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Original Article

Efficacy and safety of using topical cyclosporine A for treatment of moderate to severe dry eye disease

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Abstract

Objective: To investigate and evaluate the efficacy and safety of topical cyclosporine A for treatment of moderate to severe dry eye disease.
Materials and methods: This is a prospective study of patients with moderate to severe dry eye syndrome were recruited. All cases were selected from patients attending the ophthalmic outpatient clinic of Research institute of ophthalmology. Eligible patients were at least 21 years of age with a confirmed diagnosis of keratoconjunctivitis sicca with or without Sjogren's syndrome refractory to conventional management.
The medication used in this study were unit dose vials of unpreserved cyclosporine A 0.05% used twice daily.
The protocol was composed of a 2-week washout phase, a 12-week treatment phase, and a 4-week post treatment phase. Patients were evaluated at weeks 4, 8, 12 during the treatment phase. During these visits patients were evaluated for changes from base line in Schirmer test, rose Bengal staining, superficial punctuate erosions, BUT, impression cytology, symptoms of ocular discomfort and visual acuity. After completion of the treatment phase, patients were also evaluated at post treatment week 4, during this visit patients were assessed for Schirmer test, rose Bengal staining, superficial punctuate erosion, BUT, impression cytology, symptoms of ocular discomfort and visual acuity.
Results: Thirty two cases in the mean age of 47 (12.9), range [20–67] years; four (13%) male and 28 (87%) female were recruited in the current study. Out of them, 12 (38%) cases had Sjogren syndrome. Visual acuity improved significantly ($p = 0.012$), BUT ($p < 0.0001$) for both eyes, Schirmer measurements ($p < 0.0001$ and $p = 0.029$ for OD and OS, respectively).
Conclusions: Cyclosporine A ophthalmic emulsion 0.05% has been demonstrated to be effective and safe in human clinical trials. It reduces signs and symptoms of dry eye disease, with the fact that its effect continued to occur significantly within the treatment periods as well as improvement of ocular condition kept on, actually more slowly towards stability, despite the drug has already stopped.

Keywords: Dry eye syndrome, Cyclosporine, Keratoconjunctivitis sicca

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Introduction

Some of recent studies indicate that dry eye disease or keratoconjunctivitis sicca (KCS) affects millions of people over the world.[1] In addition, there is an increasing trend in the frequency of patients visiting eye care facilities with dry eye symptoms.[2] The most common complaint is discomfort sensation, including a gritty and foreign body sensation, depending on the duration and severity of the dryness where the to ocular surface damage may also be present.[3,4] Despite being common condition, dry eye syndrome (DES) is underdiagnosed. Clinically, DES has been classified into two separate, overlapping, categories; evaporative loss and aqueous deficiency.[5]

Additionally, a new concept of pathogenesis showed that DES maybe caused by inflammation mediated by T-cell lymphocytes and cytokines that affect lacrimal gland acini and ducts.[5,6] This effect, would lead to changes in the tear film and hence abnormal changes in the homeostasis of the ocular surface. Most of the treatment modalities of DES depend on tear substitutes or tear preservatives although they can't affect these processes.[7]

It has been found that decreased tear production and tear clearance lead to chronic inflammation on the ocular surface. This inflammatory response consists of inflammatory cell infiltration of the ocular surface, activation of the ocular surface epithelium with increased expression of adhesion molecules and inflammatory cytokines, increased concentrations of inflammatory cytokines in the tear fluid and increased activity of matrix degrading enzymes, such as matrix metalloproteinase-9 in the tear fluid.[14]

Not only has inflammation been linked to aqueous deficiency dry eye disease, but also to that of evaporative loss. Accumulation of meibum within the meibomian gland can lead to inflammation of the gland and bacterial colonization.

