

New Agents for Treating Dry Eye Syndrome

Simon E. Skalicky · Con Petsoglou · Avinash Gurbaxani ·
Clare L. Fraser · Peter McCluskey

Published online: 6 November 2012
© Springer Science+Business Media New York 2012

Abstract Dry eye syndrome (DES) is characterized by an inadequate volume and/or quality of tears resulting in chronic ocular surface irritation and inflammation. Affecting up to 30 % of adults, DES has a considerable impact on visual function and quality of life. DES may complicate allergic ocular disease and allergy medication may exacerbate DES. The pathophysiology of DES involves osmotic, mechanical and inflammatory insults to the tear film, epithelium and subepithelial nerve plexus. Various immune-related molecular targets have been the focus of research aimed at developing new therapeutic agents for treating DES. This article provides an overview of established, new and future agents for treating DES.

Keywords Dry eye syndrome · Anti-inflammatory agents · Topical therapies · Treatment · Ocular lubricants · Artificial tears · Corticosteroids · NSAIDs · Cyclosporine A · Secretagogues · Essential fatty acids · New agents

Introduction

The tear film is a trilaminar structure with a superficial lipid layer principally from Meibomian gland secretions, an aqueous midphase from lacrimal and accessory lacrimal gland secretions and a mucin basal layer [1]. Dry eye syndrome (DES) is characterized by an inadequate volume and/or quality of tears resulting in chronic dryness of the cornea

and conjunctiva associated with abnormalities of all layers of the tear film [2, 3•].

According to the Dry Eye Workshop Report, the prevalence of DES ranges from 5 to 30 % in people aged 50 years and older, of whom approximately two-thirds are women [4, 5]. In recent years, there has been an increase of DES prevalence due to the general ageing of the population as well as increased exposure to exacerbating factors such as low humidity environments, contact lens wear, prolonged computer use and certain drugs such as antidepressants, antihistamines and antihypertensives [6–11].

Common symptoms of DES include dryness, irritation, foreign body sensation, light sensitivity and itching. Ocular surface abnormalities, often best detected using fluorescein to stain the ocular surface, may include superficial punctate erosions, epithelial defects, corneal filaments and in severe cases, corneal ulcers, thinning or perforation [12, 13•]. DES has a considerable impact on visual function, daily activities, social and physical functioning, workplace productivity and quality of life [14, 15].

DES results from either decreased aqueous tear production or excessive tear evaporation; the two frequently co-exist [16]. The former, also known as keratoconjunctivitis sicca, is characterized by lacrimal gland hyposecretion and may be due to Sjogren's syndrome or other inflammatory causes, and is treated by surface lubricants, punctal occlusion and anti-inflammatory agents. Excessive tear evaporation is primarily due to Meibomian gland dysfunction resulting in rapid break-up of the tear film despite normal aqueous production, and is principally treated by improving the flow and quality of Meibomian gland secretions. This paper focuses on DES due to aqueous deficiency.

The pathophysiology of DES is complex and multifactorial involving osmotic, mechanical and inflammatory insults to the tear film, epithelium and sub-epithelial nerve plexus. Elevated tear osmolarity activates desiccating stress-associated pathways in ocular surface epithelial cells, namely

S. E. Skalicky · C. Petsoglou · A. Gurbaxani · C. L. Fraser ·
P. McCluskey
Save Sight Institute, University of Sydney,
Sydney, NSW, Australia

S. E. Skalicky (✉) · C. Petsoglou · A. Gurbaxani · C. L. Fraser ·
P. McCluskey
Sydney Eye Hospital,
Macquarie St.,
Sydney, New South Wales 2000, Australia
e-mail: seskalicky@gmail.com

mitogen-activated protein kinases c-Jun N-terminal kinase, extracellular signal-related kinase and p38 [17–19]. Stimulation of transcription factors (nuclear factor κ B and activator protein 1), and then production of pro-inflammatory cytokines (IL-1, IL-6 and TNF- α), chemokines, and matrix metalloproteases leads to activation of antigen presenting cells [19, 20•]. A predominantly T-cell-mediated immune response is initiated particularly involving CD4+ helper T-cell (T_H) subsets 1 and 17 [21]. Epithelial dysfunction, squamous metaplasia, decreased epithelial barrier function and reduced goblet cell density lead to further surface instability [22–25]. This results in sub-epithelial corneal nerve plexus exposure to mechanical and inflammatory insults, decreased density and altered morphologic structure of the corneal sub-basal nerves [26, 27].

Traditional treatments of DES due to aqueous deficiency include lubricating eye drops, ointments and punctual occlusion. These are commonly used initially to provide symptomatic relief. More recently, there has been significant research using topical therapeutics that decrease ocular surface inflammation and promote a healthy tear complex [3•]. There is a range of potential molecular targets implicated in DES including cytokine, chemokine and matrix metalloproteases in the tear film and epithelial cells, ocular surface expression of major histocompatibility complex antigens, cell adhesion molecules and pro-secretory adenosine receptor agonists [28, 29•, 30–34]. This paper aims to outline some of the newer treatments available, their benefits and risks, as well as other agents that may be used in the future treatment of DES.

