

Title

Tacrolimus vs. cyclosporin eyedrops in severe cyclosporin resistant vernal keratoconjunctivitis:
a randomized, comparative, double-blind, crossover study.

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Running Title

Tacrolimus vs. cyclosporin eyedrops in severe vernal keratoconjunctivitis

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Material in the electronic repository (if applicable): Questionnaire for the assessment of quality of life

Introduction

Vernal keratoconjunctivitis (VKC) is a chronic and sight-threatening form of bilateral conjunctivitis typically characterized by the presence of giant “cobblestone” papillae in the upper palpebral conjunctiva (tarsal form) or at the limbus (bulbar form) (1). Corneal

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involvement is often present, ranging from superficial keratitis to plaque ulcers and late corneal neovascularization (2).

The disease usually appears in the first decade of life and disappears by the second decade (1). About 80% of patients have seasonal exacerbations, starting in the spring with improvement in the fall, while the remaining 20% suffer from perennial symptoms.

The pathogenesis of this disease is still unknown. Several studies have shown a prevalent local Th2 response (3, 4). Both topical and systemic corticosteroids are effective in the treatment of VKC, however their prolonged use often causes complications such as glaucoma, cataracts, and bacterial infections (5). Other topical drugs such as antihistamines, inhibitors of mast-cells degranulation, and anti-inflammatory non-steroid (NSAID) drugs are only effective in milder forms of the disease.

In the last decades, several double-blind, placebo-controlled studies have demonstrated substantial efficacy and safety of topical cyclosporine (Cyc) (at 1% to 2% concentrations) in moderate to severe forms of VKC (6-8). Cyc seems to be safer than corticosteroids, it does not produce lens changes or increased intraocular pressure (6, 7). However, about 7-10% of patients are transiently or permanently non-responders to Cyc in agreement with our own experience.

A new Cyc 0.1% aqueous ophthalmic solution has been recently used in a large case series of VKC and AKC in a post-marketing study lasting 6 months (9). The preparation contained the non-ionic surfactant MYS-40 (polyoxyl 40 stearate) that allows for high tissue distribution.

Nevertheless, a lack of effectiveness and adverse events were reported in 6.9 % and 9.1% of patients with VKC and ACK, respectively.

In a 2-year study, a lower concentration of Cyc eyedrops (i.e. 0.05%) was more effective than ketotifene in 31 patients in terms of preventing seasonal recurrences (10).

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Tacrolimus (Tcr), like Cyc, is a calcineurin inhibitor that blocks T-lymphocyte activation. It is indicated for the prophylaxis of organ rejection in transplanted patients. Tcr topical ointment is indicated and registered worldwide as a second-line treatment of atopic dermatitis in non-immunologically compromised patients over the age of two (11). Moreover, Tcr hydrate has been used as an eye-drop formulation to treat several ocular diseases in adults (12-14), and at the meeting of the Committee for Orphan Medicinal Products in January 2004, it was designated by the European medicines Agency (EMA) as an Orphan Medicinal Product for VKC treatment (15).

Following the first description by Vichyanond et al. (16), several other reports were published highlighting both the efficacy and safety of topical Tcr in VKC (17-19). However, there are still no comparative studies on Tcr vs. Cyc topical treatments in severe VKC cases resistant to Cyc, which is considered the gold standard treatment to date.

The main purpose of this study was to investigate the efficacy of topically administered Tcr, vs. Cyc in a randomized, double-blind crossover (DBCO) trial in children with severe VKC resistant to first-course treatment with Cyc. Criteria were also established for selecting the more effective treatment between the two drugs depending on the characteristics of each single patient.

Methods

Study population. From March 2008 to August 2010, the Allergy Unit of Anna Meyer Children's Hospital recruited consecutive patients, with a diagnosis of VKC who were willing to comply with the trial protocol.

