti-inflammatory drugs, and other multiple action anti-allergic agent have been used in the treatment of chronic allergic conjunctivitis, but their effectivity is limited to mild and moderate cases. Corticosteroid is documented to be the most potent and widely used pharmacological agent to treat allergic conjunctivitis (Dupuis et al., 2020; Holland et al., 2019).

However, there are some drawbacks and limitations of corticosteroids use, including ocular adverse effects and complications, such as increased intraocular pressure, delayed wound healing, secondary glaucoma, secondary infection, and formation of cataracts. These effects limit appropriate use of corticosteroids up to 2 weeks. Prolonged use of corticosteroids in case of persistent symptoms puts patients in danger of developing such conditions (Chen et al., 2012; Comstock et al., 2012; Holland et al., 2019; Ono & Abelson, 2005; Sen et al., 2019). To counter this issue, studies have been conducted to find a suitable replacement therapy for corticosteroids. Topical cyclosporine A has emerged as a promising alternative. Cyclosporine A is effective in reducing inflammation and improving symptoms in patients with allergic conjunctivitis, including severe forms such as vernal keratoconjunctivitis (VKC) and atopic keratoconjunctivitis (AKC). This agent helps mitigate the risks associated with prolonged corticosteroid use, such as increased intraocular pressure and cataract formation (Wan et al., 2013).

Study by Oczan et al. had reported the effectiveness of cyclosporine as nonsteroidal anti-inflammatory agents in treating chronic allergic conjunctivitis (Ozcan et al., 2007). Although the efficacy and safety of cyclosporine as a treatment for allergic conjunctivitis have been described in several studies, whether cyclosporine has better efficacy compared to steroids for treating severe or chronic allergic conjunctivitis still requires further investigation. (Pucci et al., 2002; Schultz, 2014). This evidence-based case report was designed to critically analyze the effectivity of cyclosporine and steroids as a treatment for severe allergic conjunctivitis patients.

In this evidence-based case report, the authors detail a case involving an pediatric patient with severe AKC. The primary objective of the authors is to evaluate the efficacy of cyclosporine compared with corticosteroid, drawing insights from existing literature. The focus of the case revolves around an individual facing the history of allergy and asthma. This case report aligns with an evidence-based approach, aiming to provide valuable insights that contribute to the broader knowledge base in the field. This study is an evidence-based case report with clinical question “Does cyclosporine eye drops have better efficacy compared with steroid eye drops in treating severe allergic conjunctivitis?”. Then, the clinical question was broken down into PICO format:

Patient: children severe allergic conjunctivitis (including atopic and vernal keratoconjunctivitis)

Intervention: cyclosporine eye drop

Comparison: steroid eye drop

Outcome: sign and symptom improvement.

Case Illustration

An 8-year-old boy presented to the hospital exhibiting symptoms of redness, soreness, itchiness, and excessive tearing in both eyes. Additionally, he frequently complained of nasal congestion. The boy reported experiencing crustiness upon awakening in the morning, accompanied by a watery discharge. Notably, his ocular history was unremarkable. The patient had a known medical history of eczema, allergic rhinitis, and asthma. Upon physical examination, the doctor observed swelling and redness of the patient's eyelids. These clinical manifestations led to the suspicion of allergic keratoconjunctivitis. The patient falls into the severe category due to experiencing constant symptoms of itching, light sensitivity, tearing, burning, and a gritty sensation, accompanied by prominent symptoms such as enlargement of the ciliary vessels, bilateral pseudo proptosis, and grayish-yellow discharge (Robles-Contreras et al., 2011). Initial treatment involved a two-week course of Dexamethasone 1 mg eye drops (), which resulted in only slight improvement. Due to concerns about the long-term effects of steroids, the mother requested an alternative eye drop. Subsequently, the doctor decided to initiate an alternative treatment, prescribing cyclosporine eye drops. After one week, there was no clinical improvement in the patient, so the patient was eventually referred to a specialized eye hospital

Discussion

The situation involving this 8-year-old boy highlights the

intricacies associated with handling severe allergic keratoconjunctivitis, especially given the presence of pre-existing conditions like eczema, allergic rhinitis, and asthma. The shift to cyclosporine eye drops indicates a careful evaluation of available treatment choices, underscoring the significance of customizing interventions to tackle both effectiveness and potential long-term effects. Consistent follow-ups and continuous evaluations will play a pivotal role in tracking the patient's reaction to the alternate treatment, ensuring the best possible eye health outcomes.