Agents Used to Treat Dry Eye Syndrome

Several anti-inflammatory agents have an established role in the treatment of DES and more are currently undergoing evaluation in clinical trials.

Ocular Lubricants

Lubricating eye drops (artificial tears) are commonly used to treat DES and can control symptoms in most cases. Various formulations are available; these contain similar ingredients (lubricants, water, electrolytes and buffers) with differing formulations and all act to moisturise the ocular surface. Hydration and viscosity are determined by polysaccharide additives that polymerize; generally a more viscous solution has a longer duration of action but causes optical blur (Table 1) [35, 36]. Most available solutions contain preservatives (Table 1); in severe cases, treatment with non-preserved eye drops (dispensed in small plastic minims) is mandatory to avoid preservative toxicity when using the eye drops at frequent intervals. Some products are believed to improve ocular surface wetting by counteracting hypertonicity [37], dilute and physically remove surface inflammatory agents [38], prevent

Table 1 Commonly used artificial tears and lubricants, and commonly used preservatives

Commonly used artificial tears and lubricants	
Viscosity	Active ingredient
Low	Hydroxypropyl methylcellulose
	Glycerin
	Polyvinyl alcohol
	Polyethylene glycol
	Sodium hyaluronate
Medium	Carboxymethylcellulose sodium 1 %
	Carbopol
High	Paraffin
	Mineral oil
	White petrolatum
Commonly used preservatives	
Preservative	Purite® (Allergan, Irvine, CA, USA)
	Polyquad® (Alcon, Fort Worth, TX, USA)
	Sodium perborate
	Sodium chlorate
	Benzalkonium chloride

tear evaporation by adding a lipid emulsion [39], or supplement the mucin layer [40].

Corticosteroids

Corticosteroids exert their immunosuppressive effect primarily by binding to and activating the cytosolic glucocorticoid receptor, inhibiting pro-inflammatory and promoting anti-inflammatory gene expression in leucocytes, and additionally stimulating lymphocyte apoptosis [41]. Corticosteroids have a proven efficacy in the treatment of DES with supportive laboratory and clinical evidence, improving both subjective and objective features of the condition (Table 2) [42–45]. Due to complications such as ocular hypertension, cataract and opportunistic infection, they are not ideal for long-term treatment; however, they may have a role as brief courses for exacerbations of DES. Certain agents have poorer ocular penetration and as such have a reduced effect on cataractogenesis and ocular hypertension [46].

Non-Steroidal Anti-Inflammatory Drugs

Topical non-steroidal anti-inflammatory drugs reduce ocular surface inflammation in a variety of ocular inflammatory conditions, but have not been consistently shown to be effective in treating DES [44, 47•]. Furthermore, their use is limited by ocular complications such as corneal melt and reduced corneal sensitivity. For these reasons, they are not routinely used in DES [48].

Table 2 Commonly used topical corticosteroids, and non-steroidal anti-inflammatory agents

Topical corticosteroids	
Mild	Fluoromethalone 0.1 % Hydrocortisone acetate 0.5 or 1 %
Moderate	Fluoromethalone acetate 0.1 % Loteprednol etabonate 0.2 or 0.5 % Prednisolone phosphate 1 % Rimexolone 1 %
Strong	Dexamethasone 0.1 % Prednisolone acetate 1 %
Topical non-steroidal anti-inflammatory drugs	
Agent	Diclofenac sodium 0.1 % Flurbiprofen sodium 0.03 % Ketorolac tromethamine 0.5 %

Tetracycline Derivatives

In addition to their antibacterial properties, tetracyclines have a therapeutic effect in DES principally through improvement of Meibomian gland dysfunction by matrix metalloprotease inhibition [49]. They also exert an anti-inflammatory influence on the ocular surface that may be modestly beneficial in aqueous deficiency [20••]. Minocycline inhibits expression of pro-inflammatory cell-surface antigens such as MHC Class II [50]. Doxycycline inhibits the osmotic stress-related cell-signaling pathways c-Jun N terminal kinase and extracellular signal-related kinase mitogen-activated protein kinase in epithelial cells [51]. Consequently, the pro-inflammatory cytokines produced by these cell-signaling pathways are reduced. Oral administration is the most common route; however, topical formulations are available, and there is experimental evidence that liposomal-bound topical doxycycline may be useful in increasing bioavailability of topical preparations [52]. Topical azithromycin 1 % has a role in treating dry eye related to meibomian gland disease and contact lens wear [53, 54]

Secretagogues

By lubricating the corneal and conjunctival epithelial surface, mucin is a critical component of the basal layer of the tear film. Secretagogues improve mucin secretion and thereby reduce tear film instability and associated surface inflammation.

1. Diquafosol tetrasodium

Diquafosol tetrasodium, a mucin secretagogue, is a topical P2Y₂ receptor agonist that improves symptoms and ocular surface features of DES [55]. Activation of the Gq protein-coupled P2Y₂ receptor, a member of the adenosine triphosphate receptor family, results in non-

glandular secretion of mucin and water via chloride channel activation [56•]. A 3 % topical diquafosol formulation (Diquas® (Inspire Pharmaceuticals, Raleigh, NC, USA) has gained approval for DES in Japan in 2010.