Criteria for inclusion were: a) an active phase of the disease (i.e. the presence of giant tarsal papillae and/or limbal papillae), and b) a disease duration of at least 6 months, and c) an objective score index of 9 or higher of which at least 5 points were from the sum of the

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scores of giant papillae and limbal papillae. The objective ocular score for each eye consisted of the following symptoms: conjunctival hyperemia, presence of papillae, giant papillae, and limbal papillae (20). Each symptom was graded as follows: 0 = absent, 1 = mild, 2 = moderate, 3 = severe.

In addition, patients had to have been unsuccessfully treated with topical Cyc eyedrops for at least 15 days during the previous two months. They were defined as non-responders to Cyc if they had: a) no improvement in the ocular score resulting from giant tarsal papillae and papillae at limbus, and b) no improvement in scores resulting from conjunctival hyperaemia and papillae, or improvement not exceeding one point for both parameters. Patients with any systemic chronic infections, connective tissue diseases, malignancies, or immunodeficiencies were excluded from the study. Other exclusion criteria were: coexistent ocular complications such as active corneal ulcers, treatment with topical or systemic corticosteroids during the previous 3 weeks, and abnormal results in the basal blood examination. Skin-prick tests with common inhalants and food allergens (i.e. pollens, mites, molds, cat and dog epithelia, milk, albumen, soy, wheat, cod fish, peanut, latex; commercial extracts, at 0.1 mg/mL concentration Alk Abellò, Milan, Italy) were performed to better characterize the patients enrolled.

Medications. The medications used in this study were: Cyc eyedrops at 1% obtained by diluting 1 ml of a Sandimmun vial, [50mg/ml (Novartis)] in 4 ml of HypoTears [(Novartis Ophthalmics), ocular solution of 1% polyvinyl alcohol and 1% polyethylene glycol 400]; Tcr eyedrops at 0.1% obtained by diluting 1 ml of Prograf vial [5mg/ml (Astellas Pharma)] in 4 ml of Hypotears 4 ml. Neither concurrent topical medications nor systemic corticosteroids were allowed during the crossover trial.

Protocol. This was a comparative DBCO trial. Eligible patients were treated, during the active phase in spring and summer, in one eye with Cyc, and in the other eye with Tcr (1

drop 3 times daily in both eyes) for three weeks (1st phase), and after a week of washout, the two drugs were reversed for another three weeks (2nd phase). Allocation to treatment was in a random fashion based on a predetermined randomization list generated by a computer at the Epidemiology Unit of the Anna Meyer Children's Hospital. Patients, parents, allergists, and ophthalmologists were masked with regard to the identification of the eyedrops applied during the trial. Pharmacists at the Anna Meyer Children's Hospital prepared identical unit dose vials. Patients and parents were instructed to use different color-labeled vials for each eye. Patients returned for evaluation at three weeks and at the end of treatment. Patients, if older than 18 years, or parents signed a written informed consent.

This trial was funded by the Italian Medicines Agency, and approved by the Ethics Committee of the Anna Meyer Children's Hospital.

Outcome and safety measures. The primary outcome of this study was the evaluation of the severity of the disease at the end of the two trial phases, as defined by the objective ocular score. Two expert ophthalmologists independently attributed objective scores, and in case of disagreements a mean value was assigned. Furthermore, in order to continue open treatment after the trial, in each of the two crossover phases, the eligible drug was the one that determined an improvement of at least 2 score points compared to the other eye. At least one of the two points had to be attributable to giant papillae or limbal papillae.

Secondary outcomes were: a) the collecting of a subjective symptoms score which was evaluated daily by patients/parents. The subjective score symptoms were itching, photophobia, tearing, foreign-body sensation and burning sensation (20), each one graded as follows: 0 = absent, 1 = mild, 2 = moderate, 3 = severe; b) Quality of Life score [adapted from the Children's Dermatology Life Quality Index (CDLQI), Cardiff

University, UK]: a questionnaire filled out by patients and parents (see E1 in the Online Repository) (21).