The literature search encompassed three journal databases (Page et al., 2021)—PubMed, Cochrane Library, and Scopus—employing specific keywords (MID, MIK, AWA, GCP, NGA). To ensure optimal evidence retrieval, a PubMed search limitation was applied to target randomized controlled trials (RCTs), systematic reviews, or meta-analyses of RCTs. The obtained search results underwent listing to eliminate duplicates. Subsequent screening of abstracts and thorough review of full-texts were conducted based on the eligibility criteria for this evidence-based case report (**Figure 1**). The inclusion criteria for the literature search were studies with a population of children (0–18 years) diagnosed with AKC or VKC, comparing topical steroids with topical cyclosporine, and articles written in English with full text available. Exclusion criteria involved studies not comparing steroids, non-English language publications, review papers, and publications not in their final stage. No publication year restrictions were applied in this literature search. The evaluation of RCTs' quality was performed using the Centre for Evidence-Based Medicine's critical appraisal sheets, addressing internal validity, clinical importance, and external validity, with discrepancies resolved through discussion with an ophthalmologist (JDB). The summary of included RCT were shown in **Table 1**.

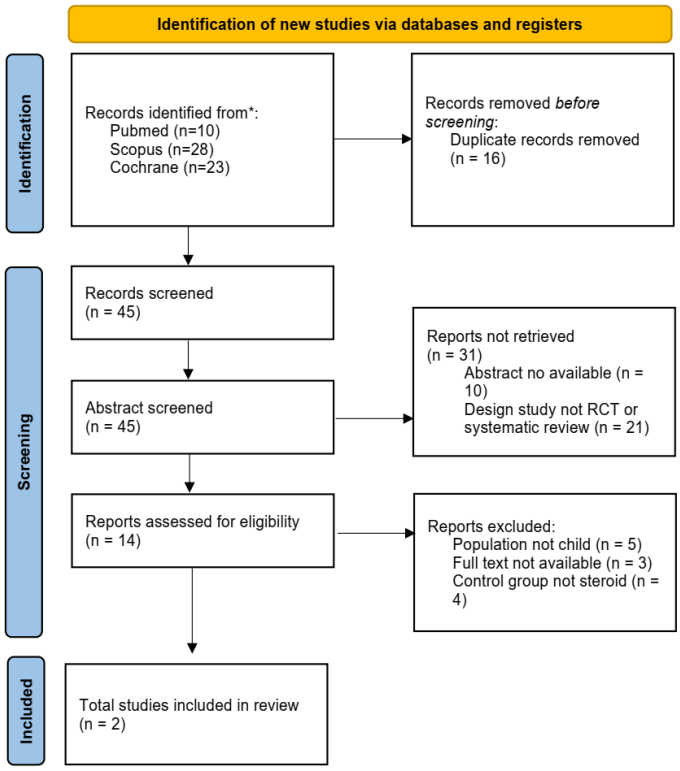

Figure 1. Flowchart of selection process for studies

Tabel 1. Characteristics of included RCT

Study	Participant Population	Intervention		Control	Outcome Measure	Follow up	LoE*
		Medication	Dose and Frequency				
Kosrirukvongs *et al*., 2003	Thailand children with severe VKC (n=10) and moderate severity VKC (n=24)	Cyclosporine 0,5%	1 drop, QID	Predni-solone acetate 1%	Symptoms and signs measurement	2 weeks	2b
De Smedt *et al*., 2012	Rwanda children with VKC (n=366)	Cyclosporine A 2% in olive oil	1 drop, QID	Dexa-methasone 0,1% drops	Symptoms and signs scoring system	8 weeks	1b

*LoE: Level of evidence, for therapeutic studies was determined using the Cochrane classification

Both of RCTs have different study populations, concentration and treatment regiments of cyclosporine, type of steroid, and duration of trials. Not only were these two remaining RCTs matched with the eligibility criteria, but they were also the only two articles which compared cyclosporine and steroid directly. RCT which was conducted by Kosrirukvongs et al., did not fulfil the internal validity criteria in the CEBM RCTs critical appraisal sheets as it only met one out of five criteria (as shown in **Appendix 2**) (Kosrirukvongs et al., 2003). Furthermore, the remaining RCT by De Smedt et al., was still considered good quality so that we can evaluate its clinical importance and external validity (De Smedt et al., 2012). The critical appraisal of this RCT was shown in **Appendix 3**. Due to differences in outcome assessment in the two studies, statistical analysis for meta-analysis was not pursued.