2. Bromhexine

Bromhexine, an oral mucolytic agent, reduces the viscosity of mucous secretions of the respiratory tract. It has also been shown to improve symptoms and objective signs of ocular surface disease in Sjogren's Syndrome [57].

3. IB-MECA (CF101)

An oral purine receptor agonist, IB-MECA (CF101) has been investigated as a potential treatment for DES. By binding to the adenosine receptor, this agent initiates downstream signal transduction to down-regulate protein kinases and TNF- α production [58]. In a phase II multicenter, randomized, double-masked, placebo-controlled trial involving 68 subjects, CF101 resulted in improved corneal staining, breakup time and meniscus height after 12 weeks [59].

Autologous Serum

Autologous serum (AS), compounded from patients' own blood, is another key therapy in the treatment of DES as well as other ocular surface conditions, such as persistent epithelial defects, superior limbic keratoconjunctivitis and neurotrophic keratopathy [60]. A ready source of the crucial tear film constituents of epidermal growth factor, neurotrophic growth factor, fibronectin, vitamin A, and lysozyme, AS provides key molecular and trophic factors to optimize the ocular surface [61]. It is used relatively commonly and can be prepared through an office centrifuge or at a dedicated blood-bank service. Patients donate 1–2 units of blood, from which the serum is extracted and stored in small plastic minims with or without dilution, that can be used immediately or frozen; this process is repeated 6–12 monthly; methods have been developed to optimize stability of growth factors in preparation and storage [62]. It is indicated in recalcitrant cases of ocular surface disease and DES. Several randomized clinical studies have reported a superior effect over non-preserved artificial tears in treating DES [63, 64].

Cyclosporine A

Since FDA approval in 2003 of a 0.05 % ophthalmic emulsion (Restasis; Allergan, Irvine, CA, USA), topical cyclosporine A (CsA) has been commonly used in treating patients with DES [65]. CsA acts as an immunosuppressive agent by binding with intra-cytoplasmic chaperone proteins cyclophilins A and D. The cyclosporine-cyclophilin A complex inhibits the calcineurin phosphatase pathway responsible for transcription of T-cell stimulating cytokines such as IL-2 [66]. The cyclosporine–cyclophilin D complex inhibits mitochondrial

permeability preventing the release of pro-apoptotic enzymes such as cytochrome c important in caspase-mediated apoptotic pathways [67]. Administration of topical CsA for 3–6 months has been shown to reduce levels of surface expression of the immune activator marker HLA-DR and apoptosis markers CD40, CD40 ligand and Fas [68, 69]. These levels are increased in DES patients with and without Sjogren's syndrome. CsA reduces squamous metaplasia, promotes goblet cell density and increases tear production possibly through promotion of parasympathetic-associated neurotransmitter release [70, 71]. In clinical evaluation, a randomized, double-masked, placebo-controlled, dose-ranging clinical trial demonstrated CsA to provide significant improvement in symptoms and signs with the 0.05 % dosage most effective [72, 73].

CsA is a hydrophobic peptide with four intramolecular hydrogen bonds that impart high rigidity to its cyclic structure [74]. For this reason, it has very low aqueous solubility, causing highly variable and incomplete absorption from conventional topical formulations [3•, 75]. Several methods of improving bioavailability have been attempted. Benzalkonium chloride as a preservative enhances corneal penetration but increases surface irritation [76]. Cyclodextrins, micelles, microspheres, liposomes and nanoparticles have been used—each system working by surrounding the hydrophobic CsA to enhance corneal penetration; however, these do not provide significant CsA levels at the ocular mucosa for an extended period of time [77–80].

Calcineurin Phosphate Inhibitors

Tacrolimus (Protopic; Astellas, Tokyo, Japan) and pimecrolimus (Elidel; Novartis, Basel, Switzerland) are commercially available topical calcineurin phosphate inhibitors. By forming a complex with macrophilin-12, an intracellular protein, these agents inhibit calcineurin-related transcription of T-cell activating cytokines [81]. Topical tacrolimus was initially used in the treatment of atopic dermatitis [82]; there is some clinical evidence of good efficacy in DES [83]. LX-214 (voclosporin) was well tolerated in a phase I study [84]. None has yet received FDA approval for DES. Systemically administered calcineurin phosphate inhibitors have been implicated in carcinogenesis, particularly post-transplant lymphoproliferative disorder and non-melanoma skin cancers [85]. It is difficult to know if this risk translates to topical administration; however, systemic absorption occurs to a certain extent with all topical ophthalmic preparations and can be minimized by punctual occlusion. It has been suggested that topical skin preparations can be used on the eyelids to improve meibomian gland function.