The colonizing bacteria have lipases that break the nonpolar wax and sterol esters into triglycerides and free fatty acids (polar lipids), thus altering the normal composition of the meibum. The polar lipids makes the mucinous layer hydrophobic. The abnormal meibum solidifies and obstructs the ducts, leading to further inflammation and perpetuating the vicious cycle. Topical cyclosporine A as a highly specific immunomodulator that primarily affects T lymphocytes may decrease the inflammation of the meibomian glands and thus, reduce their plugging and dysfunction.[5]

Systemic Cyclosporin A (CsA) is one of the powerful anti T-cell immunosupperssive agents, which does not lead to bone marrow suppression. Its main complications are hypertension and nephrotoxicity, however, when used in low doses, the incidence of nephrotoxicity is much reduced.[6] Systemic cyclosporine A can be given in the treatment of some of local ophthalmic conditions involving cytokines, for example corneal graft rejection, autoimmune uveitis and DES. Topical use of cyclosporine A avoid many side effects associated with systemic administration.[8] Treatment with topical cyclosporine A has been shown to reduce the cell mediated inflammatory reactions which associated with inflammatory ocular surface disease.[6,9,10]

Previous studies stated that treatment with topical cyclosporine A could improve symptoms and signs of DES.[9,11,12] As well as, several studies suggest that topical cyclosporine A offers the first therapeutic treatment for patients with moderate to severe DES due to aqueous deficiency.[5] All of these findings suggest that treatment with topical cyclosporine A may give a very good chance as a real curative treatment instead of the symptomatic treatments that targets only the symptoms of DES as it works on the disease pathogenesis. The most appropriate concentrations of topical cyclosporine A are 0.05% and 0.1% as there were no additional benefits were observed with higher concentrations.[7] In the current study, we aimed to investigate and evaluate the safety and efficacy of topical cyclosporine A 0.05% for treatment of moderate to severe dry eye disease.

Methods

In our prospesctive study, patients with moderate to severe DES were recruited. All cases were selected from patients attending the ophthalmic outpatient clinic of Research institute of ophthalmology. The minimum age of our patients was at least 21 years old with a confirmed diagnosis of KCS with or without Sjogren's syndrome resistant to conventional management.

The Inclusion criteria included Schirmer test (without anesthesia) of 5 mm/5 min in at least one eye; mild superficial punctuate erosions defined as a corneal punctuate fluorescein staining score of $\geq$1 in either eye (Scale 0: none to 3: severe); and one or more moderate ($\geq$+2) dry eye related symptoms; including itching, burning sensation, blurring of vision, foreign body sensation, dryness sensation, photophobia, and pain. Our exclusion criteria were any ocular surface disease or surgery or ocular trauma within the previous 6 months. Any patient with uncontrolled systemic disease, also pregnant or lactating mothers was excluded. The eye drops used in this study were preservative free vials of cyclosporine A 0.05%. The treatment protocol consisted of three phases: (I) first phase: 2-week washout phase, during this time the patients were instructed to stop the use of all topical eye drops except for preservative free tears substitutes, four times daily in each eye. (II) Second phase: 12-week treatment phase, patients who finiched the washout phase successfully were then given their topical cyclosporine A 0.05% two times daily (morning and evening) in both eyes for 12 weeks. The use of preservative free tears substitutes was allowed during the treatment phase. Patients were regularly evaluated at weeks 4, 8, 12 during the treatment phase. During these follow up visits patients were reevaluated for changes from base line in terms of schirmer test, rose Bengal staining, superficial punctuate erosions , impression cytology, ocular discomfort sensation, biomicroscopy, and vision. (III) 3rd phase: 4-week post-treatment phase, after the end of the treatment phase, patients were also evaluated again for schirmer test, rose Bengal staining, superficial punctuate erosions, impression cytology, ocular discomfort sensation, biomicroscopy, and vision.

The efficacy measures were rose Bengal staining (graded on a scale from 0 = none to 3 = severe); superficial punctate erosions (graded on a scale from 0 = none to 3 = severe); Schirmer test without anesthesia; symptoms of ocular discomfort (graded on a scale from 0 = none to 3 = severe); tear break up time. Meanwhile, treatment safety was proven using systemic blood pressure, kidney function tests, ocular tension by Goldman applanation tonometry and the vision as indicators.

Clinical examinations included: both clinical and ocular medical history taking, detailed Slit Lamp Examination, in addition to break-up time test; Rose Bengal stain; and Schirmer test.

The Impression Cytology was taken using a cellulose acetate filter paper (Millipore type GS); of a 0.22 um pore size. (Millipore Company: agent in Cairo ETAMCO).

The filter paper was placed carefully on the temporal part of the bulbar conjunctiva, just below the horizontal midline of the cornea and conjunctival sac.

The strips were left in place for 3–4 s and then gently were removed with peeling motion, avoiding shearing and twisting forces that would distort the specimen.

After the specimens were obtained, the detached conjunctival cells on the filter material were fixed and stained for microscopic examination.

