Tacrolimus ointment in the management of atopic keratoconjunctivitis

D. Benaim, F. Tetart, O. Bauvin, A. Delcampe, P. Joly, M. Muraine, J. Gueudry

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Daniel Benaim[1] ; Florence Tétart[2] ; Olivia Bauvin[2] ; Agnès Delcampe[1] ; Pascal Joly[2] ; Marc Muraine[1] ; Julie Gueudry[1]*

[1] Ophthalmology Service, Rouen University Medical Center, 1 rue de Germont, 76000 Rouen, France

[2] Dermatology Service, Rouen University Medical Center, 1 rue de Germont, 76000 Rouen, France

*Auteur correspondant

Julie Gueudry, Service d'ophtalmologie, CHU de Rouen , 1 rue de Germont, 76000 Rouen

Email : julie.gueudry@chu-rouen.fr

Tel : +33 2 32 88 80 57

Fax : +33 2 32 88 80 46

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Abstract

Introduction

Atopic keratoconjunctivitis is frequently associated with atopic eyelid dermatitis. It may require topical steroids, the prolonged use of which may cause ocular complications. Tacrolimus is an immunosuppressant used topically on the skin in atopic dermatitis. The purpose of this study is to evaluate the efficacy and tolerability of tacrolimus 0.1% ointment applied to the eyelids in atopic keratoconjunctivitis.

Patients and Methods

This is a single center, retrospective study carried out between June 2014 and February 2017. Patients presenting with atopic keratoconjunctivitis uncontrolled by first-line medical treatment were included. The main outcome was change in functional symptoms as evaluated by the NEI-VFQ25 and OSDI quality of life scores. Secondary criteria were visual acuity and topical steroids use.

Results

Among the 18 patients included, the mean age was 37.9 ± 16.8 years. The first follow-up visit occurred on average 68.3 ± 55.3 days after initiation of treatment. The NEI-VFQ25 score improved significantly for seven of the sub-scores ($p<0.05$), and the mean OSDI decreased significantly from 52.3 ± 26.2 to 22.0 ± 27.0 ($p< 0.001$), demonstrating a decrease in ocular symptoms. A significant reduction in the number of patients requiring topical steroid treatment was observed. There was no significant change in visual acuity.

Conclusion

Tacrolimus 0.1% ointment applied to the eyelids appears to be an effective treatment in the management of atopic keratoconjunctivitis.

KEYWORDS: Tacrolimus; keratitis; conjunctivitis; atopy

Introduction

Atopic keratoconjunctivitis is a chronic allergic inflammation of the ocular surface. Clinical examination reveals conjunctival hyperemia, papillae and superficial punctate keratopathy in the early stages. It is almost systematically associated with atopic eyelid dermatitis (96%) [1]. This chronic pathology has a significant effect on quality of life [2, 3]. Long-term progression may lead to blindness through severe ocular surface involvement. First line treatment relies on ocular irrigation with refrigerated normal saline solution, topical antihistamines, topical mast cell stabilizers and preservative free artificial tears, the efficacy of which remains limited [4]. The use of steroid eye drops allows good control of the disease and remains widely used for this indication. However, steroid eye drops should not be considered a long-term option, given the ophthalmic complications such as potentially blinding steroid-induced glaucoma, cataract, or infectious manifestations. To avoid complications related to prolonged topical steroid use, a switch to cyclosporine 2% eye drops may be suggested; it allows for complete discontinuation of steroids in 75% of cases, accompanied by an improvement in clinical signs and symptoms [5,6]. Its instillation has no effect on the atopic eyelid dermatitis. In France, it is relegated to tertiary care centers. Its use is sometimes limited by its poor tolerability, particularly due to burning upon instillation [7].