In chronic and more complex cases of allergic conjunctivitis, avoidance and protective measures alone are not adequate, so prompting the need of pharmacological treatment. The current first-line treatment for severe allergic conjunctivitis is steroid eye drops. However, it comes with a number of possible side effects (Holland et al., 2019; Nussenblatt & Palestine, 1986; Sen et al., 2019; Whitcup et al., 1996). Cyclosporine is a calcineurin inhibitor class of drugs which plays a role in suppressing inflammation, including inflammation of allergic conjunctivitis. An assessment of the effectiveness of cyclosporine for treating allergic conjunctivitis has been carried out since 1990 by Secchi et al. which shows an improvement in the clinical condition of patients with vernal keratoconjunctivitis (VKC), which is one of the type of allergic conjunctivitis in children (Secchi et al., 1990). The number of randomized-controlled trials in Asian and European populations have also shown a decrease in signs and symptoms of allergic conjunctivitis after the administration of cyclosporine eye drops (De Smedt et al., 2012; Gupta & Sahu, 2001; Kiliç & Gürler, 2006; Leonardi et al., 2019; Pucci et al., 2002; Spadavecchia et al., 2006). Only one out of eight cyclosporine studies display inconclusive results (Kosrirukvongs et al., 2003).

Considering the ocular side effects associated with prolonged use of steroid medication are increased ocular pressure, exophthalmos, glaucoma, blurred vision, cataracts, retinopathy, and even blindness, suitable replacement therapy is needed, and cyclosporine rises as a potential candidate (Rathi & D'Souza, 2012). Cyclosporine works by lowering the activity of T-cells through two mechanisms: Calcineurin-phosphatase pathway and prevent the opening of the mitochondrial permeability transition pore (MPTP). The ocular inflammation in keratoconjunctivitis may be relieved by cyclosporine through mechanisms mentioned above. Cyclosporine blocks Th2 lymphocyte proliferation and IL-2 production, which then through a cascade of reactions will inhibit histamine release from mast cells, reduces IL-5 production and basophils production, and reduces eosinophils recruitment to the inflamed conjunctiva and cornea (Keklikci et al., 2014).

Several studies showed consistent results regarding the effectivity of cyclosporine eye drops administration to reduce signs and symptoms of keratoconjunctivitis (Gupta & Sahu, 2001; Kiliç & Gürler, 2006; Leonardi et al., 2019; Pucci et al., 2002; Secchi et al., 1990; Spadavecchia et al., 2006). All the randomized clinical trials (RCTs) showed the effectiveness of cyclosporine in reducing severe allergic conjunctivitis (ARR = 22,6% – 71%, NNT = 1,4 – 4,4) (Gupta & Sahu, 2001; Leonardi et al., 2019; Pucci et al., 2002; Secchi et al., 1990). The validity assessment and clinical importance calculations are shown in **Appendix 4** and **Appendix 5** respectively.

The De Smedt et al. study in 2011 was the first double-blind study comparing the use of cyclosporine 2% eye drops and dexamethasone eye drops 0.1%. The administration of cyclosporine and dexamethasone for 4 weeks showed a decrease in the score of symptoms and signs of VKC, with no significant difference between the two. After the fourth week, administration of cyclosporine and dexamethasone was stopped, and symptoms were observed. The eight-week assessment showed an increase in VKC sign and symptom scores in the two groups, with no significant difference between the two (De Smedt et al., 2012).

Based on the results of study by De Smedt et al., it was found that the absolute percentages of cyclosporine and dexamethasone in reducing vernal keratoconjunctivitis's signs and symptoms were -47,42% and -49,26% respectively (p = 0.2). After 4 weeks stopping the treatment, recurrence rates of signs and symptoms were 23,65% and 21,85% for cyclosporine and dexamethasone respectively (p = 0,45). There was no significant difference found between cyclosporine and steroid efficacy in reducing signs and symptoms of allergic keratoconjunctivitis. Furthermore, relapse rates after drug discontinuation also show similar results. We could not find a conclusive result on whether or not cyclosporine has better efficacy than steroid for treatment of severe or chronic allergic conjunctivitis. However, considering the prolonged use of steroids may introduce unwanted adverse effects, cyclosporine can be prescribed to avoid this drawback (De Smedt et al., 2012).