Microscopic examination

The slides were examined using an ordinary light microscope, (Ningguang™ XSZ-107), under magnifications of 40×, 100× and 250×.

The grading was carried out mainly by determining the stage by the morphologic appearance of conjunctival epithelial and goblet cells was developed and the nucleus to cytoplasm ratio.

The samples were examined for the following cytological features:

(1) Morphological features of the nucleus.
(2) Metachromatic changes of cytoplasmic color and emergence of keratinization.
(3) Nucleus – cytoplasm ratio.

Conjunctival impressions were graded on a scale from 0 to 3.

Grade 0: Epithelial cells are small and round with eosinophilic staining cytoplasm. Nuclei are larger, with a nuclear/cytoplasmic (N/C) ratio of 1:2. Goblet cells are abundant, plump, and oval with an intensely PAS-positive cytoplasm.
Grade 1: Epithelial cells are slightly larger, with eosinophilic staining. Nuclei are smaller, N/C ratio of 1:3. Goblet cells are decreased in number but still maintain their plump, oval shape with an intensely PAS-positive cytoplasm.
Grade 2: Epithelial cells are larger and polygonal, occasionally multinucleated with variably stained cytoplasm. Nuclei are small, with a N/C ratio of 1:4 to 1:5. Goblet cells are markedly decreased in number.
Grade 3: Epithelial cells are large and polygonal, with basophilic cytoplasm. Nuclei are small, pyknotic, and in many cells completely absent. The N/C ratio is greater than 1:6.

Statistical section

Data were collected pre- and post-intervention using a specific data collection sheet, data were then cleaned, managed, and coded using Microsoft Excel 2013®; Microsoft Corporation, Redmond, Washington, USA. The analysis was done using SPSS® version 22 (IBM Inc., Chicago, Illinois, USA). Descriptive analysis was done, where categorical variables were presented in the form of frequencies and percentages while continuous variables in the form of mean (±SD). Inferential analysis was conducted to test the significance of potential change between pre- and postintervention. Wilcoxon Signed Ranks test was done to evaluate the significance of change in the assessed clinical indices, while Chi squared test was used to assess potential associations of categorical variables. The confidence interval level was set to 95% where a corresponding p value threshold was identified as 0.05 where any output p below 0.05 is interpreted as an indicator of statistical significance.

Results

Thirty two cases in the mean age of 47 (12.9), range [21–67] years; four (13%) male and 28 (87%) female were recruited in the current study. Out of them, 12 (38%) cases had Sjogren syndrome. In terms of dry eye clinical indices, comparing baseline pre-intervention assessment to the 4 week (during treatment) showed that there was a significant improvement in Visual acuity ($p = 0.012$), BUT ($p < 0.0001$) for both eyes, Schirmer measurements ($p < 0.0001$ and $p = 0.029$ for OD and OS, respectively). Moreover, comparing pre-intervention assessment to 12 month (during treatment) assessment yielded that the improvement in all of the assessed indices was highly significant ($p < 0.0001$) for Visual Acuity, BUT, and Schirmer test for both eyes.

On the other hand, comparing clinical indices at the second assessment visit to the clinical indices at the last assessment visit, demonstrated that the statistically significant improvement in such assessed indices continued to show up ($p = 0.012$ for visual acuity and $p < 0.0001$ for all of the other indices; BUT and Schirmer test for both eyes.

Moreover, comparing visit 4 (12 week end of treatment phase) and visit 5 (4 week post treatment phase), showed that the dry eye status continued further improvement with a significant p value of 0.012 for all of the assessed indices.

Comparing findings from Rose Bengal and Impression Cytology, comparison of pre-intervention assessment to 4 week (during treatment) visit showed that there is a statistically significant difference between both rose Bengal and impression cytology findings between the pre-intervention visit and the first 4 month follow up visit in both eyes ($p < 0.0001$) in terms of Rose Bengal while for the impression cytology, only the OD showed significant difference $p < 0.0001$, while OS was not found to be statistically significant, $p = 0.201$.

Likewise, comparing the pre-intervention phase assessment with the 12 week (during treatment) visit showed that the recognized statistically significant difference is quite consistent in both of the Rose Bengal and impression cytology findings ($p < 0.0001$) for both eyes in Rose Bengal and $p < 0.0001$ & $p = 0.013$ for the impression cytology in OD and OS respectively.

