

New drugs for the treatment of dry eye disease

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Abstract: Dry eye disease (DED) is one of the most commonly encountered conditions for eye care practitioners. The prevalence of DED can be as high as 30% of the population. In the past decade, only one drug has been approved for the treatment of DED by the US Food and Drug Administration (FDA) in the USA (ie, Restasis® by Allergan, Inc.). The total annual cost (ie, treatment and lost productivity due to symptoms) to the US economy of dry eye can be more than \$55 billion. Thus, the development of new drug treatments for dry eye is important for both the dry eye patient and the ophthalmic industry. There are many drugs in development for the treatment of dry eye. This manuscript reviews the drugs listed on the ClinicalTrials.gov website (FDA list of clinical trials) being investigated for the treatment of dry eye. A large number of these drugs are designed to target a specific cause of dry eye and some of these drugs will be approved for clinical use in the next 10 years. This will result in a significant increase in the clinician's choice of treatment and potentially better control of the dry eye patient's condition.

Keywords: keratoconjunctivitis sicca, clinical trials, anti-inflammatory, secretagogues

Introduction

Dry eye disease (DED) is a condition that affects the tear film and ocular surface and which can impact as much as 20% of the US population at any one time.¹ The most recent definition of DED, from a 2007 report by the International Dry Eye Workshop (DEWS), states that:

Dry eye is a multifactorial disease of the tears and ocular surface that results in symptoms of discomfort, visual disturbance, and tear film instability with potential damage to the ocular surface.²

Thus, there are many causes of dry eye that have a broad range of effects.

The two major subtypes of dry eye are aqueous tear-deficient dry eye and evaporative dry eye (EDE).² Dry eye in many patients results from a mixed etiology incorporating aspects of both subtypes.^{3,4} A comprehensive review of the different classes and subclasses of DED was published following the 2007 DEWS,² which included the major etiological causes of dry eye.

Meibomian gland dysfunction (MGD), the most common cause of EDE,^{5,6} has multiple etiologies.⁷ It was recently the focus of an international workshop, which redefined the condition and its treatments.⁶ It can be an acquired or congenital condition, with the most common forms of the acquired being simple and cicatricial MGD.

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These can be primary or secondary to seborrheic dermatitis, acne rosacea, psoriasis, trachoma, or pemphigoid.⁷ Most acquired MGD is due to reduced delivery of meibum to the lid margin in the hyposecretory or obstructive forms of the disease.⁷ Deficiencies in the lipid layer in patients with MGD leads to inability of this layer to effectively inhibit tear film evaporation, resulting in increased rates of evaporation and the condition of EDE.³

Epidemiology of DED

Epidemiological studies of DED report a wide range of prevalence for a variety of reasons. Assessment of age-specific data from large epidemiological studies have given a prevalence range of approximately 5% to over 30%.⁸ The lack of a single test that can accurately and reproducibly diagnose DED, the variability and tolerance of symptoms, the lack of correlation between tests, and the use of different diagnostic criteria have contributed to the wide variation in reported prevalence figures.⁸

Studies also indicate that sex and ethnic differences have an influence on the incidence and prevalence of DED. Studies suggest that there is a greater prevalence in women than in men⁸ and that Asian and Hispanic women are more likely than Caucasian women to have a clinical diagnosis of DED and/or report more severe symptoms.⁹ Recent general population studies of the prevalence of DED indicate that Asian races

have approximately twice the incidence of Caucasians.⁸ In addition to sex and ethnicity, a number of other risk factors for DED have been determined. These include older age,^{9,10} a low dietary intake of omega-3 essential fatty acids,¹¹ androgen deficiency,¹² vitamin A deficiency,¹³ cataract and refractive surgery,¹⁴⁻¹⁶ and wearing of contact lenses.¹⁷ These and other risk factors, arranged by the available supporting level of evidence, are summarized in Table 1.

Symptoms associated with DED

DED is characterized by symptoms of ocular surface dryness and discomfort due to insufficient tear quantity or quality caused by low tear production and/or excessive tear evaporation.¹⁸ Common symptoms reported by patients include ocular discomfort, such as dry, scratchy, or burning sensations; pain and stinging; increased blinking; itching and redness; and blurred vision. Diurnal variations exist in these symptoms, with most patients reporting greater symptomatology in the evening.¹⁹ Symptoms may be exacerbated by reduced and incomplete blinking combined with a decreased tear film break-up time during normal visual tasks.²⁰ Donshik et al²¹ reported the baseline symptomatology of 544 patients with DED entering a Phase III clinical trial. Patients suffered from a variety of symptoms with no one symptom predominating. Daily diaries from patients included reports of foreign-body sensation (29%), photophobia (27%), itching

Table 1 Risk factors for dry eye

Category	Level of evidence		
	Mostly consistent	Suggestive	Unclear
Demographics	Older age Female sex	Asian race	Hispanic ethnicity
Medications	Antihistamines	Tricyclic antidepressants Selective serotonin reuptake inhibitor Diuretics Beta blockers	Anticholinergics Anxiolytics Antipsychotics Oral contraceptives
Systemic associations	Connective tissue disorder Vitamin A deficiency Hepatitis C infection Androgen deficiency	Diabetes mellitus HIV/HTLVI infection Sarcoidosis Ovarian dysfunction	Acne Gout Menopause Pregnancy
Prior treatment or surgery	Postmenopausal estrogen therapy Radiation therapy Hematopoietic stem cell transplantation	Systemic chemotherapy Isotretinoin Large-incision ECCE and penetrating keratoplasty	Botulinum toxin injection
Miscellaneous	LASIK and refractive excimer laser surgery Omega-3 and Omega-6 fatty acids	Low-humidity environment	Cigarette smoking Alcohol