Essential Fatty Acids

Orally-administered essential polyunsaturated fatty acids (FAs) omega-3 (α -linolenic acid) and omega-6 (linolenic

acid) have a demonstrated positive effect in various inflammatory conditions including rheumatoid arthritis, ulcerative colitis and Sjogren's syndrome [86]. Essential fatty acids are eicosanoid precursors (prostaglandins, prostacyclins, thromboxanes and leukotrienes) involved in immunomodulation; omega-3 is predominantly anti-inflammatory while omega-6 is pro-inflammatory [87•]. Clinical and experimental data support the anti-inflammatory effect of omega-3 when applied topically [88, 89]. At the cellular level, Omega-3 FAs reduce pro-inflammatory eicosanoids prostaglandin E2, leukotriene B4 and cytokines IL-1 and TNF [89, 90]. Topically administered Resolvin E1, an omega-3 FA derivative, promoted tear production, corneal epithelial integrity, and decreased COX-2 expression in a murine model of DES [91]. It has completed Phase II investigation in a clinical trial [92].

Mucoprotective Agents

Rebamipide is a mucoprotective agent used in the treatment of gastric ulcers and stimulates mucus secretion by inducing prostaglandin E2 production [93]. There is experimental evidence that it improves ocular surface mucin secretion, and it is currently under Phase III investigation for DES [94•]. Ecabet sodium is another medication targeting mucin secretion via the prostaglandin E2 pathway and used for the treatment of gastrointestinal ulcers for which phase III trials are currently underway for DES [94•].

Future Directions

With an exponential increase of information regarding the immunopathogenesis of DES, the success of new systemic anti-inflammatory agents including biological agents in treating inflammatory disease and the continued discovery of potential inflammatory molecular targets there is hope of new therapeutic agents to treat DES in the near future. A thorough review of the current therapeutic targets under investigation is beyond the scope of this article. To name a few, tasocitinib (CP-690,550; Pfizer, New York, NY, USA), a Janus kinase 3 (JAK) inhibitor, has had some promising results in rheumatoid arthritis and increasingly there is supportive evidence on other inflammatory diseases [95]. JAKs are receptor-associated kinases found only in immune cells that are involved in signal transduction for pro-inflammatory cytokines [96]. Aquaporins contribute to fluid secretion by the lacrimal gland, and their expression in Sjogren's disease is altered [97•]; aquaporin as a therapeutic target in DES is yet to be elucidated. Other molecular targets that have been implicated in DES immunopathogenesis, including integrin $\alpha 4 \beta 1$ and the T_H17 subset of lymphocytes, may be promising [98, 99].

Conclusions

DES is a common, chronic ocular surface disorder associated with reduced visual function and often poor quality of life. With increased understanding of the predominantly inflammatory pathogenesis, new molecular targets are being identified and may lead to new therapeutic developments. Hopefully, new immunomodulatory and tear film-enhancing agents will lead to overall improved treatment of this condition.

Disclosure Dr. McCluskey has received payment for development of educational presentations (including service on speakers' bureaus) from Novartis.

Drs. Skaliky, Petsoglou, Gurbaxani, and Fraser reported no potential conflicts of interest relevant to this article.

