Libertas Academica
FREEDOM TO RESEARCH

Open Access: Full open access to this and thousands of other papers at http://www.la-press.com.

Ophthalmology and Eye Diseases

Safety and Efficacy of Cyclosporine in the Treatment of Chronic Dry Eye

Clyde Schultz[1,2]

[1]Department of Biology, University of Calgary, Calgary, Alberta, Canada. [2]Biogram Inc., Ponte Vedra Beach, FL, USA.

ABSTRACT: Dry-eye syndrome (DES) is a multifactorial disease affecting millions of individuals worldwide. Various factors, including age, hormonal status, genetics, sex, immune status, innervation status, nutrition, pathogens, and environmental stress, can alter the cellular and molecular structure or function of components of the ocular surface system. The resulting imbalance increases susceptibility to desiccation and epithelial damage, leading to a vicious circle in which inflammation amplifies and sustains further damage by chronic deregulation of the system. Lubricating agents and steroids have been used as treatment options. However, as the causes of the disease become better elucidated, the more chemically complex cyclosporine A has become an increasingly useful treatment option and in the United States is currently the only Food and Drug Administration (FDA)-approved prescription drug for the treatment of dry eye. The safety and efficacy of cyclosporine have been shown in numerous studies.

KEYWORDS: dry eye, cyclosporine, inflammation, steroid, tear film

CITATION: Schultz. Safety and Efficacy of Cyclosporine in the Treatment of Chronic Dry Eye. *Ophthalmology and Eye Diseases* 2014:6 37–42 doi: 10.4137/OED.S16067.

RECEIVED: April 10, 2014. **RESUBMITTED:** May 7, 2014. **ACCEPTED FOR PUBLICATION:** May 12, 2014.

ACADEMIC EDITOR: Joshua Cameron, Editor in Chief

TYPE: Concise Review

FUNDING: Author discloses no funding sources.

COMPETING INTERESTS: Author discloses no potential conflicts of interest.

COPYRIGHT: © the authors, publisher and licensee Libertas Academica Limited. This is an open-access article distributed under the terms of the Creative Commons CC-BY-NC 3.0 License.

CORRESPONDENCE: schultzc@ucalgary.ca

This paper was subject to independent, expert peer review by a minimum of two blind peer reviewers. All editorial decisions were made by the independent academic editor. All authors have provided signed confirmation of their compliance with ethical and legal obligations including (but not limited to) use of any copyrighted material, compliance with ICMJE authorship and competing interests disclosure guidelines and, where applicable, compliance with legal and ethical guidelines on human and animal research participants. Provenance: the author was invited to submit this paper.

Introduction

Dry-eye syndrome (DES), also known as keratoconjunctivitis sicca or keratitis sicca, is a multifactorial disease of the tears and ocular surface found both in humans and some domesticated animals, which is associated with either increased tear film evaporation on the surface of the eye or decreased tear production by the meibomian glands. DES results in symptoms of ocular discomfort (such as a burning sensation, itching, redness, stinging, pain, and foreign body sensation), visual disturbance, and tear film instability, with potential damage to the ocular surface. It is accompanied by increased osmolarity of the tear film and inflammation of the ocular surface.[1,2] The diagnosis of DES is usually based on the presence of symptoms, but various tests are available for diagnosis in certain cases.[3] For example, Schirmer's test measures the amount of moisture bathing the eye. Lysozyme concentrations associated with the tear film are also sometimes measured.

Although the reported prevalence of DES varies among populations, DES affects millions of individuals worldwide. In American men, Schaumberg et al.[4] found prevalence rates ranging from 3.9% in men aged 50–54 years to 7.7% in those 80 years or older. In American women, the prevalence also increased with age, from 5.7% among women younger than 50 years to 9.8% among women aged 75 years or older.[5] Other studies have found DES in 14% of individuals aged 65–85 years.[6] Prevalence rates in Asian populations appear to be even higher.[6,7] However, at least some of the variation between studies relates to differences in the definition of disease used.[6]