Notes: Mostly consistent evidence implies the existence of at least one adequately powered and otherwise well-conducted study published in a peer-reviewed journal, along with the existence of a plausible biological rationale and corroborating basic research or clinical data. Suggestive evidence implies the existence of either: 1) inconclusive information from peer-reviewed publications; or 2) inconclusive or limited information to support the association, but either not published or published somewhere other than in a peer-reviewed journal. Unclear evidence implies either directly conflicting information in peer-reviewed publications or inconclusive information but with some basis for a biological rationale. Modified from: *The Ocular Surface*. 5(2), [No authors listed], The epidemiology of dry eye disease: report of the Epidemiology Subcommittee of the International Dry Eye Workshop (2007), 93-107, Copyright 2007, with permission from Elsevier.⁸

Abbreviation: ECCE, extracapsular cataract extraction.

(21%), and burning/pain (11%).²¹ Another study has shown that there is little correlation between the severity or type of symptoms experienced and the clinical manifestations of the disease.²²

However, it should be noted that poor correlations have been found between symptoms reported by patients and clinical DED tests.²³ Patient symptoms have been observed to be better correlated with a global clinician grade of DED.¹⁹ This may imply that severity grading of DED is more influenced by patient symptoms than clinical test results.¹⁹

Dry eye symptoms can result in a significant financial cost to society. In the USA alone, the cost of medical care for dry eye patients has been reported to be as high as \$3.84 billion per year.²⁴ If other factors such as the loss of productivity of dry eye patients are included, then the annual costs can be \$55.4 billion.²⁴ Thus, the development of new treatments for dry eye can have a significant impact on the individual dry eye patients as well as society as a whole.

Table 1 demonstrates that there are many factors associated with the development of dry eye and the symptoms that it causes are varied. Since there are many causes of dry eye, a variety of new drugs with different mechanisms of action will need to be developed to address these causes. This will result in a significant expansion in the field of dry eye treatment. In fact, GlobalData predicted on June 12, 2013 that the compound annual growth rate until the year 2022 will be 12.8% for dry eye drug sales in Europe, Asia, and the USA.²⁵ The growth will result from an increased number of patients with dry eye and new improved drugs for its treatment.

Current treatments for DED

The DEWS reviewed the current treatments for dry eye (Figure 1) and ranked those treatments based on the therapeutic effect reported in the clinical and research literature.²⁶ They suggested that the treatment should be based on the severity of the dry eye condition. The DEWS report listed artificial tear supplements, gels, moisture chamber spectacles, anti-inflammatory agents, tetracyclines, punctal plugs, secretagogues, serum, contact lenses, systemic immunosuppressives, and surgery as accepted treatments for dry eye.²⁶ This review will discuss the drugs that have been investigated since the DEWS report. The drugs that have been in clinical trials for dry eye are listed in Table 2. Many of the drugs discussed in the following section are in early stages of development and may not have been described in peer-reviewed published papers. Thus, much of the following information is taken from the ClinicalTrials.gov website, which was started following the US *Food and Drug Administration Modernization Act* of 1997.

Table 2 organizes the drugs based on the phase of the clinical trial. Phase I trials are testing a new drug on a small group of people to determine its safety and side effects. Phase II trials are using the drug on a greater number of people to see if it is effective and further assess safety. Phase III trials use the drug on a large number of patients to confirm effectiveness, monitor side effects, compare it to other treatments, and collect information to allow the drug to be used safely. Phase IV studies are done after the drug has been marketed to look at its effect on different populations and look for side effects associated with long-term use.

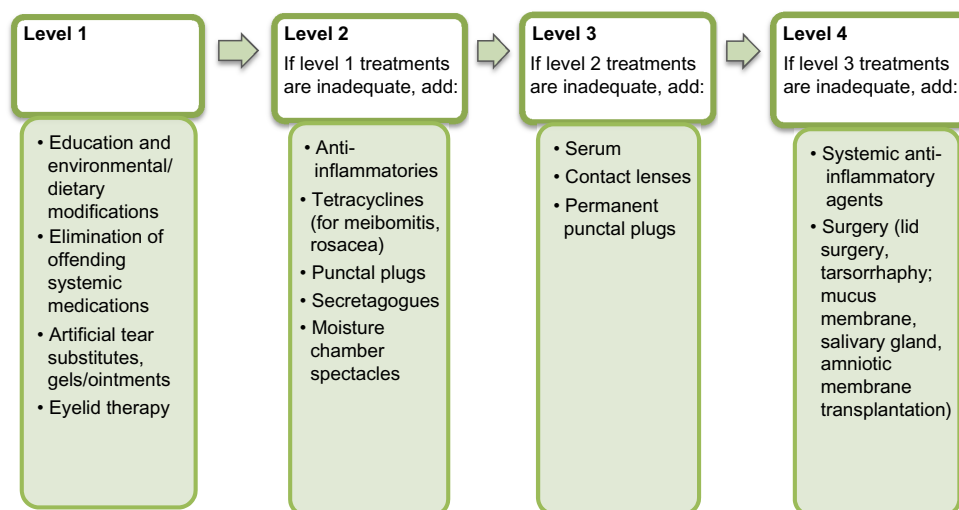


Figure 1 Treatment recommendations by severity level.