Primarily the ophthalmologists assessed the treatment safety after each of the two crossover phases by evaluating the presence of possible local side effects, mainly on the corneal surface. In addition, red and white blood cell counts, serum alanine aminotransferase (s-ALT, normal levels: 10-60 UI/L, international units), serum aspartate aminotransferase (s-AST, normal levels: 10-45 UI/L), were analyzed at the beginning and at the end of the crossover study, as safety parameters. Moreover, serum creatinine (s-Creatinine, normal levels: 0.3-1.0 mg/dl) and blood levels of Cyc (undetectable values: < 20 ng/ml), and Tcr (undetectable values: < 1.5 µg/L) were checked at the end of the study,

Statistical analysis

The means were compared using Student's t test. Analyses were performed with IBM SPSS Statistics, version 9 software.

Results

Thirty patients were enrolled in the study; their demographic characteristics are reported in Table 1. Twenty-four out of 30 patients were persistently non-responders to Cyc over the course of the past years, while in 6 of them the drug had been partially effective. Five patients withdrew from the study during the 1st phase of the crossover: two patients voluntary withdrew because in their opinion both the drugs resulted equally poorly effective, three patients were withdrawn by the investigators for the following reasons: concurrent use of corticosteroids, severe corneal damage in the Cyc treated eye, and poor

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tolerability of both types of eyedrops. Objective score values in each phase of the trial are shown in Figure 1.

Eyes treated with Tcr showed a significantly greater improvement of both scores compared to eyes treated with Cyc in both phases of the DBCO trial. At the end of the washout period the scores worsened, so that at the beginning of the second phase the ocular score was similar for both eyes. Table 2 contains the mean subjective score values: a substantial overlap can be observed with the objective scores. QoLQs score significantly improved after the DBCO trial (basal values $\pm$ SD: 32.10 ± 9.05 and after the trial: 35.40 ± 8.31 , $p < 0.001$). Details of the QoLQ scores for the different domains are illustrated in Table 3.

The degree of improvement of the objective score in patients treated with Tcr was independent of sex, type, presentation, and atopy (Table 4).

The mean blood values of s-ALT, s-AST, and s-Creatinine were always within the normal range both before and after treatment, with the exception of one patient who had a slight increase in ALT (61UI/L), although the value returned to normal (51 UI/L) after 5 days. Blood Cyc and Tcr levels were undetectable at end of the study.

All patients reported burning, and 11 patients ocular stinging, 8 of them also reported pain on administration of the eyedrops, irrespective of the drug used. These side effects tended to improve within 1-2 weeks in 19 out of the 25 patients who completed the study, while 6 patients continued to report burning, and 1 also stinging. In 24 of the 25 patients who completed the DBCO trial, Tcr was the eligible drug as it determined greater improvement than Cyc according to the criteria established.

Discussion

This is the first DBCO trial to demonstrate that topically administered Tcr is effective and safe in children with severe VKC who do not respond to topical Cyc treatment.

The characteristics of the studied population did not differ from the overall VKC population; with a prevalence of males (i.e. 80%). Moreover a high prevalence of cases with a perennial trend (40%) indicates greater severity of the disease in these patients.

On the basis of the objective score, Tcr was significantly more effective when compared with Cyc in each of the 2 phases of the DBCO trial (Fig. 1 and Table 2). Interestingly, from the beginning to the end of the second phase, Cyc was poorly effective ($p = 0.055$), however the improvement in the Tcr-treated eye was significantly greater ($p < 0.001$). Two patients (6.6%) dropped out of the study due to a lack of efficacy of both drugs while it was not possible to evaluate the efficacy in two other withdrawn patients: one has not complied with the study design having used steroids, and the other did not tolerate the drug. A fifth patient responded to Tcr but left the study for severe corneal damage in the Cyc treated eye.

Even the subjective score (Table 2) indicated that Tcr was the only effective drug.

QoL showed a significant improvement when assessed at the end compared to the beginning of the DBCO trial (Fig. 2, $p < 0.001$). This result is notable, even questionable, given that only one eye was successfully treated during each study phase.