For the assessment of the improvement stability, comparing visit 2 to week 12 findings showed that the improvement also continued to show up in both Rose Bengal ($P < 0.0001$ for both eyes) and $P < 0.021$ & $P = 0.002$ for OD and OS in terms of the impression cytology.

Finally, in the post intervention phase, comparing the 12 week visit to the post intervention visit assessments, the difference continued to be significant for the Rose Bengal in OD

(p = 0.014) while it was not significant in the OS (p = 0.998). Meanwhile, the difference continued to be significant in the impression cytology reading (p = 0.014 for both eyes).

Discussion

Keratoconjunctivitis sicca (KCS) or dry eye syndrome is a very common problem in ophthalmic practice. The recent committee of the national eye institute/industry classified KCS into two new categories.[13] The two new categories are aqueous production – deficient and evaporative loss dry eyes. The aqueous production-deficient category includes Sjogren-associated KCS (SS-KCS) and non-Sjogren-associated KCS (NSS-KCS).

This study aimed to evaluate efficacy and safety of topical CsA 0.05% twice daily in treatment of moderate to severe dry eye. Findings from our series showed that there were significant improvements in the eye conditions (stage of the disease severity). This improvement continued to occur within the treatment period. Despite the fact that the treatment has already stopped, improvements kept on, actually more slowly towards stability. No systemic harm has been detected in blood pressure and/or in kidney function as well.

Efficacy, safety, formulation tolerability, and optimum dose of a novel CsA oil-in-water emulsion formulation for the treatment of moderate to severe dry eye disease was investigated by Stevenson and his colleagues in 2000. Observations from Stevenson et al. study showed that treatment with topical CsA 0.05–0.4% ophthalmic emulsion significantly led to improvement in the ocular manifestations of moderate to severe dry eye disease and that these improvements resulted in a significant improvement of vision-related functioning. These finding support the results of our study that demonstrated a positive effect of topical Cs A on DES. This improvement continued to occur significantly during the two successive (within- treatment) follow-ups.[7]

Other studies have demonstrated a favourable effect of topical CsA on dry eye in Sjogren Syndrome and enlarge the range of patients who may get benefit from CsA to those with moderate to severe DES with or without Sjogren syndrome. This matches with our study in which the two patient groups (SS-KSC and NSS-KSC) improved with the use of topical CsA.[11,12]

The mechanisms of dry eye disease are still being explained, but many lines of evidence suggest that dry eye disease is the result of a cytokines and receptor mediated inflammatory process. This inflammatory process affects the lacrimal gland acini and ducts, leading to abnormalities in the tear film and in turn disrupting the homeostasis of the ocular surface. This hypothesis was evidenced by the observations of infiltration of the lacrimal glands of the patients with DES with Sjogren dyndrome by lymphocytic infiltrates and proinflammatory cytokines.[15]

The ability of the immunomodulatory agent topical cyclosporine A to improve manifestations of moderate to severe dry eye disease without Sjogren's syndrome gives further support to the hypothesis that stated, cell mediated inflammatory processes may contribute to development of dry eye disease regardless of the cause.[16]

The effect of the inflammatory process on dry eye disease unrelated to systemic inflammatory disease has also been demonstrated in histologic studies,[17,18] which demonstrated that evidence of the inflammatory processes was associated with abnormal lacrimal gland histologic findings, suggesting that inflammation in dry eye may lead to the progression of the disease by causing permanent damage to the lacrimal gland.

It is important to note that there were safety findings in our study; no systemic harm was detected in blood pressure and/or in kidney function. In The study made by Stevenson et al. 2000 the most important safety findings were that there were no ocular infections occurred in any of the treated patients. In addition, blood analysis showed that even the greatest concentrations of topical cyclosporine A used resulted in minimal systemic absorption[7].

Topical Cyclosporine A 0.1% ophthalmic emulsion over 1–3 year period in moderate to severe dry eye disease patients as the main outcome measures of Barber et al. and Sall et al. studies were corneal staining, Schirmer test, and symptoms severity assessment were conducted during the first 12-month period, with a patient survey during the second 12-month period. Biomicroscopy and visual acuity examinations, intraocular pressure measurements and adverse effects queries occurred at 6-month intervals. Treatment during the first 12-month period resulted in moderate improvements in objective measures of dry eye disease and no change in subjective measures, which was expected because partients had been treated with cyclosporine emulsion (either 0.05% or 0.1%) for 6–12 months before the baseline assessment.[19,20]

In our study, there was stability of visual acuity and IOP, the apparent improvement of vision is an indirect determinant of a comfortable eye feeling. In Barber et al. study,[19] diminished visual acuity over the course of the study was slightly more frequent than increased visual acuity. However, diminution of vision in these patients was likely due to the visual problems that commonly affect the elderly population (e.g., cataract, age related macular degeneration).