Notes: Modified from: Behrens A, Doyle JJ, Stern L, et al. Dysfunctional tear syndrome: A Delphi approach to treatment recommendations. *Cornea*. 2006;25(8):900-907. Copyright © 2006, (C) 2006 Lippincott Williams. With permission from Wolters Kluwer Health, Inc.⁸⁰

Table 2 Dry eye disease drugs under development

Phase	Manufacturer/sponsor name	Drug name	ClinicalTrials.gov identifier	Study completion date	
Phase IV	Merck Sharp and Dohme Corp	Azithromycin	NCT01014078 and NCT01105624	March 2010 and November 2010	
Phase III	Santen Pharmaceutical Co.	Cyclosporine A (NOVA22007)	NCT00814515	September 2009	
	Eyegate Pharmaceuticals, Inc.	Dexamethasone phosphate (EGP-437)	NCT01129856	April 2011	
	ISTA Pharmaceuticals, Inc. and Bausch & Lomb Incorporated	Bromfenac	NCT01212471	December 2011	
	Merck and Co, Inc.	Diquafosol tetrasodium (DE-089)	NCT01101984	April 2012	
	Sanofi-Aventis	Hydroxychloroquine	NCT00632866	May 2012	
	Acucela Inc. and Otsuka Pharmaceutical Co, Ltd	Rebamipide (OPC-12759)	NCT01632137	June 2013	
	Can-Fite BioPharma	CFI01	NCT01235234	December 2013	
	Shire	Lifitegrast (SAR 118)	NCT01636206 and NCT02284516	March 2014 and September 2015	
	Mimetogen Pharmaceuticals USA, Inc.	MIM-D3	NCT01960010	August 2014	
	Eleven Biotherapeutics	EBI-005	NCT01998802	April 2015	
	DH Bio Co, Ltd	Cyclosporine (Haporine-S)	NCT01804361	February 2014	
	Alcon Research	Rimexolone (AL-2178)	NCT00471419	August 2007	
	Phase II/III	Bausch & Lomb Incorporated	Ecabet sodium	NCT00198536	December 2005
		IDEC Pharmaceuticals	Rituximab	NCT00740948	January 2013
Hoffmann-La Roche Ltd		Tocilizumab	NCT01782235	March 2017	
Phase II	Michigan Cornea Consultants, PC	Thymosin beta-4 eyedrops (RGN-259)	NCT01393132	December 2012	
	Mitotech, SA	SkQI	NCT02121301	May 2014	
	Kala Pharmaceuticals, Inc.	KPI-121	NCT02188160	March 2015	
	Herantis Pharma Plc	cis-UCA	NCT02326090	April 2015	
	Alcon Research	LME636	NCT02365519	October 2015	
	Allergan	AGN-223575	NCT02435914	December 2016	
	InSite Vision	ISV-101 (bromfenac in DuraSite)	NCT01478555	January 2017	
	Ocular Therapeutix, Inc.	OTX-DP	NCT02468700	December 2015	
	Allergan	Cyclosporine (Restasis X®)	NCT02013791	July 2017	
	Santen Pharmaceutical Co.	Rivoglitazone (DE-101)	NCT01468168	November 2012	
	Bausch & Lomb Incorporated	Mapracorat (BOL-303242-X)	NCT01163643	July 2011	
	Resolvix	Resolvin (RX-10045)	NCT00799552	June 2009	
	Phase I/II	Pfizer	Tasocitinib/tofacitinib (CP-690550)	NCT00784719	October 2009
		R-Tech Ueno, Ltd	RU-101	NCT01843894	July 2014
Genentech, Inc.		DNase	NCT02193490	December 2016	
Lux Biosciences		Voclosporin (LX214)	NCT00851734	April 2009	
Phase I	Parion Sciences	P-321	NCT02242032	March 2015	
	Stemnion, Inc.	ACCS	NCT02369861	December 2015	
	Allergan	AGN-232411	NCT02420730	June 2016	

Abbreviations: ACCS, amnion-derived cellular cytokine solution; cis-UCA, cis-urocanic acid.

Drugs in the later-phase studies have passed many hurdles in the US Food and Drug Administration (FDA) approval process and are closer to being approved and marketed for clinical use.

New drug treatments for DED

Anti-inflammatory drugs

Corticosteroids and nonsteroidal anti-inflammatory drugs

Dexamethasone phosphate

Dexamethasone is a glucocorticoid with anti-inflammatory and immunosuppressive properties. Dexamethasone phosphate (EGP-437) is manufactured by EyeGate Pharmaceuticals, Inc.

(Waltham, MA, USA) as a treatment for dry eye. The drug is administered by iontophoresis to increase drug permeability to the tissue. In a Phase II study ([http://www.ClinicalTrials.gov/identifier: NCT00765804](http://www.ClinicalTrials.gov/identifier:NCT00765804)),²⁷ a total of 105 patients were randomized to a low drug dose (7.5%), a high drug dose (10.5%), or a placebo group. The treatment groups showed statistically significant improvements in signs and symptoms of dry eye at various time points; however, the primary endpoints were not achieved. The primary endpoints of the study concerned ocular discomfort and corneal staining at study visit 5. These were not statistically different among the treatment groups. Adverse events were common, but most were mild, and no severe adverse events were observed.