In addition to older age and female sex, some of the risk factors for DES include postmenopausal estrogen therapy, medications such as antihistamines, connective tissue disease, LASIK and refractive excimer laser surgery, low intake of omega-3 essential fatty acids, and radiation therapy.[6] Manaviat et al.[8] have linked DES with type 2 diabetes. In their study of 199 patients with type 2 diabetes, 108 patients (54.3%)

had DES. The prevalence of DES was significantly related to duration of diabetes, but not to sex or age. However, the authors did not speculate as to an etiologic link. DES may also be exacerbated by environmental factors such as contact lens wear, low-humidity environments, smoking, use of various medications such as antidepressants, antihypertensives, and medications to treat benign prostatic hyperplasia, prolonged computer use, watching television, reading, living at higher elevations, and excessive wind or air conditioning.[4,9–11]

Predicting the onset of DES is an ongoing issue in ophthalmic and optometric practice. Pult and coworkers[12] performed a series of studies comparing several dry-eye clinical evaluative tests in a population of non-contact lens wearers. The combination of the number of lid-parallel conjunctival folds and duration of non-invasive break-up time (the time between the full opening of the eyelids after a complete blink and the first break in the tear film) was more predictive of the development of dry-eye symptoms than any individual tests in this patient population.

DES can seriously impair the affected individual's quality of life.[4,7,13] In addition to the negative effects of ocular pain, DES can also have adverse effects on mental health, such as depression and anxiety.[14] Miljanovic et al.[15] reported in a study of 690 participants that DES affected the ability to perform common daily activities, such as driving, television viewing, and computer work.

Treatment for DES depends on the severity of the condition. Environmental conditions that increase tear evaporation and factors that may decrease tear production should be minimized or eliminated.[16] Artificial tears or ocular lubricants (preservative free) are often successful in ameliorating symptoms, especially in mild cases.[9] Nutritional supplementation with omega-3 fatty acids may be useful, but research in this area is limited and the results somewhat inconclusive to date.[17] Based on the concept that inflammation is a key component of the pathogenesis of dry eye, a number of anti-inflammatory agents have been used, including corticosteroids, tetracyclines, and cyclosporine.[16,18] Other treatments may include intraductal meibomian gland probing, application of simultaneous heat and pressure to the eyelid to affect the meibomian glands, and N-acetyl-cysteine.[19] Severe or prolonged dry-eye cases may require surgical procedures, such as lid surgery, tarsorrhaphy, or mucus membrane, salivary gland, or amniotic membrane transplantation.[16]

About 8.5 million Americans annually spend more than US$300 million on artificial tear preparations and other over-the-counter treatments.[7] With the introduction of newer treatment options, the cost of treating DES is increasing. A study of 54,052 patients in Singapore showed an increase of 0.8% between years 2008 and 2009 in direct costs of patients for all types of medicaments purchased, and a 6.69% increase in expenditure per patient episode.[20] Therefore, evidence regarding the safety and efficacy of available treatment options is needed to enable appropriate treatment decisions for individual patients.

Among the plethora of available treatment options, cyclosporine A (Restasis, Allergan, Irvine, CA) is the only prescription drug approved by the US Food and Drug Administration (FDA) specifically for patients with DES and seems to be the most widely used current therapy for DES.[7,21] The aim of the present manuscript is to review the safety and efficacy of cyclosporine A in the treatment of DES.

Rationale for Anti-Inflammatory Treatment

The eye has a complex ocular surface system that functions to provide a smooth refractive surface to the cornea (the ocular surface) and to protect and maintain that surface.[1] The tear film is a mixture of lipids, carbohydrates, proteins, and mucin in an aqueous suspension, with the lipids found in the different layers of the film. The aqueous layer, which makes up most of the tear film by weight, provides both nutrients and waste disposal, not unlike the gastrointestinal tract (and also allows optimal absorption of topical ophthalmic drugs).