De Smedt et al. emphasized the minimization of selection bias by recruiting subjects in the long dry season, where cases of VKC were common. However, there were several limitations: Paltry data on stability and bioavailability of locally produced cyclosporine and the maintenance dose for cyclosporine were not yet known (De Smedt et al., 2012).

Moreover, there are several considerations concerning about this case study. First, studies that we found have various intervention characteristics, such as concentrations, doses, frequencies, or type of steroid, so we could not make an exact conclusion. Second, there have been limitations on number of articles that we found. We only found few clinical trials that compared cyclosporine and placebo, and only two articles that compare directly between cyclosporine and steroids. Hence, we found no comparison on identical studies and no conclusions can be drawn about which one has better efficacy.

There are some limitations from available evidence. Additional well-designed and powerful RCTs that compare cyclosporine and steroids directly, and particularly in children are needed. There were no RCTs include the side effect of treatment as an outcome. Current outcomes are only including signs and symptoms relieve. Participants should be large enough to provide enough statistical power to assess the safety of cyclosporine and to detect clinically relevant cyclosporine

efficacy in relieving severe allergic conjunctivitis' signs and symptoms.

Conclusion

Cyclosporine demonstrates comparable efficacy to steroids in alleviating symptoms of allergic conjunctivitis, and notably, the use of topical cyclosporine is associated with no reported serious side effects. In summary, the data suggests that topical cyclosporine offers both clinical and symptomatic relief for vernal keratoconjunctivitis without any significant difference with topical corticosteroid, presenting an opportunity to minimize the reliance on topical steroids in patients with this condition. In the context of the presented case, the administration of cyclosporine eye drops emerges as a viable alternative for patients who do not experience symptom relief with steroid eye drops. Consequently, the utilization of topical cyclosporine presents a potential strategy for reducing the dependence on steroids in the treatment of allergic conjunctivitis, particularly vernal keratoconjunctivitis.

Conflict of interest

The authors declare no conflict of interest.

Ethical Declaration and Consent

The patient's family and doctor responsible for the patient have agreed to permission to use clinical data as publication material, while maintaining patient confidentiality.

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Appendices

Appendix 1. Keywords used in databases for literature searching

Database	Terminology	Hits	Selected Articles
PubMed	((((allergic conjunctivitis OR atopic keratoconjunctivitis OR vernal keratoconjunctivitis))) AND (cyclosporine eye drops OR cyclosporin* OR CYC)) AND ((Steroid$ OR Corticosteroid$))))	10	2
Scopus	TITLE-ABS-KEY ((allergic AND conjunctivitis OR atopic AND keratoconjunctivitis OR vernal AND keratoconjunctivitis) AND (cyclosporine AND eye AND drops OR cyclosporin* OR CYC) AND (steroid$ OR corticosteroid)) AND (LIMIT-TO (DOCTYPE, "ar")) AND (LIMIT-TO (LANGUAGE, "English"))	28	0
Cochrane	((allergic conjunctivitis OR atopic keratoconjunctivitis OR vernal keratoconjunctivitis) in Title Abstract Keyword AND (cyclosporine eye drops OR cyclosporin* OR CYC) in Title Abstract Keyword AND (Steroid$ OR corticosteroid) in Title Abstract Keyword	15	0

Appendix 2. Validity assessment of included randomized controlled trials.

Study	Randomisation	Intention to Treat	Blinding	Equally Treated	Baseline Similarity	Total	Are the results of this single preventive or therapeutic trial valid?
Kosrirukvongs et al., 2003	-	-	-	+	-	1/5	No
De Smedt et al., 2011	+	-	+	+	+	4/5	Yes

Appendix 3. Critical appraisal randomized controlled trials written by De Smedt et al.