Dermatologic steroids are one of the first line treatments used in atopic eczema, including palpebral involvement. In the long term, they can have adverse effects: skin atrophy, stretch marks, pigmentary change, facial acne, and skin infections. They are also responsible for ocular complications such as cataract or steroid glaucoma [8]. Emollients are used in conjunction, so as to treat the associated dryness. Tacrolimus is an immunosuppressant macrolide belonging to the calcineurin inhibitor class, like cyclosporine. It is used systemically especially for prevention of graft rejection and topically on the skin in atopic dermatitis [9]. It permits steroid

sparing in the treatment of atopic dermatitis, since it has efficacy comparable to topical dermatologic corticosteroids, even better on the face [9,10]. Tacrolimus is a drug restricted to prescription by dermatologists and pediatricians in France. It has market approval in France for the treatment of moderate to severe atopic dermatitis in cases of inadequate response to or intolerance of conventional treatments, such as topical dermatologic corticosteroids. The 0.03% form is indicated in adults and children over age 2 years, while the concentrated 0.1% form is indicated in adults and teenagers at least 16 years of age. Several studies suggest its usefulness for the associated atopic keratoconjunctivitis [11-14]. Our study aims to evaluate the efficacy on atopic keratoconjunctivitis of tacrolimus 0.1% ointment applied to the eyelids.

Patients and methods

We performed a single center retrospective study at the Rouen University Medical Center from June 2014 to February 2017. It included patients presenting with chronic atopic keratoconjunctivitis uncontrolled by first line topical medication, which might include topical steroid treatment; it might be an eye drop or a dermatologic corticosteroid applied to the eyelids. The degree of severity of the atopic keratoconjunctivitis was defined by the lack of control of the functional symptomatology by a first line medication, which might include topical steroids, despite variable corneal involvement depending on the patient. Patients received an application to the eyelid skin of tacrolimus 0.1% ointment (Protopic®, LEO Pharma, Voisins-Le-Bretonneux, France) twice per day, prescribed by a dermatologist. Patients were evaluated at the initiation of treatment with a dermatologic and ophthalmologic examination and at the first follow-up visit with an ophthalmologic examination. The purpose of this study was to evaluate the efficacy of tacrolimus ointment in atopic keratoconjunctivitis. The main outcome criterion was measured with the National Eye Institute – Visual Function Questionnaire 25 (NEI-VFQ25) and Ocular Surface Disease Index

(OSDI) quality of life questionnaires translated into French, which the patients completed on paper forms. Secondary outcome criteria were the need for topical steroids and visual acuity.

Atopic keratoconjunctivitis may significantly affect quality of life, due to its chronicity and ophthalmologic symptoms. These questionnaires were chosen, since they evaluate the effect on activities in relation to ocular disease and one area of the symptoms found in these patients.

The NEI-VFQ25 [16] evaluates the effect on quality of life of chronic ocular disease by 25 questions distributed into 12 sub-groups, with scores between 0 and 100 (with 0 indicating a major effect on quality of life). The sub-groups are designated: general health, overall vision, eye pain, near vision, distance vision, social life, mental health, daily living, dependency, driving, color vision, and peripheral vision. The questions related to driving were not presented to the patients. The global NEI-VFQ25 score was not calculated, since the evaluation was performed with the scores of only the eleven sub-groups.

Atopic keratoconjunctivitis is described by certain authors as an entry point to dry eye, and these pathologies have numerous symptoms in common [17]. That is why we used the Ocular Surface Disease Index [18] (OSDI) as a main outcome criterion. The OSDI explores the quality of life and vision in dry eye through 12 items which bring out the frequency of symptoms, limitation on activities and influence of environmental factors. The items are described between 0 and 4 (with 0 meaning never, 1 sometimes, 2 half the time, 3 the majority of the time, and 4 all the time). The OSDI is evaluated on a scale from 0 to 100, with the higher scores representing larger visual disability.

Best-corrected visual acuity on examination and usage of topical steroids were reported in the physicians' notes. Upon treatment with tacrolimus ointment, the patients receiving topical steroids were asked to decrease their use of topical steroids once the functional symptomatology was controlled. They were variably permitted to use ocular irrigation, topical antihistamines, mast cell stabilizers, and artificial tears, which were not specifically evaluated. Only one patient was on systemic treatment with tetracyclines to treat associated cutaneous rosacea.

Statistical analysis was performed with the paired Student t-test to compare visual acuity as well as the NEI-VFQ25 and OSDI quality of life scores before and after treatment.
The Fisher test was used to compare the proportion of patients using steroids. A p value < 0.05 was considered statistically significant.