In a homeostatic balance, the eye is moist. This is essential for optical reasons as well as healthy physiology. Various factors, including age, hormonal status, genetics, sex, immune status, innervation status, nutrition, pathogens, and environmental stress, can alter the cellular and molecular structure or function of components of this system.[22] Disturbances caused by changes in these factors are thought to lead to dry eye by creating an imbalance between secretion and degradation of the components of the tear film, resulting in decreased tear secretion, delayed clearance, or changes in the tear film or corneal epithelial surface composition. This instability increases susceptibility to desiccation and epithelial damage, which leads to release of inflammatory mediators. A vicious circle is created in which inflammation amplifies and sustains further damage by chronic deregulation of the ocular surface system. Because this syndrome is not infectious, the use of antibiotics as a first line of therapy is not warranted. The use of anti-inflammatory agents to treat an essentially subcellular disturbance appears to be based on a more well-grounded rationale.

Cyclosporine

Cyclosporine A belongs to a group of immunosuppressive compounds that were first isolated in Norway from the fungus *Tolypocladium inflatum*. These drugs exert their effects essentially by lowering the activity of T-cells, thereby suppressing the associated immune response. Thus, both cyclosporine A and tacrolimus have long been used in transplant patients because of their anti-rejection effects. As the two drugs are largely similar in ability to prevent acute rejection, practitioners often choose between these drugs based on their respective interactions with other medications a transplant patient may be prescribed.[23]

Cyclosporines have also been used to treat a variety of conditions that have an underlying inflammatory basis, including psoriasis, rheumatoid arthritis, and ulcerative colitis, as well as

ocular inflammation.[2,24,25] The use of cyclosporine A to treat ocular conditions has been met with somewhat mixed results in the treatment of nonspecific, noninfectious inflammatory disease. However, more recently developed compounds may provide a greater level of treatment activity without the acute adverse reactions associated with the more historical use of cyclosporine A.[21]

Chemistry and Mechanism of Action of Cyclosporine

Cyclosporine has a molecular formula of $C_{62}H_{111}N_{11}O_{12}$ and molecular weight of 1202.6 g/mol. It is a non-ribosomal peptide that contains one D-amino acid. The structure of the molecule is very rigid because of the hydrogen bonding associated with the cyclic structure. Thus, cyclosporines have a low water solubility with variable cellular absorption.[26] Cyclosporines belong to the group of compounds known as calcineurin inhibitors, which also includes tacrolimus and voclosporin. The drug binds to cyclophilin (lymphocytes), and this complex inhibits calcineurin, ultimately preventing it from activating the transcription product of interleukin-2 (IL-2). Because IL-2 is necessary for T-cell replication, cyclosporine is a potent inhibitor of T-cell proliferation and thereby inhibits T-cell-mediated immune responses.

Cyclosporine may also prevent the mitochondrial permeability transition pore from opening, with one of the effects of inhibiting cytochrome c release, resulting in an adverse effect on apoptosis.

Preclinical Studies and Adverse Effects

Animal modeling has been used extensively to evaluate both efficacy and safety of cyclosporine. Thomas et al.[27] used a rabbit model to show that tear production was improved by topical cyclosporine treatment following induced autoimmune dacryoadenitis. Activated peripheral blood lymphocytes were injected into an animal's inferior lacrimal gland. Animals that demonstrated disease were treated with cyclosporine (formulated as Restasis) and sacrificed six months after the injection. Findings from this group indicated that cyclosporine was able to modify dry-eye pathology in New Zealand white rabbits. Schirmer's test results in treated rabbits were significantly different from controls. Tear break-up time results were also significantly improved.

Many authors have noted renal toxicity with systemic use of cyclosporine. O'Connell and colleagues[28] noted that cyclosporine used in concert with sirolimus had the effect of enhancing neural toxicity. Cyclosporine has also been shown to promote neoplasm and may cause neurotoxicity, hypertension, hyperlipidemia, and nephrotoxicity.[29,30] There may be an "inflamed" sensation in the finger tips. Use of cyclosporine may also increase the risk of viral and fungal infections because of "disruption" of the normal functioning of the immune system. Furthermore, Zheng et al.[31] have shown that secondary metabolites of cyclosporine A may be associated with toxicity in kidney transplant patients. These authors evaluated cyclosporine and its major metabolites using liquid chromatography–mass spectrometry from whole blood in volunteers, and found that intra-renal accumulation of cyclosporine A and its secondary metabolites was related to the CYP3A5 genotype of the liver and kidneys. Thus, genetic factors may contribute to differences among patients in cyclosporine-induced toxicity.