A Phase III clinical trial (NCT01129856) with 198 patients was completed in April 2011 in which two different concentrations of EGP-437 were compared to placebo in a controlled adverse environment.²⁷ Results of this study have not been released.

Rimexolone

Alcon Laboratories, Inc. (Fort Worth, TX, USA) developed the anti-inflammatory drug rimexolone (AL-2178). Rimexolone inhibits cytokine production of activated CD4 T-cells and it inhibits T-cell proliferation. Vexol 1% (rimexolone) is on the market as an ophthalmic suspension. It is approved to treat postoperative inflammation after ocular surgery and anterior uveitis. A Phase III interventional randomized double-blind study (NCT00471419) which had a projected enrollment of 750 dry eye patients was completed in August 2007. The ClinicalTrials.gov website was last updated in 2012, but the results have not been entered. Vexol, similar to other steroids like Lotemax (Bausch & Lomb Incorporated, Bridgewater, NJ, USA), Alrex (Bausch & Lomb Incorporated), and FML® (Allergan, Inc., Irvine, CA, USA), have been used off-label to treat dry eye.

Loteprednol etabonate

Kala Pharmaceuticals, Inc. (Waltham, MA, USA) is developing KPI-121. KPI-121 uses mucus-penetrating particle technology developed by Kala Pharmaceuticals, Inc. KPI-121 is loteprednol etabonate. The results of a Phase II clinical trial (NCT02188160) were recently (April 1, 2015) reported on by Kala Pharmaceuticals, Inc.²⁸ The trial used 0.25% KPI-121 four times per day on 150 dry eye patients. The results achieved statistical significance for the primary clinical sign endpoint (ie, bulbar conjunctival hyperemia, $P=0.0387$). There was not a statistical improvement in dry eye symptoms. The drug was well tolerated in the study, with the most common adverse event being instillation site pain in 6.9% of the patients. Instillation site pain was reported in 3.8% of the patients on vehicle.

Dexamethasone

Ocular Therapeutix, Inc. (Bedford, MA, USA) is developing OTX-DP. This is a sustained-release dexamethasone that is administered as a one-time absorbable intracanalicular plug. The plug delivers a 4-week tapered dose of dexamethasone. It is being developed: to treat ocular inflammation and pain following cataract surgery; to treat allergic conjunctivitis; and as a possible treatment for dry eye. Two Phase III studies (NCT02034019 and NCT02089113) which enrolled 247 cataract patients were just recently completed. The company

reported that OTX-DP met both primary efficacy measures, achieving a statistically significant improvement in the reduction of inflammatory cells and pain in cataract patients.

A Phase II study (NCT02468700) is ongoing to assess the safety and efficacy of OTX-DP (0.4 mg dexamethasone) in dry eye patients. The study is expected to enroll 43 dry eye patients and the completion date is December 2015. No study results are available.

Bromfenac

Bromfenac, a nonsteroidal anti-inflammatory drug, was developed by ISTA Pharmaceuticals, Inc. (Irvine, CA, USA) and Bausch & Lomb Incorporated. An animal study indicates that concentrations of 0.07% and 0.09% penetrate the ocular tissues well.²⁹ In humans, following cataract surgery, it has a good safety profile.³⁰ The results of a Phase II clinical trial (NCT00758784) with 38 dry eye patients indicated that a low dose of bromfenac (0.09%) was effective at statistically decreasing conjunctival (lissamine green test) and corneal (sodium fluorescein test) staining from baseline. Patients also achieved statistically significant improvements in subjective symptoms measured by the Ocular Surface Disease Index (OSDI). A randomized, interventional, Phase III study (NCT01212471) was carried out to evaluate safety and efficacy of bromfenac ophthalmic solution in DED. A total of 840 subjects were enrolled in the study, which was completed in December 2011. The results have not been posted on the ClinicalTrials.gov website. Bromfenac is marketed with the brand names of Xibrom, Prolensa, and Bromday.

A recent publication reported the effect of bromfenac use in 26 dry eye patients.³¹ Patients were chosen that were inadequately controlled with artificial tears. They reported that the addition of bromfenac to the artificial tear use resulted in an improvement in corneal staining, tear film breakup time, and subjective dryness scores, but no improvement in Schirmer scores. No adverse events were reported.

Cytokine inhibitors

EBI-005

Eleven Biotherapeutics (Cambridge, MA, USA) has developed the interleukin (IL)-1 receptor antagonist EBI-005 for the treatment of DED.³² EBI-005 is the end product of joining two IL-1 receptor ligands (IL-1 β and IL-1Ra). EBI-005 was optimized for ocular delivery and binds to IL-1R1. An animal study with mouse models of dry eye indicated that topical formulations of 5% IL-1Ra result in decreased corneal staining.³³ A Phase Ib/IIa study (NCT01745887) with 74 dry eye patients was completed in November 2012. The

results, although not statistically significant, suggested that EBI-005 improved signs and symptoms of dry eye. There were no adverse events in this study and the drug was well tolerated. A Phase III (NCT01998802) multicenter, double-masked, randomized, efficacy and safety study of EBI-005 (5 mg/mL topical ophthalmic solution) versus vehicle completed enrollment of 670 patients in early 2015. Results were recently reported at an Association for Research in Vision and Ophthalmology (ARVO) meeting.³⁴ The authors indicated that using EBI-005 three times per day for 6 weeks is safe and well tolerated. There were no treatment-related serious ocular or nonocular adverse events. There was a significant improvement in signs and symptoms at 6 weeks compared to baseline ($P < 0.001$).