References

- Papers of particular interest, published recently, have been highlighted as:
 - Of importance
 - Of major importance
1. Basic and Clinical Science Course. Section 8. External disease and cornea, American Academy of Ophthalmology, 2008.
2. 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.
3. • Yavuz B, Bozdağ Pehlivan S, Unlü N. An overview on dry eye treatment: approaches for cyclosporin A delivery. *ScientificWorldJournal.* 2012;2012:194848. *A concise overview of the pharmacokinetics of topical cyclosporine and new drug delivery systems.*
4. 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.
5. Schaumborg DA, Sullivan DA, Buring JE, Dana MR. Prevalence of dry eye syndrome among US women. *Am J Ophthalmol.* 2003;136(2):318–26.
6. Moss SE, Klein R, Klein BE. Prevalence of and risk factors for dry eye syndrome. *Arch Ophthalmol.* 2000;118(9):1264–68.
7. Brewitt H, Sistani F. Dry eye disease: the scale of the problem. *Surv Ophthalmol.* 2001;45 Suppl 2:S199–202.
8. Ding J, Sullivan DA. Aging and dry eye disease. *Exp Gerontol.* 2012;47(7):483–90.
9. Guillon M, Maissa C. Contact lens wear affects tear film evaporation. *Eye Contact Lens.* 2008;34(6):326–30.
10. Yee RW, Sperling HG, Kattak A, Paukert MT, Dawson K, Garcia M, Hilsenbeck S. Isolation of the ocular surface to treat dysfunctional tear syndrome associated with computer use. *Ocul Surf.* 2007;5(4):308–15.
11. Pflugfelder SC. Prevalence, burden, and pharmacoeconomics of dry eye disease. *Am J Manag Care.* 2008;14(3 Suppl):S102–6.
12. Lemp MA. Report of the National Eye Institute/Industry workshop on Clinical Trials in Dry Eyes. *The CLAO Journal.* 1995;21(4):221–32.
13. • Pult H, Purslow C, Murphy PJ. The relationship between clinical signs and dry eye symptoms. *Eye (Lond).* 2011;25(4):502–10. *A 47-patient cohort study comparing clinical symptoms of dry eye with new and traditional clinical tests. When used in combination, these tests correlate with symptomatic severity of dry eye syndrome.*
14. Li M, Gong L, Sun X, Chapin WJ. Anxiety and depression in patients with dry eye syndrome. *Curr Eye Res.* 2011;36(1):1–7.
15. Miljanović B, Dana R, Sullivan DA, Schaumborg DA. Impact of dry eye syndrome on vision-related quality of life. *Am J Ophthalmol.* 2007;143(3):409–15.
16. McGinnigle S, Naroo SA, Eperjesi F. Evaluation of dry eye. *Surv Ophthalmol.* 2012;57(4):293–316.
17. Luo L, Li DQ, Corrales RM, Pflugfelder SC. Hyperosmolar saline is a proinflammatory stress on the mouse ocular surface. *Eye Contact Lens.* 2005;31(5):186–93.
18. De Paiva CS, Pangelinan SB, Chang E, et al. Essential role for c-Jun N-terminal kinase 2 in corneal epithelial response to desiccating stress. *Arch Ophthalmol.* 2009;127(12):1625–31.
19. Li DQ, Luo L, Chen Z, Kim HS, Song XJ, Pflugfelder SC. JNK and ERK MAP kinases mediate induction of IL-1 β , TNF- α and IL-8 following hyperosmolar stress in human limbal epithelial cells. *Exp Eye Res.* 2006;82(4):588–96.
20. •• Stevenson W, Chauhan SK, Dana R. Dry eye disease: an immune-mediated ocular surface disorder. *Arch Ophthalmol.* 2012;130(1):90–100. *An excellent overview of the immunopathogenesis of dry eye and the associated molecular targets for anti-inflammatory treatment of dry eye syndrome.*
21. El Annan J, Chauhan SK, Ecoiffier T, Zhang Q, Saban DR, Dana R. Characterization of effector T cells in dry eye disease. *Invest Ophthalmol Vis Sci.* 2009;50(8):3802–3807.
22. De Paiva CS, Chotikavanich S, Pangelinan SB, et al. IL-17 disrupts corneal barrier following desiccating stress. *Mucosal Immunol.* 2009;2(3):243–53.
23. Chen YT, Nikulina K, Lazarev S, et al. Interleukin-1 as a phenotypic immunomodulator in keratinizing squamous metaplasia of the ocular surface in Sjogren's syndrome. *Am J Pathol.* 2010;177(3):1333–43.
24. De Paiva CS, Villarreal AL, Corrales RM, et al. Dry eye-induced conjunctival epithelial squamous metaplasia is modulated by interferon- γ . *Invest Ophthalmol Vis Sci.* 2007;48(6):2553–60.
25. Yeh S, Song XJ, Farley W, Li DQ, Stern ME, Pflugfelder SC. Apoptosis of ocular surface cells in experimentally induced dry eye. *Invest Ophthalmol Vis Sci.* 2003;44(1):124–9.
26. Benitez-Del-Castillo JM, Acosta MC, Wassfi MA, et al. Relation between corneal innervation with confocal microscopy and corneal sensitivity with noncontact esthesiometry in patients with dry eye. *Invest Ophthalmol Vis Sci.* 2007;48(1):173–81.
27. Hosai BM, Ornek N, Zilelioğlu G, Elhan AH. Morphology of corneal nerves and corneal sensation in dry eye: a preliminary study. *Eye (Lond).* 2005;19(12):1276–9.
28. Yoon KC, Jeong IY, Park YG, Yang SY. Interleukin-6 and tumor necrosis factor- α levels in tears of patients with dry eye syndrome. *Cornea.* 2007;26(4):431–7.
29. • Enriquez-de-Salamanca A, Castellanos E, Stern ME, et al. Tear cytokine and chemokine analysis and clinical correlations in evaporative-type dry eye disease. *Mol Vis.* 2010;16:862–73. *An evaluation of cytokines and other inflammatory molecules in the tear films of patients with mild-to-moderate dry eye syndrome compared to healthy subjects. Interleukin (IL) 1-receptor antagonist, IL-6, IL-8/CXCL-8 and epidermal growth factor levels correlated with symptoms and signs of dry eye syndrome.*
30. Chotikavanich S, de Paiva CS, Li Q, et al. Production and activity of matrix metalloproteinase-9 on the ocular surface increase in dysfunctional tear syndrome. *Invest Ophthalmol Vis Sci.* 2009;50(7):3203–9.