Wen and colleagues[32] used a single dose of cyclosporine A (1, 5, or 10 mg/kg body weight) as a treatment for acute kidney injury following an intraperitoneal dose of folic acid in male CD-1 mice. Cyclosporine doses of 1 and 5 mg/kg resulted in significant decreases in IL-6 activity, neutrophil activity, and kidney cell apoptosis ($P < 0.05$). However, the largest dose (10 mg/kg of body weight) was shown to cause a worsening of kidney function. The authors attributed the protective effects of the 1 and 5 mg/kg doses of cyclosporine A to inhibition of cell death, inflammatory reaction, interstitial cell infiltration, and fibrosis.

Cyclosporine A treatment has also been shown to block HTLV-1 expression in a rabbit model if given one week after exposure to the virus. In contrast, pretreatment with cyclosporine A before virus exposure enhanced early viral expression.[33]

Karavana et al.[34] showed that cyclosporine release from a bioadhesive gel could be effective at treating recurrent aphthous stomatitis. The studies were conducted in rabbits. The end point in the study was wound healing on the oral mucosa. When treated animals were compared to controls, there was a statistically significant difference in the rate of wound closure as measured from day 3 through day 12 ($P < 0.05$).

Liang and co-workers[35] compared topical cyclosporine (formulated as Restasis) with (1) a cyclosporine formulated as a cationic emulsion and (2) a cyclosporine formulated in oil. Phosphate buffered saline (PBS) and 0.02% benzalkonium chloride (BAK) were used as negative and positive controls, respectively. The three cyclosporine formulations were significantly better at closing wounds than either the negative (PBS) or the positive (BAK) control. The authors reported a slight decrease in inflammation when the cyclosporine formulated in a cationic emulsion was evaluated in a rabbit model. Khan et al.[36] compared a cyclosporine nanosphere formulation with Restasis in a rabbit model. They found less irritation with the nanosphere formulation compared with Restasis, and excellent penetration of the nanosphere formulation.

Ophthalmic Clinical Uses

Topical cyclosporine A (Restasis) is indicated to increase tear production in patients whose tear production is presumed to be suppressed because of ocular inflammation associated with DES (keratoconjunctivitis sicca). Topical application exerts a therapeutic effect without causing systemic side effects, because only small amounts can penetrate into the bloodstream after topical application.[21]

Cyclosporine can be delivered to the eye in aqueous drop form,[37] but the low solubility of cyclosporine in water

limits penetration. Olive oil or corn oil solutions allowed greater penetration. However, Williams[37] reported that cyclosporine delivered by olive oil solution caused a burning sensation on the conjunctiva. Penetration enhancers such as cyclodextrins have also been used to increase corneal penetration of cyclosporine.[21] Poor tolerance of such drugs presented a major drawback, although evidence for enhanced delivery was also reported. Emulsions provide effective topical ophthalmic drug delivery systems with a potential for sustained drug release.[21] The currently approved drug Restasis has 0.05% oil in water emulsion. Various other delivery systems are under investigation.

Clinical studies of 0.05% cyclosporine ophthalmic emulsion in patients with DES are summarized in Table 1. A study conducted in Korea of 392 patients with moderate to severe DES showed that most (72%) were satisfied with cyclosporine treatment to relieve dry-eye symptoms.[38] Ocular symptoms and Schirmer's test scores improved over the three-month study period. Some adverse reactions were noted in the study including ocular pain and ocular irritation.

Perez-Rico and coworkers[39] studied 0.05% cyclosporine A topically delivered to 29 patients with DES over a 12-month period. The aim of the study was to assess changes to the corneal epithelium. The data obtained showed no changes in endothelial density values. Thus, no clinical evidence of endothelial damage was found.