Tocilizumab

Tocilizumab is being developed by Hoffmann-La Roche Ltd (Basel, Switzerland). Tocilizumab is an IL-6 inhibitor that is approved to treat rheumatologic and autoimmune disease.³⁵ Preclinical animal studies have not found tocilizumab to cause ocular or systemic toxicity.³⁶ A randomized, double-blind, placebo-controlled Phase II/III trial to evaluate the efficacy of tocilizumab for the treatment of primary Sjögren's syndrome is in progress (NCT01782235). The study will be completed in March 2017 and has an estimate of 110 enrolled subjects.

CF101

Can-Fite BioPharma Ltd (Petah-Tikva, Israel) is developing CF101 as an oral drug to treat dry eye. CF101 is an anti-inflammatory drug (an A₂ adenosine receptor agonist) that modulates signaling proteins like P13K, PKA, PKB/Akt, IKK, and NF- κ B. This modulation then inhibits cytokine production. Several animal studies have reported the anti-inflammatory effects of CF101 in arthritis, inflammatory bowel disease, osteoarthritis, and septic peritonitis.³⁷⁻⁴² The results of a Phase II study (NCT00349466) in dry eye patients were recently reported.⁴³ Sixty-eight (35 on placebo and 33 on CF101) patients completed the study. Treatment with CF101 resulted in a statistically significant improvement in the mean change from baseline to week 12 of the corneal staining, tear breakup time, and tear meniscus height in the CF101-treated group. The authors reported that CF101 was well tolerated and exhibited an excellent safety profile with no serious adverse events.⁴³ A Phase III study (NCT01235234) of the safety and efficacy of daily IB-MECA CF101 (0.1 mg or 1 mg) administered orally in patients with moderate-to-severe DED was completed in December 2013. The final results have not been reported.

T-cell inhibitors

Cyclosporine A

Cyclosporine A (0.05%) is currently marketed in the USA as Restasis® (an anionic emulsion) by Allergan, Inc. New versions of cyclosporine A are being investigated to improve bioavailability, increase absorption rate, and reduce dosage. Allergan, Inc. is currently testing Restasis X in a Phase II study (NCT02013791) that will enroll 138 subjects (moderate-to-severe dry eye). This study will not be completed until July 2017.

Cyclosporine A

NOVA22007

Santen Pharmaceutical Co. (Osaka, Japan) (formerly known as Novagali Pharma) is developing NOVA22007 (cyclosporine A). NOVA22007 is a cationic nanoemulsion.⁴⁴ Preclinical studies suggested that a cationic emulsion may be superior to an anionic emulsion.^{44,45} Two Phase II studies have been carried out. The initial trial enrolled 53 Sjögren's patients. The purpose of this study was to assess ocular tolerance and systemic safety of three concentrations of cyclosporine A (0.025%, 0.05%, and 0.1%). Over the 3-month trial, there were no safety concerns. The 0.1% concentration resulted in the greatest improvement in corneal and conjunctival staining over the 3-month trial. The second Phase II trial (NCT00739349) examined 132 mild-to-moderate dry eye patients over 3 months using the controlled adverse environment chamber. Two concentrations of cyclosporine A were examined (0.05% and 0.1%). A significant improvement in corneal staining and ocular discomfort was not found. Santen Pharmaceutical Co. received FDA approval for a Phase III trial (NCT00814515) in the USA with NOVA22007 in moderate-to-severe dry eye. The estimated enrollment was 482 patients. The study was completed in 2009 but the results of the Phase III trial have not been released.

In Europe, NOVA22007 is called Ikervis. In January 2015, the Committee for Medicinal Products for Human Use of the European Medicines Agency recommended the granting of a marketing authorization for Ikervis (1 mg/mL cyclosporine).⁴⁶ It is approved to treat severe keratitis in adult dry eye patients.

Haporine-S

DH Bio Co, Ltd is investigating the development of cyclosporine A (Haporine-S) as a nanoparticle. This is believed to increase the absorption rate and allow for dose reduction. A Phase III study (NCT01804361) to compare the efficacy and safety of topical Haporine-S versus Restasis (0.05%) in patients with moderate-to-severe DED was com-

pleted in February 2014 with an enrollment of 90 subjects. The final results are not posted on the ClinicalTrials.gov website.