Results

Eighteen patients were included, with a mean age of 37.9 ± 16.8 years and a majority of males with a male/female ratio of 2. The first follow-up visit took place on average 68.3 ± 55.3 days after the initiation of treatment. At this time, the quality of life questionnaires, visual acuity and quantity of topical steroids were evaluated. One out of two patients answered the questionnaires at the evaluation visits; for the remainder of the group, the responses were collected retrospectively. Of the eighteen patients included, 11 patients initially used topical steroids: 7 patients by eye drop, 3 patients by dermatologic corticosteroids applied to the eyelids, and one of the patients used compounded versions of both. Initially, 2 patients were treated with cyclosporine 2% eye drops which were discontinued when the eyelid application of tacrolimus ointment became available for both patients.

Efficacy

The mean OSDI decreased significantly from 52.3 ± 26.2 initially to 22.0 ± 27.0 at the first follow-up visit ($p < 0.001$), showing a decrease in ocular symptoms (Figure 1). The NEI-VFQ25 score showed a significant improvement in 7 of the 11 quality of life sub-scores at the first follow-up visit, which represents a decrease in symptoms across all areas ($p < 0.05$): general health, overall vision, eye pain, near vision, distance vision, dependency, and mental health (Figure 2). The sub-scores evaluating social life, color vision and color vision [sic] showed no significant improvement ($p > 0.05$) (Table 1).

Steroid sparing

A significant reduction in the number of patients requiring topical steroid treatment was observed, with 11/18 patients (61.11%) initially vs. only 3/18 patients (16.67%) at the first follow-up visit ($p < 0.01$).

Visual acuity

There was no significant improvement in mean visual acuity in the eye with the worst visual acuity at the first follow-up in the secondary evaluation of our study, with 0.45 ± 0.86 LogMAR (or approximately 4/10 on the Monoyer scale) initially vs. 0.33 ± 0.73 LogMAR (or approximately 5/10 on the Monoyer scale) at the first follow-up visit ($p=0.59$).

Tolerability

Four patients discontinued the treatment out of the 22 patients to whom the treatment was initially offered. They complained of pain and intolerable burning on application of the tacrolimus ointment to the lids. These patients were not included in the statistical analysis.

Discussion

The use of tacrolimus 0.1% ointment applied to the eyelids improves quality of life, reduces ocular symptoms and decreases the need for steroids at the first follow-up visit in the management of atopic keratoconjunctivitis.

These data correspond to those recently described in the literature [19] with regard to treatment of atopic keratoconjunctivitis, notably the study published in 2003 by Rikkers *et al.* [18], which describes an improvement in ocular symptoms as a secondary benefit of treatment of atopic eyelid dermatitis. The suggested treatment was tacrolimus 0.03% ointment, a lower concentration than that which we used. The frequency of application was the same as in our study. The study population had a mean age of 56.2 years and consisted of 5 patients.

The choice of quality of life questionnaires is debatable, particularly since they have not been validated in the evaluation of atopic keratoconjunctivitis, with, for example, itching not being taken into account, despite it's being a symptom very frequently encountered in this disease. However, the symptoms described by these patients are similar to those of dry eye disease, for which the OSDI has been validated, and the activities included in the NEI-VFQ25 broadly cover the areas in which patients may have disabilities.

In addition, it also allows for steroid sparing. Tacrolimus 0.1% eye drops, available in some countries, allow freedom from topical steroid use as described in a recent Japanese retrospective study [20], which found similar efficacy of tacrolimus 0.1% drops with or without adjunctive topical steroids.

Prescription of tacrolimus ointment in France is restricted to dermatologists and pediatricians. Their expertise is established since they can manage the atopic disease cross-sectionally. At the Rouen University Medical Center, we put into place a multidisciplinary consultation with the dermatology service, which allows us a global evaluation upon prescription of this medication.

With regard to visual acuity, we found no significant improvement at the first follow-up visit. Two thirds of the patients had visual acuity greater than or equal to 8/10, which did not allow much room for statistical improvement. The remaining third of the patients had visual acuity less than or equal to 4/10 due to corneal scars, for which the treatment should not have any effect a priori. However, for these patients, the improvement of the ocular surface and the eyelid lesions may permit fitting with scleral contact lenses [21].