Cyclosporine has also been used as a treatment for dry eye, which may be secondary to other diseases. In a 2013 study of 30 patients with Stevens–Johnson syndrome,[40] all 17 patients who completed the study showed significant improvement in dry-eye symptoms, conjunctival injection and corneal staining, Schirmer I test, and fluorescein clearance test (FCT) ($P < 0.05$). However, eight patients (26.7%) withdrew because of side effects of cyclosporine A treatment, and five patients were lost to follow-up.

Dastjerdi and coworkers[41] used topical cyclosporine (0.05%) to treat dry-eye disease secondary to ocular graft-versus-host disease (GVHD) or Sjögren's syndrome in 22 patients who had shown an inadequate response to at least a four-month course of treatment with twice-daily use of topical cyclosporine 0.05%. Of the 22 patients, 13 had ocular GVHD and 9 had primary or secondary Sjögren's syndrome. Dosing was increased to three to four times daily (termed by the authors as high-frequency treatment). Overall dry-eye symptoms were improved in 15 patients (68.2%), and the physicians' global assessment of dry-eye status reflected improvement in 16 (72.7%) patients. Mean corneal fluorescein staining improved significantly from baseline, both in patients with GVHD and in those with Sjögren's syndrome. In three patients, increased daily use of cyclosporine led to new onset of symptoms consisting of burning or irritation. Deveci and Kobak[42] investigated the efficacy of 0.05% topical cyclosporine A in 26 patients with keratoconjunctivitis sicca because of primary or secondary Sjögren's syndrome compared to 22 control patients treated with saline solution. All subjective symptoms and objective signs (Schirmer's test, tear break-up time, and redness) were significantly improved after one-week and one-month follow-up examinations in patients receiving cyclosporine A compared with controls ($P = 0.0001$).

Cyclosporine treatment was studied in 32 patients with DES following cataract surgery.[43] The patients were monitored at baseline, one week, two weeks, and one, two, and three months following surgery. Cyclosporine or normal saline (0.9%) was administered to each eye according to random assignment. Both groups showed significant improvement in the Schirmer's test at three months, but at three months improvement was significantly greater in the eyes treated with cyclosporine than in those treated with normal saline ($P = 0.02$). At two and three months, eyes treated with cyclosporine showed significantly greater improvement in tear film break-up time and symptoms compared with saline-treated eyes. No toxic reactions were noted in this study, even though the patients had undergone major surgery before the cyclosporine treatments.

The PERSIST (physician's evaluation of Restasis satisfaction in second trial) study was a multicenter retrospective chart review of a second course of cyclosporine treatment (Restasis) in patients who had previously discontinued topical cyclosporine after less than 12 weeks.[44] A total of 35 patients at three different treatment centers were included. The study was limited because of its nature as a retrospective study. However, consistent with previous studies, the results showed that 80% of patients were judged by the physician to have received clinical benefit from the second course of treatment.

Conclusion

A large amount of information is available concerning cyclosporine and its use both as an ophthalmic treatment and as an immunomodulator, and the mechanism of action is well understood. Cyclosporine 0.05% (formulated as Restasis) is the only FDA-approved prescription drug available for patients with DES. It has also been used as a treatment for other conditions that may be secondary to DES. Positive effects are consistently seen with the use of this drug for treatment of DES. In contrast to systemic use of cyclosporine, topical application has few side effects, because only small amounts can penetrate into the bloodstream after topical application.

Considering the potential for increased quality of life with successful treatment of the symptoms of DES, then cyclosporine should have a great impact on dry-eye sufferers worldwide. In prescribing cyclosporine, doctors should work with their patients to develop a strategy that ensures maximum patient compliance to the treatment plan. Strategies for glaucoma treatment, in which doctors may tailor a regimen to patient lifestyle, might serve as useful models for such plans.

Table 1. Clinical use of 0.05% cyclosporine ophthalmic emulsion for DES.