Lifitegrast

Lifitegrast (SAR 1118) ophthalmic solution (5%) is being investigated by Shire (Lexington, MA, USA). Lifitegrast is a small-molecule integrin inhibitor. It binds to lymphocyte function-associated antigen-1 (LFA-1) and blocks the interaction of LFA-1 with ICAM-1. This results in a decrease in T-cell activation. One Phase III study is complete (NCT01636206) and a second is ongoing (NCT02284516). The first study evaluated the safety of a 5.0% concentration of lifitegrast ophthalmic solution compared to a placebo in dry eye subjects. A total of 332 subjects were enrolled in the study, which was completed in March 2014. The second Phase III study is still recruiting patients. It is expected to enroll 700 patients and the study will be completed in September 2015. Some of the results have been published.^{47,48} Sheppard et al, reported that lifitegrast met the primary objective of the study in comparison to the placebo. This was a significant decrease in inferior corneal staining ($P=0.0007$). It also significantly reduced superior ($P=0.0392$) and total ($P=0.0148$) corneal fluorescein staining and conjunctival lissamine staining (nasal, $P=0.0039$; total conjunctiva, $P=0.0086$) at day 84 versus placebo. The study did not meet the co-primary subjective measure of the visual-related function subscale score of the OSDI ($P=0.7894$). There were no unanticipated or serious ocular adverse events.⁴⁷ Based on these results, Shire has applied for a new drug application with the FDA for lifitegrast for the treatment of dry eye. A decision by the FDA is expected in October 2015.

mRNA translation inhibitors

Azithromycin

Azithromycin ophthalmic solution (1%) was developed by Merck and Co, Inc. (Kenilworth, NJ, USA). Azithromycin demonstrates antibacterial, anti-inflammatory, and immunomodulatory properties. Two Phase IV studies (NCT01014078 and NCT01105624) have been carried out. The objective of the first study was to compare the safety and efficacy of 1% azithromycin ophthalmic solution in dry eye subjects over a 4-week treatment period using placebo as a comparison. The study enrolled 112 subjects and was completed in March 2010. The second trial compared azithromycin to rewetting drops in patients that complained of a contact lens-related dry eye. This study enrolled 50 patients and was completed in November 2010. These studies indicated that topical treat-

ment with azithromycin was well tolerated and improved contact lens wearing time.^{49,50}

Hemozoin biocrystallization inhibitors

Hydroxychloroquine

Hydroxychloroquine, a hemozoin biocrystallization inhibitor, was developed by the Public Hospital of Paris (Paris, France) in collaboration with Sanofi-Aventis (Bridgewater, NJ, USA) for the treatment of DED. An interventional randomized placebo-controlled Phase III clinical trial (NCT00632866) on the safety of hydroxychloroquine (200 mg/day for 24 weeks) in primary Sjögren's syndrome enrolled 120 subjects and was completed in May 2012. The published results indicate that hydroxychloroquine compared to placebo did not improve symptoms in primary Sjögren's syndrome patients.⁵¹ However, there are publications suggesting that hydroxychloroquine increases tear production in dry eye patients and improves symptomology.^{52,53} Thus, hydroxychloroquine may prove beneficial in treating dry eye, but because of some of its severe side effects (ie, toxic retinopathy, cramps, dizziness, headache), it may not be practical.^{54,55}

B-cell antibodies

Rituximab

IDEC Pharmaceuticals (San Diego, CA, USA) has developed rituximab. A multicenter, randomized, double-blind, placebo-controlled Phase II/III clinical trial (NCT00740948) was conducted by the University Hospital of Brest (Brest, France) to study the tolerance and efficacy of rituximab in Sjögren's syndrome. The study enrolled 120 subjects and was completed in January 2013. Rituximab (1 g) was injected two times on the first day and one time on the 14th day of the trial. The placebo was sodium chloride or glucose. The results of this study were recently reported.⁵⁶ No significant difference was found at the primary endpoint between the rituximab and placebo groups. Adverse events were similar between groups except for a higher rate of infusion reactions with rituximab. It was concluded that rituximab alleviated some symptoms at earlier time points but not in patients with primary Sjögren's syndrome at week 24.

Mucin secretagogues

MIM-D3

Mimetogen Pharmaceuticals (Gloucester, MA, USA) developed a mucin agonist called MIM-D3. MIM-D3 is a partial agonist of the nerve growth factor (NGF) receptor TrkA. A Phase III clinical study (NCT01960010) of 1% MIM-D3 ophthalmic solution was recently completed in August 2014. A total of 403 subjects were recruited

in the study. MIM-D3 was well tolerated. The company reported that improvements over the placebo were seen for corneal staining and the OSDI questionnaire. A recent report at an ARVO meeting also indicated that MIM-D3 1% resulted in improvements in signs and symptoms in dry eye patients.⁵⁷

Rebamipide

Acucela Inc. (Seattle, WA, USA) and Otsuka Pharmaceutical Co, Ltd (Tokyo, Japan) investigated rebamipide (OPC-12759) for the treatment of dry eye. Rebamipide was approved in Japan in 2011 to treat dry eye and it is currently marketed in the People's Republic of China, Japan, Indonesia, Malaysia, and Thailand. Rebamipide is an amino acid analog of 2(1H)-quinolinone and increases mucin levels over the conjunctiva and cornea.^{58,59} It upregulates the gene and protein expression of MUC1, MUC4, and MUC16 in human corneal epithelial cells.^{60,61} It has recently been shown to increase epithelial cell proliferation.⁶² A Phase III clinical trial (NCT01632137) was recently completed (June 2013) in which rebamipide 2% was used four times per day. Several reports have indicated that rebamipide is safe, well tolerated, and effective in decreasing the signs and symptoms of dry eye.^{63,64} In dry eye patients with short tear breakup times, rebamipide use for 4 weeks (four times per day of 2% rebamipide) has been shown to improve post-blink higher-order aberrations ($P < 0.05$) and increase tear breakup times ($P < 0.001$).