The number of goblet cells as well as epithelial turnover in patients with non-Sjogren syndrome associated with keratoconjunctivitis sicca (NSS-KCS) have been compared to those with SS-KCS before and after 6 months of treatment with topical cyclosporine A (CsA) ophthalmic emulsion. The study showed that treatment of dry eye syndrome for 6 months with topical CsA resulted in an increase in the number of Goblet cells in patients with NSS-KCS and SS-KCS and a decrease in epithelial turnover in those with NSS-KCS.[21]

Our study findings showed that we the impression cytology was improved in all stages comparing pre to post intervention and with a pattern of stability within the treatment period. A study by Kujawa and Rozycki in which all groups of patients were treated by 0.05% cyclosporine topically twice daily, showed that using 0.05% cyclosporine solution is effective in treating patients with dry eye syndrome but without systemic disease. In such cases a short term, three-month treatment is sufficient. The treatment with 0.05% cyclosporine is just as effective in patients with SS-KCS, yet in such cases the treatment has to be longer and take six months.[22]

Another study by Wilson and Perry reported that topical cyclosporine A treatment appears to be associated with a cure of symptoms and signs in subgroup of chronic dry eye patients. In such patients, apparently there is effective elimination of inflammatory processes underlying chronic dry eye disease. Such patients should be monitored long term

because a return of disease may be noted these results suggest that topical cyclosporine treatment stops progression of chronic dry eye in some patients.[23] In our study, it is clear that there was a high degree of stability, not only this, but also the treatment impact is still functioning (as clear by the continued improvement in objective & subjective measures including impression cytology).

Finally, despite the fact the treatment was stopped and improvement kept on, actually more slowly towards stability is a phenomenon that can be taken as an indicator of the drug successful impact.

Accordingly, a practical protocol for the management of keratoconjunctivitis sicca can be recommended as follows: Good history taking for symptoms suggestive of dry eye, assessment of the BUT test as screening test for dry eye, patient should be examined superficial punctate erosions. Confirmed diagnosis can be done via Schirmer test and/or impression cytology test. Treatment modality can go through using a lubricating eye drops for mild cases, to supplement a patient's natural tears, administering topical 0.05% cyclosporine A as the first line of therapeutic treatment for patients with moderate-to-severe dry eye disease due to tear deficiency in addition to tear substitutes. In very severe cases, we can consider punctual occlusion either temporary or permenant to improve the residence time of the tears that the patient can produce.

Conclusions

Cyclosporine A ophthalmic emulsion 0.05% is the first difnitive treatment that targets an underlying the pathological mechanism for chronic dry eye: immune-mediated inflammation. Cyclosporine A ophthalmic emulsion 0.05% has been demonstrated to be effective and safe in human clinical trials. It decreases signs and symptoms of dry eye disease, with the fact that its effect continued to occur significantly within the treatment periods as well as improvement of ocular condition kept on, actually more slowly towards stability, despite the drug has already stopped.

It is well-tolerated without ocular side effects. Its use is not associated with any systemic side effects. No microbial overgrowth or ocular infections happened during clinical studies. Topical cyclosporine A 0.05% is well accepted by patients as they can expect results in 3–6 months of treatment. Most importantly, this agent provides rational pharmacological therapy where none currently exists.

Conflict of interest

The authors declared that there is no conflict of interest.