Aspects	Questions	In This Paper	Comments
Validity	Was the assignment of patients to treatments randomised? -and was the randomisation list concealed?	Yes	In this clinical trial, pharmacists were masked to the clinical evaluation of the participants allocations which divided participants into two groups by block randomisation using a random-number generator sheet. Then, each participant received two bottles.
	Were all patients who entered the trial accounted for at its conclusion? -and were they analysed in the groups to which they were randomised?	No	Due to lost to follow-up, only 364 were assessed from 366 subjects who received treatment, and the lost-follow-up ones were not analyzed as failure treatments.
	Were patients and clinicians kept "blind" to which treatment was being received?	Yes	Consecutive patients with VKC were randomised in a prospective, double-masked, clinical trial to receive either topical CsA 2% dissolved in olive oil vehicle or dexamethasone 0.1% drops for 4 week.
	Aside from the experimental treatment were the groups treated equally?	Yes	Both eyes were assessed at baseline and at 2, 4 and 8 weeks. At each visit, participants were interviewed using a questionnaire based on VKC-related symptoms, best-corrected visual acuity was measured using a logMAR E Chart.
	Were the groups similar at the start of the trial?	Yes	The intervention groups were similar with respect to age and sex distribution, disease

Aspects	Questions	In This Paper	Comments
			duration and severity, eye care history, VKC subtype and VKC-related scores of symptoms and signs.
	Are the results of this single preventive or therapeutic trial valid?		Yes
Importance	On the first 4 weeks, the absolute percentages of cyclosporine and dexamethasone in reducing vernal keratoconjunctivitis's signs and symptoms were -47,42% and -49,26% respectively (p = 0,2). After 4 weeks stopping the treatment, recurrence rates of signs and symptoms were 23,65% and 21,85% for cyclosporine and dexamethasone respectively (p = 0,45).		
Applicability	Is your patient so different from those in the trial that its results can't help you?	No	African and Indonesian children have different genetic backgrounds and race, but the characteristics, signs, and symptoms of VKC are still the same. Also, they are still in the range of children's age.
	Do these results apply to your patient	Yes	Indonesia has a lot of cases of vernal keratoconjunctivitis and we're still using with topical steroids as our first line treatment. Also, cyclosporine A is available in our hospital.
	How great would the potential benefit of therapy actually be for your individual patient?	Beneficial	Due to the fact that we could not calculate both RRR and NNT on this study, we assume that this therapy would be beneficial as there are not much difference is expected regarding the risk of outcome in my patient relative to the patients in the trial
	Are your patient's values and preferences satisfied by the regimen and its consequences?		
	Do your patient and you have a clear assessment of their values and preferences?	Yes	Prolonged use of topical steroids leads to several problems in the future, hence we search for better options. Both we and the patients want the best treatment that has the best efficacy and safety.
	Are they met by this regimen and its consequences?	Yes	Topical cyclosporine A is available in our hospital. Moreover, there were no severe side-effects found in this regimen that caused to discontinue the medication.

Appendix 4. Validity assessment of supporting randomized controlled trials.

Studies	Randomisation	Intention to Treat	Blinding	Equally Treated	Baseline Similarity	Are the results of this single preventive or therapeutic trial valid?
Secchi et al., 1990	-	+	+	+	N/A	Yes
Gupta et al., 2001	+	+	+	+	-	Yes
Pucci et al., 2002	+	+	+	+	+	Yes
Kilic et al., 2006	-	N/A	+	+	+	Yes
Spadavecchia et al., 2006	+	+	+	+	+	Yes
Leonardi et al., 2018	+	-	+	+	+	Yes

Appendix 5. Clinical importance assessment of supporting randomized controlled trials**.**

Studies	Overall Results (treatment preference)	RRR	ARR (95% CI)	NNT (95% CI)
Secchi et al., 1990	Cyclosporine over placebo (FT)*	1	66,7% (35,9% – 97,5%)	1,5 (1,03 – 2,8)
Gupta et al., 2001	Cyclosporine over placebo (FT)*	1,51	50% (16% – 84%)	2 (1,19 – 6,25)
Pucci et al., 2002	Cyclosporine over placebo (FT)*	0,71	71% (53% – 89%)	1,4 (1.12 – 1.89)
Kilic et al., 2006	Cyclosporine over placebo (FT)*	Cannot be calculated	Cannot be calculated	Cannot be calculated
Spadavecchia et al., 2006	No difference between Cyclosporine 1,25% and 1%	Cannot be calculated	Cannot be calculated	Cannot be calculated
Leonardi et al., 2018	High dose cyclosporine over placebo (FT)*	34,5	22,6% (4,8 – 40,4)	4,4 (2,5 – 20,8)
	Low dose cyclosporine over placebo (FT)*	40,6	26,6% (4,9% – 40,3%)	3,8 (2,5 – 20,4)

95% CI: confidence interval; RRR: Relative Risk Reduction; ARR; Absolute Risk Reduction; NNT = Number Needed to Treat; *: favours treatment.