AUTHOR (YEAR)	NUMBER OF PATIENTS		INDICATION	FREQUENCY& DURATION	OUTCOME	ADVERSE EFFECTS
	STARTED	COMPLETED				
Byun et al (2011)[38]	392	362	DES	2x/d 3 mo	Significant improvement in symptoms and objective tests (Schirmer; conjunctival staining scores); 72% (270/375) satisfied	Ocular pain in 11.0% (43/392); ocular irritation in 5.9% (23/392)
Perez-Rico et al (2013)[39]	29	29	DES	2x/d 12 mo	No clinical evidence of endothelial damage; ie, no substantial change in corneal endothelial cell density, coefficient of variation of the cell size, or percentage of hexagonal cells	No systemic adverse effects
Prabhasawat et al (2013)[40]	30	17	Stevens–Johnson	2x/d 6 mo	Significant improvement in symptoms, conjunctival injection, corneal staining, Schirmer I test, and FCT ($P < 0.05$)	Pain, redness, and eyelid swelling resulted in withdrawal in 26.7% (8/30)
Dastjerdi et al (2009)[41]	–	22[a]	Ocular GVHD or Sjögren syndrome + inadequate response to 2x/d for ≥4 mo	3–4x/d/ ≥2 mo (range, 4–14 mo)	Subjective symptoms improved in 68.2% (15/22); global physician assessment improved in 72.7% (16/22); significant improvement in corneal fluorescein staining score ($P < 0.001$)	New-onset symptoms of burning or irritation in 13.6% (3/22); no other adverse effects
Deveci and Kobak (2014)[42]	26	26	Primary or secondary Sjögren syndrome	1 mo	Significant improvement in subjective symptoms and in Schirmer's test, tear break-up time, and redness compared to baseline ($P = 0.0001$) and to controls ($P = 0.0001$)	None reported
Chung et al (2013)[43]	32	32	After cataract surgery	2x/d 3 mo	Significant improvement in Schirmer's test (compared to baseline, $P < 0.01$; compared to control eyes, $P = 0.02$), in tear break-up time ($P < 0.01$), and in OSDI scores ($P < 0.01$)	None reported
Mah et al (2012)[44]	–	35[a]	Second trial of cyclosporine after previous treatment failure	Median, 10 mo; range, 1 wk–45 mo	Physicians reported clinical benefit in 80% (28/35); complete clearing of corneal staining in 33.3% (6/18)	Burning and stinging resulted in withdrawal in 5.7% (2/35)

Note: [a]Retrospective study.
Abbreviations: DES, dry-eye syndrome; FCT, fluorescein clearance test; GVHD, graft-versus-host disease; OSDI, Ocular Surface Disease Index.

Author Contributions

Conceived and designed the experiments: CS. Analyzed the data: CS. Wrote the first draft of the manuscript: CS. Contributed to the writing of the manuscript: CS. Agree with manuscript results and conclusions: CS. Jointly developed the structure and arguments for the paper: CS. Made critical revisions and approved final version: CS. The author reviewed and approved of the final manuscript.