Four patients experienced adverse effects from the application of the tacrolimus ointment to the eyelids. Among the 18 patients included in the statistical analysis, none had any complications while applying the tacrolimus 0.1% ointment to the eyelids, although admittedly a rather small sample size. Likewise, recent publications on small sample sizes found no complications at 4 years [14,22]. We must keep in mind, however, the letter to health care professionals published in May 2012 which called attention to the risk of cutaneous lymphoma suggested, but not established, by certain studies with numerous confounding factors in the evaluation of the imputability of topical tacrolimus. In addition, there is a theoretical risk of conjunctival carcinoma with the use of cyclosporine eye drops, a molecule with a mechanism of action similar to that of tacrolimus. Three cases have been reported in the literature, of which 2 had concomitant exposure to systemic cyclosporine A without a demonstrable link [23].

In our study, we did not evaluate adjuvant treatment such as use of artificial tears or emollients. Thus, this study focused on the functional symptoms of which patients complain. This constitutes a limitation in the overall evaluation of efficacy, along with its retrospective nature.

Conclusion

Tacrolimus 0.1% ointment applied to the eyelids allows for significant improvement in the symptoms of atopic keratoconjunctivitis as well as for steroid sparing. It is part of the available therapeutic arsenal and must be integrated into the overall management of atopic disease. Prescription of it, however, remains restricted to certain non-ophthalmologic specialists.

Disclosure of interest

The authors have no conflicts of interest to disclose in connection with this article.

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TABLE 1

Mean values of NEI-VFQ25 sub-scores at treatment initiation and first follow-up visit. p values were obtained according to the Student t test on paired series, and the mean values of the sub-scores were used to generate the histogram in figure 2.

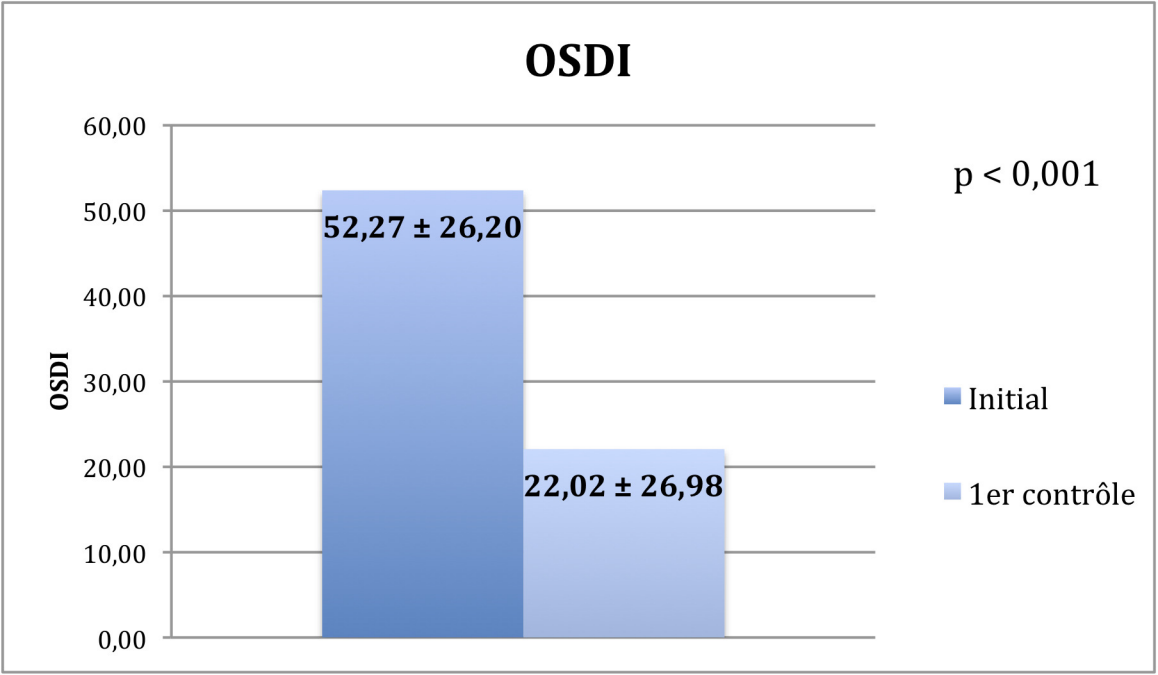
NEI-VFQ25 sub-scores	Initial	First follow-up	p value
General health	43.06 ± 26.85	55.56 ± 26.51	0.035
Overall vision	56.67 ± 25.90	72.22 ± 25.79	0.002
Eye pain	47.22 ± 27.97	75.69 ± 24.81	<0.001
Near vision	69.44 ± 28.58	83.89 ± 26.70	0.007
Distance vision	73.15 ± 32.16	84.72 ± 26.55	0.014
Social life	68.75 ± 35.68	81.25 ± 30.39	0.088
Dependency	64.81 ± 39.87	83.80 ± 32.90	0.013
Color vision	86.11 ± 29.98	91.67 ± 24.25	0.259
Peripheral vision	79.17 ± 34.57	86.11 ± 24.59	0.056
Mental health	54.86 ± 35.26	71.18 ± 30.33	0.002
Daily living	68.75 ± 35.68	81.25 ± 30.39	0.089