The safety profile evaluations were definitely within normal range. Tcr and Cyc blood levels were always found under the minimum detectable value, although only one eye was treated with both drugs.

In about 2/3 of patients ocular stinging, pain, and mostly burning on administration of the eyedrops tended to improve within 1-2 weeks, while they persisted almost stably in about 1/3 of the children.

Topical Tcr has been successfully used in adults with atopic blepharoconjunctivitis (12), ocular pemphigoid (13), and rejection of limbal allograft transplantation (14). So far no adverse effects have been reported.

The 0.1% Tcr eye ointment was administered in an early 4-week open trial in 10 children with severe VKC (16). Most cases were without symptoms at the end of the trial, with minimal drug absorption and no significant side effects.

The efficacy of topical Tcr at 0.1% in severe conjunctivitis cases vs. placebo has been previously demonstrated in a randomized controlled trial (17). A total of 15 patients with VKC and 41 with AKC were enrolled. After 4 weeks of treatment with one eyedrop twice-daily, a significant improvement was observed in the active treatment group vs. the placebo group ($p=0.004$).

In a recent study, 52 patients were treated with 0.1% Tcr ophthalmic suspension for 12 weeks (18), 15 of whom were suffering from VKC and 37 from AKC. The authors demonstrated a good safety profile, as the maximum blood concentration detected was less than 2 ng/mL, and about 75% of the patients treated had blood levels below 0.5 ng/mL.

A double-masked comparative study with 0.1% Tcr ophthalmic ointment (twice-daily) and 2% Cyc eyedrops (four times/day) has been recently conducted (19). The trial lasted 8 weeks followed by an open trial of 4 more weeks with Tcr. Twenty-four children suffering from active VKC with similar clinical characteristics were randomly enrolled in the 2 treatment groups. Both drugs were effective, and at each time point (i.e. 1, 4, 8, and 12 weeks), no significant differences were observed in the objective symptom scores between the two groups. This article is protected by copyright. All rights reserved.

groups. The results of our study are different as the study design was clearly different: it was a DBCO trial in which only patients resistant to Cyc have been enrolled.

In 2005, the Pediatric Advisory Committee of the US FDA implemented a 'black box' warning for Tcr ointment and pimecrolimus cream in the treatment of atopic dermatitis, due to the lack of long-term safety data and the potential risk of developing cutaneous malignancies. The FDA position has been criticized by authoritative scientific societies (22, 23). To date, there is insufficient evidence in epidemiological literature to infer whether topical calcineurin inhibitors might be the cause of malignancy (24), although recent reports indicate a high level of safety in the administration of these drugs (25, 26). In conclusion, topical Cyc has been widely used to treat mild-to-severe VKC, although about 7 - 10% of patients are transiently or totally unresponsive. This study demonstrates how 0.1% topical Tcr is very effective and safe for short-term use in these severe cases. Additional patients to those described in this study have subsequently been treated with Tcr eyedrops in an open trial which is still ongoing, to evaluate the long-term efficacy and safety of the drug.

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Table 1 Study population.

Study population (no. 30 patients)		
Age yrs		
mean $\pm$ SD	9.05 $\pm$ 2.12	%
(range)	(5 – 13)	
Sex (m/f)	24/6 (4/1)	80/20
T-B-M	6-15-9	20/50/30
S/P	18/12	60/40
Atopy* yes/no	12/18	40/60
Disease duration† (range)	mean 19.13 mths (7-31 mths)	-

TBM = Tarsal/Bulbar/Mixed form; S/P = Seasonal/Perennial form; *At least 1 skin prick test positive for common inhalants or food allergens. †Including periods of remission in seasonal forms

Table 2 Means ($\pm$ SD) of Subjective Scores during the comparative cross-over trial.