REFERENCES

1. The definition and classification of dry eye disease: report of the Definition and Classification Subcommittee of the International Dry Eye WorkShop (2007). *Ocul Surf*. 2007;5(2):75–92.
2. Javadi MA, Feizi S. Dry eye syndrome. *J Ophthalmic Vis Res*. 2011;6(3):192–8.
3. Methodologies to diagnose and monitor dry eye disease: report of the Diagnostic Methodology Subcommittee of the International Dry Eye WorkShop (2007). *Ocul Surf*. 2007;5(2):108–52.
4. Schaumberg DA, Dana R, Buring JE, Sullivan DA. Prevalence of dry eye disease among US men: estimates from the Physicians' Health Studies. *Arch Ophthalmol*. 2009;127(6):763–8.
5. Schaumberg DA, Sullivan DA, Buring JE, Dana MR. Prevalence of dry eye syndrome among US women. *Am J Ophthalmol*. 2003;136(2):318–26.
6. Epidemiology DEWS Subcommittee, Smith JA, Albeitz J, et al. The epidemiology of dry eye disease: report of the Epidemiology Subcommittee of the International Dry Eye WorkShop (2007). *Ocul Surf* 2007;5(2):93–107.
7. Gayton JL. Etiology, prevalence, and treatment of dry eye disease. *Clin Ophthalmol*. 2009;3:405–12.
8. Manaviat MR, Rashidi M, Afkhami-Ardekani M, Shoja MR. Prevalence of dry eye syndrome and diabetic retinopathy in type 2 diabetic patients. *BMC Ophthalmol*. 2008;8:10.
9. Bhavsar AS, Bhavsar SG, Jain SM. A review on recent advances in dry eye: Pathogenesis and management. *Oman J Ophthalmol*. 2011;4(2):50–6.
10. Tomlinson A, Madden LC, Simmons PA. Effectiveness of dry eye therapy under conditions of environmental stress. *Curr Eye Res*. 2013;38(2):229–36.
11. Gupta N, Prasad I, Himashree G, D'Souza P. Prevalence of dry eye at high altitude: a case controlled comparative study. *High Alt Med Biol*. 2008;9(4):327–34.
12. Pult H, Purslow C, Murphy PJ. The relationship between clinical signs and dry eye symptoms. *Eye (Lond)*. 2011;25(4):502–10.
13. Fox RI, Howell FV, Bone RC, Michelson P. Primary Sjögren syndrome: clinical and immunopathologic features. *Semin Arthritis Rheum*. 1984;14(2):77–105.
14. Le Q, Zhou X, Ge L, Wu L, Hong J, Xu J. Impact of dry eye syndrome on vision-related quality of life in a non-clinic-based general population. *BMC Ophthalmol*. 2012;12:22.
15. Miljanovic B, Dana R, Sullivan DA, Schaumberg DA. Impact of dry eye syndrome on vision-related quality of life. *Am J Ophthalmol*. 2007;143(3):409–15.
16. Management and therapy of dry eye disease: report of the Management and Therapy Subcommittee of the International Dry Eye WorkShop (2007). *Ocul Surf*. 2007;5(2):163–78.
17. Rand AL, Asbell PA. Nutritional supplements for dry eye syndrome. *Curr Opin Ophthalmol*. 2011;22(4):279–82.
18. Kymionis GD, Bouzoukis DI, Diakonis VF, Siganos C. Treatment of chronic dry eye: focus on cyclosporine. *Clin Ophthalmol*. 2008;2(4):829–36.
19. Qiao J, Yan X. Emerging treatment options for meibomian gland dysfunction. *Clin Ophthalmol*. 2013;7:1797–803.
20. Waduthantri S, Yong SS, Tan CH, et al. Cost of dry eye treatment in an Asian clinic setting. *PLoS One*. 2012;7(6):e37711.
21. Yavuz B, Bozdag Pehlivan S, Unlu N. An overview on dry eye treatment: approaches for cyclosporin a delivery. *Scientific World J*. 2012;2012:194848.
22. Research in dry eye: report of the Research Subcommittee of the International Dry Eye WorkShop (2007). *Ocul Surf*. 2007;5(2):179–93.
23. Zarrinpar A, Busuttil RW. Immunomodulating options for liver transplant patients. *Expert Rev Clin Immunol*. 2012;8(6):565–78. ; quiz 578.
24. Lichtiger S, Present DH, Kornbluth A, et al. Cyclosporine in severe ulcerative colitis refractory to steroid therapy. *N Engl J Med*. 1994;330(26):1841–5.
25. Kaçmaz RO, Kempen JH, Newcomb C, et al. Cyclosporine for ocular inflammatory diseases. *Ophthalmology*. 2010;117(3):576–84.