Ecabet sodium

Bausch & Lomb Incorporated was developing ecabet sodium, a drug that stimulates mucous secretion. Ecabet sodium is marketed in Japan by Senju Pharmaceuticals (Osaka, Japan) as an oral drug for gastric ulcers. A Phase II/III clinical trial (NCT00198536) was sponsored by Bausch & Lomb Incorporated. The efficacy and safety of ecabet ophthalmic solution (2.83% and 3.70%) was examined in 159 enrolled patients. The study was completed in 2005. Results were not reported on the ClinicalTrials.gov website. Two other Phase II studies (NCT00370747, NCT00667004) were carried out by Bausch & Lomb Incorporated from 2006 to 2008. These were designed to examine the safety and efficacy of ecabet sodium applied four times per day in dry eye patients. A total of 345 dry eye patients were to be enrolled. No results from these studies have been released.

Diquafosol tetrasodium

Diquafosol tetrasodium, developed by Merck and Co, Inc. is a P2Y2 receptor agonist used to treat dry eye. It is a stable

derivative of uridine 5'-triphosphate. It increases mucin and fluid secretion.⁶⁵⁻⁶⁷ Diquafosol ophthalmic solution (diquafosol tetrasodium 3%, six times per day) was approved in 2010 by the Japanese Ministry of Health, Labor and Welfare to treat dry eye. It is also approved for use in Korea. A Phase III clinical trial (NCT01101984) by Santen Pharmaceutical Co was completed in April 2012 with 400 enrolled subjects. An early report indicated that diquafosol 3% was well tolerated and had a good safety profile.⁶⁸ It was better than sodium hyaluronate (0.1%) in improving conjunctival staining. Corneal staining was the same for the two ophthalmic solutions. More recently, the results of this clinical trial have been published with a greater number of patients.⁶⁹ A total of 497 patients were evaluated in this report. The corneal and conjunctival staining results were the same as in the earlier publication by Takamura et al.⁶⁸ The most common adverse events for diquafosol were eye discharge (4.5%), eye itching (3.3%), and eye irritation (2.8%). The adverse event rate for hyaluronic acid was less than that for diquafosol. A recent review of publications concerning 3% diquafosol tabulated reported drug reactions.⁷⁰ Adverse events were reported in 23.7% of the 655 patients enrolled in clinical trials with diquafosol. The drug reactions reported were eye irritation (6.7%), eye discharge (4.7%), conjunctival injection (3.7%), eye pain (2.7%), eye pruritus (2.4%), foreign body sensation (2.1%), and eye discomfort (1.1%). Most of these reactions were mild. In summary, 3% diquafosol tetrasodium improves dry eye signs as good as, if not better than, hyaluronic acid, but the incidence of mild side effects is greater.

Early-stage drugs for dry eye (Phase I/II)

In addition to the drugs discussed earlier, there are many drugs that are in the early stages of development for treatment of dry eye. For example, Allergan, Inc. has two compounds (AGN-232411 and AGN-223575) in Phase I or II trials (NCT02420730 and NCT02435914). Neither of these trials are enrolling subjects yet and their expected completion date is 2016. Alcon, Inc. has a Phase II study (NCT02365519) of LME636 that is currently enrolling subjects. The expected completion date is October 2015. Stemnion, Inc. (Pittsburgh, PA, USA) also has a Phase I study (NCT02369861) with their drug ACCS (amniotic-derived cellular cytokine solution). It is also enrolling subjects and has an expected completion date of December 2015. Genentech, Inc. (South San Francisco, CA, USA) has DNase (0.1%) in a Phase I/II study (NCT02193490). This study is examining the safety and efficacy of recombinant human DNA in Sjögren's patients.

The expected completion date is December 2016. Herantis Pharma Plc (Helsinki, Finland) recently completed a Phase II study (NCT02326090) of cis-urocanic acid (1% and 2.5%). No results are posted. InSite Vision (Alameda, CA, USA) is planning a Phase II study (NCT01478555) to examine the safety and efficacy of ISV-101 (bromfenac in DuraSite) in dry eye patients. The study start date is January 2016. Parion Sciences (Durham, NC, USA) just completed a Phase I study (NCT02242032) of P-321 ophthalmic solution in 53 dry eye subjects. The purpose of the study was to assess the safety and efficacy of P-321. The results have not been posted.

Michigan Cornea Consultants, PC (Southfield, MI, USA) completed a Phase II study (NCT01393132) of thymosin beta-4 (T β 4) eyedrops (RGN-259) in severe dry eye patients. T β 4 promotes healing of the corneal surface. The results of a study on a mouse model of wound healing demonstrated that T β 4 reduces wound healing time.⁷¹ In the Phase II study (NCT01393132), nine patients with severe dry eye were treated with either RGN-259 (0.1%) or vehicle control six times per day. The results of the study suggest that RGN-259 is safe and well tolerated. The treated dry eye patients also had a reduction in signs and symptoms.⁷² A second Phase II trial (NCT01387347), with 72 dry eye subjects, was completed in December 2011. No adverse events were reported for T β 4. The company reported an improvement in signs and symptoms on the ClinicalTrials.gov website.

Mitotech, SA (Moscow, Russia) completed a Phase II study (NCT02121301) with SkQ1 for the treatment of dry eye in 91 patients. SkQ1 is a drug designed to reduce oxidative stress in mitochondria. The results were reported at the 2015 ARVO meeting.⁷³ The authors reported that SkQ1 was safe and the drug decreased total corneal staining and improved symptoms.