1	Tcr	T0	30	6.300	3.415	<0.001		
		3wks	30	1.833	3.184			
2	Cyc	T0	30	6.566	3.349	0.370		
		3wks	30	5.750	4.565			
<i>cross - over</i>								
1	Cyc	4wks	25	25	6.200	3.752	3.372	0.123
		7wks			5.720			
2	Tcr	4wks	25		6.320	3.613	<0.001	
		7wks	25		2.000	2.768		

TCR = tacrolimus ; CYC = cyclosporine; T0 = beginning; 3wks = after 3 weeks; 4wks = after 4 weeks; 7wks = after 7 weeks

Table 3 Quality of life items at beginning (1) and at the end (2, after 7 weeks) of the DBCO trial.

Quol-item	no.	mean	SD	<i>p</i>
Quol-mood 1	25	1.720	0.935	<i>0.03</i>
Quol-mood 2	25	2.120	0.600	
Quol-school 1*	20	12.150	3.616	<i>0.07</i>
Quol-school 2*	20	12.950	3.440	
Quol-home 1	25	11.960	3.006	< <i>0.001</i>
Quol-home 2	25	12.800	2.630	
Quol-outdoor 1	25	6.520	2.535	<i>0.001</i>
Quol-outdoor 2	25	7.560	2.467	

*Five patients were enrolled in the period of school closure; therefore only 20 completed the Quol-school questionnaire.

Table 4 Objective score difference between the beginning and the end of the 1st (Δ_1) and the second (Δ_2) phase of the C-O trial in 25 patients who completed the study, according to sex, type of conjunctiva involved, seasonal vs perennial form, atopy.

		no.	Δ_1	<i>p</i>	Δ_2	<i>p</i>
Sex	M	21	4.00	0.75	4.02	0.34
	F	4	3.62		5.25	
Type	T	5	4.40	0.97	3.70	0.51
	B	12	4.16		4.41	
	T	5	4.40	0.50	3.70	0.63
	M	8	3.43		4.25	
	B	12	4.16	0.24	4.41	0.87
	M	8	3.43		4.25	
Seasonal		15	4.10	0.49	4.13	0.80
Perennial		10	3.70		4.35	
Atopy*	yes	10	4.45	0.17	4.00	0.70
	no	15	3.60		4.36	

T = Tarsal; B = Bulbar; M = Mixed form;

*At least 1 positive skin prick test for common inhalants or food allergens.