31. Brignole F, Pisella PJ, Goldschild M, De Saint Jean M, Goguel A, Baudouin C. Flow cytometric analysis of inflammatory markers in conjunctival epithelial cells of patients with dry eyes. *Invest Ophthalmol Vis Sci.* 2000;41(6):1356–63.
32. Gao J, Morgan G, Tieu D, et al. ICAM-1 expression predisposes ocular tissues to immune-based inflammation in dry eye patients and Sjogrens syndrome-like MRL/lpr mice. *Exp Eye Res.* 2004;78(4):823–35.
33. Zheng X, de Paiva CS, Li DQ, Farley WJ, Pflugfelder SC. Desiccating stress promotion of Th17 differentiation by ocular surface tissues through a dendritic cell mediated pathway. *Invest Ophthalmol Vis Sci.* 2010;51(6):3083–91.
34. Chauhan SK, Dana R. Role of Th17 cells in the immunopathogenesis of dry eye disease. *Mucosal Immunol.* 2009;2(4):375–6.
35. Lee JH, Ahn HS, Kim EK, Kim TI. Efficacy of sodium hyaluronate and carboxymethylcellulose in treating mild to moderate dry eye disease. *Cornea.* 2011;30(2):175–9.
36. McDonald CC, Kaye SB, Figueiredo FC, Macintosh G, Lockett C. A randomised, crossover, multicentre study to compare the performance of 0.1 % (w/v) sodium hyaluronate with 1.4 % (w/v) polyvinyl alcohol in the alleviation of symptoms associated with dry eye syndrome. *Eye (Lond).* 2002;16(5):601–7.
37. Brignole F, Pisella PJ, Dupas B, et al. Efficacy and safety of 0.18 % sodium hyaluronate in patients with moderate dry eye syndrome and superficial keratitis. *Graefes Arch Clin Exp Ophthalmol.* 2005;243(6):531–8.
38. Lemp MA. Management of dry eye. *Am J Managed Care.* 2008;14:S088–101.
39. Scaffidi RC, Korb DR. Comparison of the efficacy of two lipid emulsion eyedrops in increasing tear film lipid layer thickness. *Eye Contact Lens.* 2007;33(1):38–44.
40. Benelli U. Systane lubricant eye drops in the management of ocular dryness. *Clin Ophthalmol.* 2011;5:783–90.
41. Coutinho AE, Chapman KE. The anti-inflammatory and immunosuppressive effects of glucocorticoids, recent developments and mechanistic insights. *Mol Cell Endocrinol.* 2011;335(1):2–13.
42. De Paiva CS, Corrales RM, Villarreal AL, et al. Apical corneal barrier disruption in experimental murine dry eye is abrogated by methylprednisolone and doxycycline. *Invest Ophthalmol Vis Sci.* 2006;47(7):2847–56.
43. Lekhanont K, Leyngold IM, Suwan-Apichon O, Rangsin R, Chuck RS. Comparison of topical dry eye medications for the treatment of keratoconjunctivitis sicca in a botulinum toxin B-induced mouse model. *Cornea.* 2007;26(1):84–9.
44. Avunduk AM, Avunduk MC, Varnell ED, Kaufman HE. The comparison of efficacies of topical corticosteroids and nonsteroidal anti-inflammatory drops on dry eye patients: a clinical and immunocytochemical study. *Am J Ophthalmol.* 2003;136(4):593–602.
45. Pflugfelder SC, Maskin SL, Anderson B, et al. A randomized, double-masked, placebo controlled, multicenter comparison of loteprednol etabonate ophthalmic suspension, 0.5 %, and placebo for treatment of keratoconjunctivitis sicca in patients with delayed tear clearance. *Am J Ophthalmol.* 2004;138(3):444–57.
46. Pavesio CE, Decory HH. Treatment of ocular inflammatory conditions with loteprednol etabonate. *Br J Ophthalmol.* 2008;92:455–9.
47. • Zhu L, Zhang C, Chuck RS. Topical steroid and non-steroidal anti-inflammatory drugs inhibit inflammatory cytokine expression on the ocular surface in the botulinum toxin B-induced murine dry eye model. *Mol Vis.* 2012;18:1803–12. *Botulin toxin B-induced mouse tear-deficiency dry eye model has been shown to mimic human non-Sjogren's disease. In this study, topical fluoromethalone and not NSAIDs reduced staining of tumor necrosis factor α and IL-1 β in corneal and conjunctival epithelia.*