26. el Tayar N, Mark AE, Vallat P, Brunne RM, Testa B, van Gunsteren WF. Solvent-dependent conformation and hydrogen-bonding capacity of cyclosporin A: evidence from partition coefficients and molecular dynamics simulations. *J Med Chem*. 1993;36(24):3757–64.
27. Thomas PB, Samant DM, Zhu Z, et al. Long-term topical cyclosporine treatment improves tear production and reduces keratoconjunctivitis in rabbits with induced autoimmune dacryoadenitis. *J Ocul Pharmacol Ther*. 2009;25(3):285–92.
28. O'Connell S, Slattery C, Ryan MP, McMorrow T. Sirolimus enhances cyclosporine a-induced cytotoxicity in human renal glomerular mesangial cells. *J Transplant*. 2012;2012:980910.
29. Henry ML, Elkhammas EA, Davies EA, Ferguson RM. A clinical trial of cyclosporine G in cadaveric renal transplantation. *Pediatr Nephrol*. 1995;9(suppl):S49–51.
30. Ojo AO, Held PJ, Port FK, et al. Chronic renal failure after transplantation of a nonrenal organ. *N Engl J Med*. 2003;349(10):931–40.
31. Zheng S, Tasnif Y, Hebert MF, et al. CYP3A5 gene variation influences cyclosporine A metabolite formation and renal cyclosporine disposition. *Transplantation*. 2013;95(6):821–7.
32. Wen X, Peng Z, Li Y, et al. One dose of cyclosporine A is protective at initiation of folic acid-induced acute kidney injury in mice. *Nephrol Dial Transplant*. 2012;27(8):3100–9.
33. Haynes RA2nd, Ware E, Premanandan C, et al. Cyclosporine-induced immune suppression alters establishment of HTLV-1 infection in a rabbit model. *Blood*. 2010;115(4):815–23.
34. Karavana SY, Gökçe EH, Rençber S, et al. A new approach to the treatment of recurrent aphthous stomatitis with bioadhesive gels containing cyclosporine A solid lipid nanoparticles: in vivo/in vitro examinations. *Int J Nanomedicine*. 2012;7:5693–704.
35. Liang H, Baudouin C, Daull P, Garrigue JS, Brignole-Baudouin F. Ocular safety of cationic emulsion of cyclosporine in an in vitro corneal wound-healing model and an acute in vivo rabbit model. *Mol Vis*. 2012;18:2195–204.
36. Khan W, Aldouby YH, Avramoff A, Domb AJ. Cyclosporin nanosphere formulation for ophthalmic administration. *Int J Pharm*. 2012;437(1–2):275–6.
37. Williams DL. A comparative approach to topical cyclosporine therapy. *Eye (Lond)*. 1997;11(pt 4):453–64.
38. Byun YS, Rho CR, Cho K, Choi JA, Na KS, Joo CK. Cyclosporine 0.05% ophthalmic emulsion for dry eye in Korea: a prospective, multicenter, open-label, surveillance study. *Korean J Ophthalmol*. 2011;25(6):369–74.
39. Perez-Rico C, Germain F, Castro-Rebollo M, Moreno-Salgueiro A, Teus MA. Effect of topical 0.05% cyclosporine A on corneal endothelium in patients with dry eye disease. *Int J Ophthalmol*. 2013;6(4):471–4.
40. Prabhasawat P, Tesavibul N, Karnchanachetanee C, Kasemson S. Efficacy of cyclosporine 0.05% eye drops in Stevens Johnson syndrome with chronic dry eye. *J Ocul Pharmacol Ther*. 2013;29(3):372–7.
41. Dastjerdi MH, Hamrah P, Dana R. High-frequency topical cyclosporine 0.05% in the treatment of severe dry eye refractory to twice-daily regimen. *Cornea*. 2009;28(10):1091–6.
42. Deveci H, Kobak S. The efficacy of topical 0.05% cyclosporine A in patients with dry eye disease associated with Sjögren's syndrome. *Int Ophthalmol*. January 9; 2014. doi: 10.1007/s10792-014-9901-4.
43. Chung YW, Oh TH, Chung SK. The effect of topical cyclosporine 0.05% on dry eye after cataract surgery. *Korean J Ophthalmol*. 2013;27(3):167–71.
44. Mah F, Milner M, Yiu S, Donnenfeld E, Conway TM, Hollander DA. PERSIST: physician's evaluation of Restasis® satisfaction in second trial of topical cyclosporine ophthalmic emulsion 0.05% for dry eye: a retrospective review. *Clin Ophthalmol*. 2012;6:1971–6.