FIGURE 1

Change in mean OSDI score before and after introduction of tacrolimus 0.1% ointment in patients with refractory atopic keratoconjunctivitis.

FIGURE 2

Change in NEI-VFQ25 sub-scores before and after introduction of tacrolimus 0.1% ointment in patients with refractory atopic keratoconjunctivitis.


OSDI
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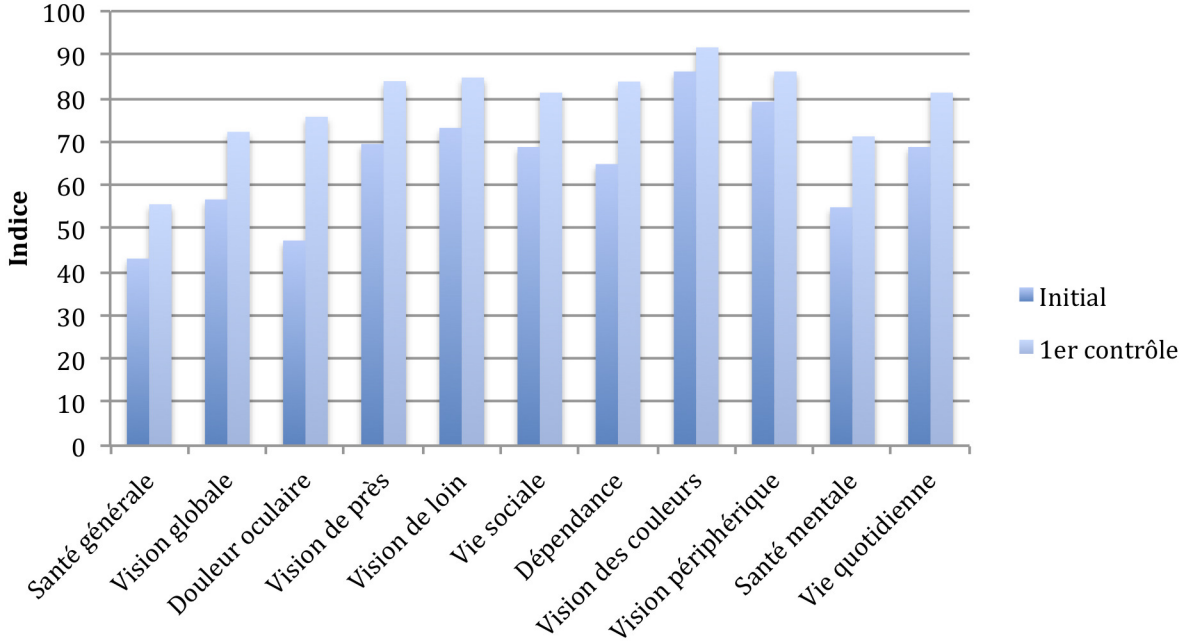
OSDI
52,27 ± 26,20
22,02 ± 26,98
p < 0,001
Initial
1er contrôle


Indice
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Santé générale
Vision globale
Douleur oculaire
Vision de près
Vision de loin
Vie sociale
Dépendance
Vision des couleurs
Vision périphérique
Santé mentale
Vie quotidienne