R-Tech Ueno, Ltd (Tokyo, Japan) is developing RU-101, an ophthalmic solution containing recombinant human serum albumin. This mechanism of action is different from other drugs currently under development to treat dry eye. A Phase I/II clinical trial (NCT01843894) was recently completed (July 2014). The study was designed to determine the safety and efficacy of RU-101 in 104 dry eye patients. RU-101 was instilled six times per day for 4 weeks. The company reported a significant improvement in the corneal staining score at 4, 8, and 12 weeks after starting instillation. However, the corneal staining score did not reach statistical significance when compared to placebo. No safety concerns were reported.

Rivoglitazone (DE-101) is an anti-inflammatory drug developed by Santen Pharmaceutical Co. It is a peroxi-

some proliferator-activated receptor gamma agonist which directly acts on corneal and conjunctival epithelial cells by enhancing the barrier function of the epithelium. In a Phase II (NCT01468168) randomized placebo-controlled trial, high and low doses of DE-101 were compared to placebo in patients with dry eye. An estimated 183 subjects were enrolled in the study, which was completed in November 2012. In August 2013, Santen Pharmaceutical Co. discontinued the development of DE-101 as the drug was judged to be unable to meet achievement criteria. No study results were reported.

RX-10045 is an immune response mediator derived from resolvin, which is a group of lipid modulators derived from naturally occurring omega-3 fatty acids. RX-10045, developed by Resolvix (Cambridge, MA, USA), helps to resolve inflammation and promote healing in dry eye. In murine models, a treatment regimen of resolvin was found to reverse corneal epithelial damage associated with dry eye as well as improve both corneal staining and goblet cell density.^{74,75} A 28-day, randomized, multicenter, placebo-controlled Phase II study (NCT00799552) in 232 patients with moderate dry eye was completed in June 2009. Three different doses of RX-10045 were compared to placebo to evaluate the safety, tolerability, and efficacy of RX-10045 administered twice daily. The company reported that RX-10045 produced a dose-dependent, statistically significant improvement in the primary endpoints for both the signs and symptoms of dry eye, and was generally shown to be safe and well tolerated. However, final data have not been published.

Voclosporin (LX214) is an anti-inflammatory drug developed by Lux Biosciences (Jersey City, NJ, USA) which acts against calcineurin and enhances metabolic stability. In a Phase I (NCT00851734) dose escalation study to assess the safety and tolerability of LX214, 35 patients with dry eye were randomized into LX214 (0.02% and 0.2%) and placebo. The study was completed in April 2009. The company website reported that the data from the trial showed LX214 to be well tolerated at the two doses studied with its safety measurements indistinguishable from placebo. Besides this, clinically meaningful improvements were observed in both signs and symptoms of dry eye.

Mapracorat (formerly ZK-245186 and subsequently BOL-303242-X) is a novel, selective glucocorticoid receptor agonist developed by Bausch & Lomb Incorporated to treat dry eye. In an animal study, it has been shown to have an anti-inflammatory efficacy similar to dexamethasone with less effect on intraocular pressure.⁷⁶ In a Phase II study

(NCT01163643), 350 patients with dry eye were randomized into BOL-303242-X (0.3%, 1%, and 2%) or placebo groups. The study was completed in July 2011 and no results are posted on the ClinicalTrials.gov website.

Pfizer Inc. (New York, NY, USA) developed a selective inhibitor of the Janus kinase (JAK) family (tofacitinib, also known as tasocitinib and CP-690550). JAK is involved in the activation of immune cells, proinflammatory cytokine production, and cytokine signaling.⁷⁷ Tofacitinib inhibits JAK1, JAK2, and JAK3.⁷⁸ Tofacitinib was employed in a Phase I/II clinical trial (NCT00784719) in dry eye patients and the results have been published.⁷⁹ This was an 8-week study in which several dosage levels of tofacitinib (taken once or twice per day) were compared to vehicle and cyclosporine ophthalmic emulsion. All doses of tofacitinib exhibited a good safety profile and were well tolerated. The trial demonstrated improvement in the signs and symptoms of dry eye. These results suggest that JAK inhibitors may be useful in the treatment of dry eye.

Summary and conclusion

Currently, most dry eye patients are treated with artificial tears and/or punctal plugs. These treatments, however, may not be adequate as the disease progresses. In the last decade, only one drug (ie, Restasis) has been approved for the treatment of dry eye in the USA. Several other drugs have been approved for use in Europe (ie, Ikervis) and Asia (ie, diquafosol tetrasodium and rebamipide). In the past 10 years, many drugs have been and are currently being investigated by several different companies to treat dry eye. Some of these drugs (eg, the steroids) are being repurposed from other uses to see if they are effective in treating dry eye. New categories of drugs have also been developed to treat dry eye. These new categories of drugs are believed to treat the underlying cause of dry eye and not just act as palliative agents. The results of these investigations indicate that some of the drugs may not be good treatments for dry eye. Other drugs (eg, lifitegrast) are close to being approved by the FDA for use in the USA. In the next decade, many new drugs will be investigated and some will be approved by the FDA, which will significantly increase the treatment options for dry eye. Dry eye patients may then have their condition better controlled with these new drugs, which may decrease the cost to society of this disease.

Disclosure

The authors report no conflicts of interest in this work.

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