48. Congdon N, Schein O, Kulajta P, Lubomski L, Gilbert D, Katz J. Corneal complications associated with topical ophthalmic use of nonsteroidal anti-inflammatory drugs. *J Cataract Refract Surg.* 2001;27:622–31.
49. De Paiva CS, Corrales RM, Villarreal AL, Farley WJ, Li DQ, Stern ME, Pflugfelder SC. Corticosteroid and doxycycline suppress MMP-9 and inflammatory cytokine expression, MAPK activation in the corneal epithelium in experimental dry eye. *Exp Eye Res.* 2006;83:526–35.
50. Luo L, Li DQ, Doshi A, Farley W, Corrales RM, Pflugfelder SC. Experimental dry eye stimulates production of inflammatory cytokines and MMP-9 and activates MAPK signaling pathways on the ocular surface. *Invest Ophthalmol Vis Sci.* 2004;45:4293–301.
51. Nikodemova M, Watters JJ, Jackson SJ, Yang SK, Duncan ID. Minocycline down-regulates MHC II expression in microglia and macrophages through inhibition of IRF-1 and protein kinase C (PKC) α /betaII. *J Biol Chem.* 2007;282(20):15208–16.
52. Shafaa MW, El Shazly LH, El Shazly AH, El Gohary AA, El Hossary GG. Efficacy of topically applied liposome-bound tetracycline in the treatment of dry eye model. *Vet Ophthalmol.* 2011;14(1):18–25.
53. Veldman P, Colby K. Current evidence for topical azithromycin 1 % ophthalmic solution in the treatment of blepharitis and blepharitis-associated ocular dryness. *Int Ophthalmol Clin.* 2011;51(4):43–52.
54. Nichols JJ, Bickle KM, Zink RC, Schiewe MD, Haque RM, Nichols KK. Safety and efficacy of topical azithromycin ophthalmic solution 1.0 % in the treatment of contact lens-related dry eye. *Eye Contact Lens.* 2012;38(2):73–9.
55. Tauber J, Davitt WF, Bokosky JE, et al. Double-masked, placebo controlled safety and efficacy trial of diquafosol tetrasodium (INS365) ophthalmic solution for the treatment of dry eye. *Cornea.* 2004;23:784–92.
56. • Matsumoto Y, Ohashi Y, Watanabe H, Tsubota K. Diquafosol Ophthalmic Solution Phase 2 Study Group. Efficacy and safety of diquafosol ophthalmic solution in patients with dry eye syndrome: a Japanese Phase 2 Clinical Trial. *Ophthalmology* 2012;119(10):1954–60. *A randomized, double-masked, multicenter clinical trial comparing topical diquafosol (1 %, n=96, 3 %, n=96) to placebo (n=94). There was a dose-dependent improvement in fluorescein staining and an improvement in symptom score in both treatment groups.*
57. Frist-Larsen K, Isager H, Manthorpe R. Sjogren's syndrome treated with bromhexine: a randomized clinical study. *Br Med J.* 1978;1:1579–81.
58. Peral A, Domínguez-Godínez CO, Carracedo G, Pintor J. Therapeutic targets in dry eye syndrome. *Drug News Perspect.* 2008;21(3):166–76.
59. Avni I, Garzozzi HJ, Barequet IS, et al. Treatment of dry eye syndrome with orally administered CF101: data from a phase 2 clinical trial. *Ophthalmology.* 2010;117(7):1287–93.
60. Geerling G, MacLennan S, Hartwig D. Autologous serum eye drops for ocular surface disorders. *Br J Ophthalmol.* 2004;88:1467–74.
61. Kojima T, Higuchi A, Goto E, Matsumoto Y, Dogru M, Tsubota K. Autologous serum eye drops for the treatment of dry eye diseases. *Cornea.* 2008;27 Suppl 1:S25–30.
62. Bradley JC, Simoni J, Bradley RH, McCartney DL, Brown SM. Time- and temperature-dependent stability of growth factor peptides in human autologous serum eye drops. *Cornea.* 2009;28(2):200–5.
63. Kojima T, Ishida R, Dogru M, et al. The effect of autologous serum eye drops in the treatment of severe dry eye disease: a prospective randomized case-control study. *Am J Ophthalmol.* 2005;139:242–6.
64. Urzua CA, Vasquez DH, Huidobro A, Hernandez H, Alfaro J. Randomized double-blind clinical trial of autologous serum versus artificial tears in dry eye syndrome. *Curr Eye Res.* 2012;37(8):684–8.