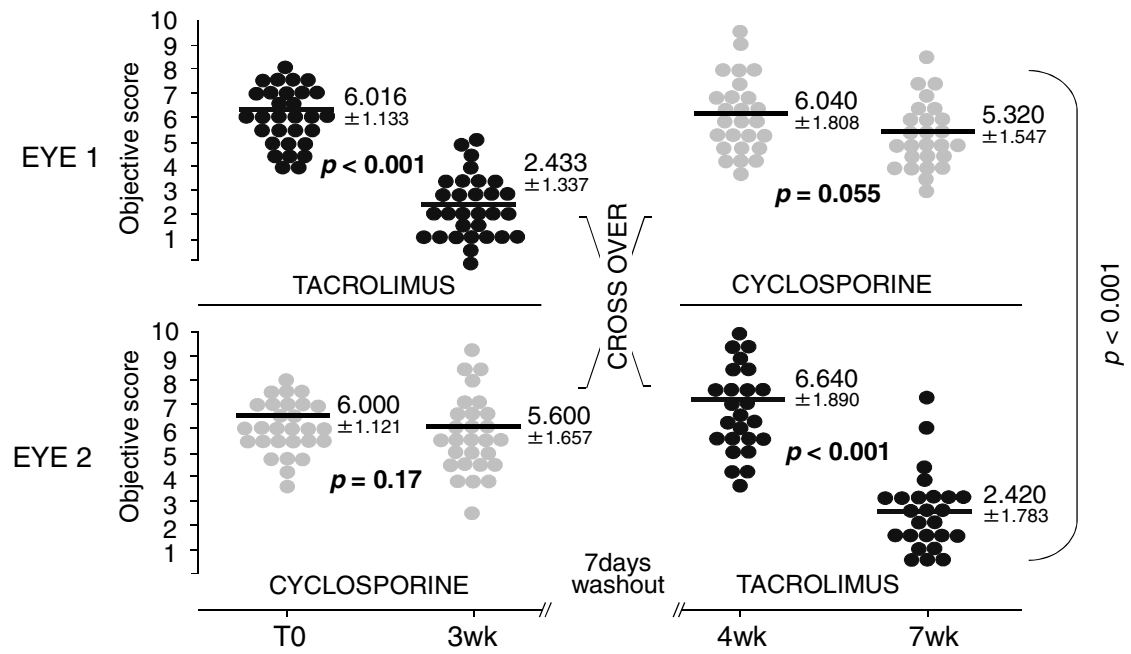


Figure 1.

V I S I T - C A R D

Patient no.				Initials:				Centre:			Visit:		
--------------------	--	--	--	------------------	--	--	--	----------------	--	--	---------------	--	--

Date of visit | | |
 day month year

QoL

QUESTIONNAIRE FOR THE ASSESSMENT OF QUALITY OF LIFE

What mood was your child in over the last two weeks?

- ☐ cried often, in an extremely difficult mood
- ☐ very nervous
- ☐ slightly nervous
- ☐ happy

What problems did conjunctivitis create for your child during school lessons over the last two weeks?

- Did your child have difficulties of adapting to the light?
☐ Continuously ☐ Very often ☐ Infrequently ☐ Never
- Did your child have reading difficulties?
☐ Continuously ☐ Very often ☐ Infrequently ☐ Never
- Did your child have trouble concentrating?
☐ Continuously ☐ Very often ☐ Infrequently ☐ Never
- Did your child have difficulties playing sport at school?
☐ Continuously ☐ Very often ☐ Infrequently ☐ Never
- Did your child have difficulties in peer relationships?
☐ Continuously ☐ Very often ☐ Infrequently ☐ Never
- Did your child have problems dealing with teacher relationships?
☐ Continuously ☐ Very often ☐ Infrequently ☐ Never

What problems did conjunctivitis create for your child during time spent at home over the last two weeks?

- **Did your child have difficulties of adapting to the morning light?**

☐ Continuously ☐ Very often ☐ Infrequently ☐ Never

-

- **Did your child have difficulties in family relationships (parents, brothers /sisters, grandparents)?**

☐ Continuously ☐ Very often ☐ Infrequently ☐ Never

- **Did your child have difficulties watching television, playing with the computer or tv games?**

☐ Continuously ☐ Very often ☐ Infrequently ☐ Never

- **Did your child have difficulties playing with friends or pets?**

☐ Continuously ☐ Very often ☐ Infrequently ☐ Never

- **Did your child have difficulty settling down for sleep?**

☐ Continuously ☐ Very often ☐ Infrequently ☐ Never

- **Did your child have difficulty concentrating while doing homework?**

☐ Continuously ☐ Very often ☐ Infrequently ☐ Never

What problems did conjunctivitis create for your child during extracurricular activities and outdoor activities over the last two weeks?

- **Did your child have difficulties of adapting to the light?**

☐ Continuously ☐ Very often ☐ Infrequently ☐ Never

- **Did your child have difficulties adjusting to air-conditioning?**

☐ Continuously ☐ Very often ☐ Infrequently ☐ Never

- **Did your child have problems performing indoor leisure activities (i.e. gym, pool)?**

☐ Continuously ☐ Very often ☐ Infrequently ☐ Never

- Did your child have problems performing outdoor leisure activities (i.e. sport)?

☐ Continuously ☐ Very often ☐ Infrequently ☐ Never

- Did your child have difficulties in family relationships?

☐ Continuously ☐ Very often ☐ Infrequently ☐ Never

- Did your child have difficulties in relationships with peers?

☐ Continuously ☐ Very often ☐ Infrequently ☐ Never

Notes to the questionnaire

The questionnaire consists of four sections:

- 1) Mood
- 2) At School
- 3) At Home
- 4) Outdoors

Each question has four answers graded according to the severity. Each answer corresponds to a score from **zero** to **three**.