References

1. Schein OD, Tielsch JM, Munoz B, Bandeen-Roche K, West S. Relation between signs and symptoms of dry eye in the elderly A population-based perspective. *Ophthalmology* 1997;**104**:1395–401.
2. Doughty MJ, Fonn D, Richter D, Simpson T, Caffery B, Gordon K. A patient questionnaire approach to estimating the prevalence of dry eye symptoms in patients presenting to optometric practices across Canada. *Optom Vis Sci* 1997;**74**:624–31.
3. Mackie IA, Seal DV. Diagnostic implications of tear protein profiles. *Br J Ophthalmol* 1984;**68**:321–4.
4. Seal DV. The effect of ageing and disease on tear constituents. *Trans Ophthalmol Soc UK* 1985;**104**(Pt 4):355–62.
5. Perry HD, Donnenfeld ED. Topical 0.05% cyclosporin in the treatment of dry eye. *Expert Opin Pharmacother* 2004;**5**:2099–107.
6. Strong B, Farley W, Stern ME, Pflugfelder SC. Topical cyclosporine inhibits conjunctival epithelial apoptosis in experimental murine keratoconjunctivitis sicca. *Cornea* 2005;**24**:80–5.
7. Stevenson D, Tauber J, Reis BL. Efficacy and safety of cyclosporin A ophthalmic emulsion in the treatment of moderate-to-severe dry eye disease: a dose-ranging, randomized trial. The Cyclosporin A Phase 2 Study Group. *Ophthalmology* 2000;**107**:967–74.
8. Lallemand F, Felt-Baeyens O, Besseghir K, Behar-Cohen F, Gurny R. Cyclosporine A delivery to the eye: a pharmaceutical challenge. *Eur J Pharm Biopharm* 2003;**56**:307–18.
9. Power WJ, Mullaney P, Farrell M, Collum LM. Effect of topical cyclosporin A on conjunctival T cells in patients with secondary Sjogren's syndrome. *Cornea* 1993;**12**:507–11.
10. el-Asrar AM, Tabbara KF, Geboes K, Missotten L, Desmet V. An immunohistochemical study of topical cyclosporine in vernal keratoconjunctivitis. *Am J Ophthalmol* 1996;**121**:156–61.
11. Laibovitz RA, Solch S, Andriano K, O'Connell M, Silverman MH. Pilot trial of cyclosporine 1% ophthalmic ointment in the treatment of keratoconjunctivitis sicca. *Cornea* 1993;**12**:315–23.
12. Gunduz K, Ozdemir O. Topical cyclosporin treatment of keratoconjunctivitis sicca in secondary Sjogren's syndrome. *Acta Ophthalmol (Copenh)* 1994;**72**:438–42.
13. Lemp MA. Report of the national eye institute/industry workshop on clinical trials in dry eyes. *CLAO J* 1995;**21**:221–32.
14. Pflugfelder SC, Jones D, Ji Z, Afonso A, Monroy D. Altered cytokine balance in the tear fluid and conjunctiva of patients with Sjogren's syndrome keratoconjunctivitis sicca. *Curr Eye Res* 1999;**19**:201–11.
15. Kroemer G, Martinez C. Cytokines and autoimmune disease. *Clin Immunol Immunopathol* 1991;**61**:275–95.
16. Stern ME, Beuerman RW, Fox RI, Gao J, Mircheff AK, Pflugfelder SC. The pathology of dry eye: the interaction between the ocular surface and lacrimal glands. *Cornea* 1998;**17**:584–9.
17. Damato BE, Allan D, Murray SB, Lee WR. Senile atrophy of the human lacrimal gland: the contribution of chronic inflammatory disease. *Br J Ophthalmol* 1984;**68**:674–80.
18. Williamson J, Doig WM, Forrester JV, Tham MH, Wilson T, Whaley K, et al. Management of the dry eye in Sjogren's syndrome. *Br J Ophthalmol* 1974;**58**:798–805.
19. Barber LD, Pflugfelder SC, Tauber J, Foulks GN. Phase III safety evaluation of cyclosporine 0.1% ophthalmic emulsion administered twice daily to dry eye disease patients for up to 3 years. *Ophthalmology* 2005;**112**:1790–4.
20. Sall K, Stevenson OD, Mundorf TK, Reis BL. Two multicenter, randomized studies of the efficacy and safety of cyclosporine ophthalmic emulsion in moderate to severe dry eye disease. CsA Phase 3 Study Group. *Ophthalmology* 2000;**107**:631–9.
21. Kunert KS, Tisdale AS, Gipson IK. Goblet cell numbers and epithelial proliferation in the conjunctiva of patients with dry eye syndrome treated with cyclosporine. *Arch Ophthalmol* 2002;**120**:330–7.
22. Kujawa A, Rozycki R. A 0.05% cyclosporine treatment of the advanced dry eye syndrome. *Klin Oczna* 2005;**107**:280–6.
23. Wilson SE, Perry HD. Long-term resolution of chronic dry eye symptoms and signs after topical cyclosporine treatment. *Ophthalmology* 2007;**114**:76–9.