65. Donnenfeld E, Pflugfelder SC. Topical ophthalmic cyclosporine: pharmacology and clinical uses. *Surv Ophthalmol*. 2009;54(3):321–38.
66. Eckstein LA, Van Quill KR, Bui SK, et al. Cyclosporin A inhibits calcineurin/nuclear factor of activated T-cells signaling and induces apoptosis in retinoblastoma cells. *Invest Ophthalmol Vis Sci*. 2005;46:782–90.
67. Waldmeier PC, Zimmermann K, Qian T, et al. Cyclophilin D as a drug target. *Curr Med Chem*. 2003;10:1485–506.
68. Brignole F, Pisella PJ, De Saint Jean M, et al. Flow cytometric analysis of inflammatory markers in KCS: 6-month treatment with topical cyclosporin A. *Invest Ophthalmol Vis Sci*. 2001;42:90–5.
69. Brignole F, Pisella PJ, Goldschild M, et al. Flow cytometric analysis of inflammatory markers in conjunctival epithelial cells of patients with dry eyes. *Invest Ophthalmol Vis Sci*. 2000;41:1356–63.
70. 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.
71. Yoshida A, Fujihara T, Nakata K. Cyclosporin A increases tear fluid secretion via release of sensory neurotransmitters and muscarinic pathway in mice. *Exp Eye Res*. 1999;68(5):541–6.
72. Sall K, Stevenson OD, Mundorf TK, et al. CsA Phase 3 Study Group. Two multicenter, randomized studies of the efficacy and safety of cyclosporine ophthalmic emulsion in moderate to severe dry eye disease. *Ophthalmology*. 2000;107:631–9.
73. 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(5):967–74.
74. El Tayar N, Mark AE, Vallat P, et al. 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.
75. Liu H, Wang Y, Li S. Advanced delivery of cyclosporin A: present state and perspective. *Expert Opin Drug Deliv*. 2007;4(4):349–58.
76. Skalkicky SE, Goldberg I, McCluskey P. Ocular surface disease and quality of life in glaucoma patients. *Am J Ophthalmol*. 2012;153(1):1–9.
77. Kanai A, Alba RM, Takano T, et al. The effect on the cornea of alpha cyclodextrin vehicle for cyclosporin eye drops. *Transplant Proc*. 1989;21(1):3150–52. part 3.
78. Schechter BA. Ketorolac during the induction phase of cyclosporin-A therapy. *J Ocul Pharmacol Ther*. 2006;22(2):150–4.
79. Milani JK, Pleyer U, Dukes A, et al. Prolongation of corneal allograft survival with liposome-encapsulated cyclosporine in the rat eye. *Ophthalmology*. 1993;100(6):890–6.
80. Dillen K, Bozdag S, Vandervoort J, Ludwig A. Evaluation of the physicochemical characteristics and activity of various kinds of ciprofloxacin HCl-loaded cationic nanoparticles. *J Drug Del Sci Tech*. 2007;17(1):49–56.
81. Sárdy M, Ruzicka T, Kuhn A. Topical calcineurin inhibitors in cutaneous lupus erythematosus. *Arch Dermatol Res*. 2009;301(1):93–8.
82. Russell JJ. Topical tacrolimus: a new therapy for atopic dermatitis. *Am Fam Physician*. 2002;66(10):1899–903.
83. Moscovici BK, Holzchuh R, Chiacchio BB, Santo RM, Shimazaki J, Hida RY. Clinical treatment of dry eye using 0.03 % tacrolimus eye drops. *Cornea*. 2012;31(8):945–9.
84. Products and technologies. Lux BioSciences. 2011. Available at: <http://www.luxbio.com/LX214.htm>. Accessed July 2012.
85. Ormerod AD. Topical tacrolimus and pimecrolimus and the risk of cancer: How much cause for concern? *Br J Dermatol*. 2005;153:701–5.
86. Aragona P, Bucolo C, Spinella R, Giuffrida S, Ferreri G. Systemic omega-6 essential fatty acid treatment and pge1 tear content in Sjogren's syndrome patients. *Invest Ophthalmol Vis Sci*. 2005;46(12):4474–9.
87. • Rosenberg ES, Asbell PA. Essential fatty acids in the treatment of dry eye. *Ocul Surf*. 2010;8(1):18–28. *A well-written review of the literature regarding essential fatty acids for the prevention or treatment of dry eye syndrome. All the studies demonstrated that essential fatty acid supplementation resulted in some improvement in dry eye syndrome yet the evidence is not strong.*
88. Barabino S, Rolando M, Camicione P, et al. Systemic linoleic and gamma-linolenic acid therapy in dry eye syndrome with an inflammatory component. *Cornea*. 2003;22:97–101.
89. Rashid S, Jin Y, Ecoiffier T, Barabino S, Schaumberg D, Dana R. Topical omega-3 and omega-6 fatty acids for treatment of dry eye. *Arch Ophthalmol*. 2008;126:219–25.
90. James MJ, Gibson RA, Cleland LG. Dietary polyunsaturated fatty acids and inflammatory mediator production. *Am J Clin Nutr*. 2000;71 Suppl 1:343S–8S.
91. Li N, He J, Schwartz CE, Gjorstrup P, Bazan HE. Resolvin E1 improves tear production and decreases inflammation in a dry eye mouse model. *J Ocul Pharmacol Ther*. 2010;26(5):431–9.
92. US National Institutes of Health Clinical Trials. 2011. Available at: <http://clinicaltrials.gov/ct2/show/NCT00799552>. Accessed July, 2012.
93. Takeji Y, Urashima H, Aoki A, Shinohara H. Rebamipide increases the mucin-like glycoprotein production in corneal epithelial cells. *J Ocul Pharmacol Ther*. 2012;28(3):259–63.
94. • Fahmy AM, Hardten DR. Treating ocular surface disease: new agents in development. *Clin Ophthalmol*. 2011;5:465–472. *A review of new agents in the treatment of ocular surface disease.*
95. Coombs JH, Bloom BJ, Breedveld FC, et al. Improved pain, physical functioning and health status in patients with rheumatoid arthritis treated with CP-690,550, an orally active Janus kinase (JAK) inhibitor: results from a randomised, double-blind, placebo-controlled trial. *Ann Rheum Dis*. 2010;69:413–6.
96. Schindler C, Levy DE, Decker T. JAK-STAT signaling: from interferons to cytokines. *J Biol Chem*. 2007;282(28):20059–63.
97. • Ding C, Nandoskar P, Lu M, Thomas P, Trousdale MD, Wang Y. Changes of aquaporins in the lacrimal glands of a rabbit model of Sjögren's syndrome. *Curr Eye Res*. 2011;36(6):571–8. *Protein and mRNA levels of aquaporin-4 and -5 were assessed in the lacrimal glands of rabbits with induced autoimmune dacryoadenitis compared to age-matched controls. Levels were altered in the diseased lacrimal glands, being greater or less than normal depending on the site (ductal or acinar cells) and aquaporin type (-4 or -5).*
98. Ecoiffier T, El Annan J, Rashid S, Schaumberg D, Dana R. Modulation of integrin $\alpha\beta 1$ (VLA-4) in dry eye disease. *Arch Ophthalmol*. 2008;126(12):1695–9.
99. Chauhan SK, El Annan J, Ecoiffier T, et al. Autoimmunity in dry eye is due to resistance of Th17 to Treg suppression. *J Immunol*. 2009;182(3):1247–52.