Ophthalmics, Anti-Inflammatory/Immunomodulator Therapeutic Class Review (TCR)

April 8, 2022

The materials contained herein represent the opinions of the collective authors and editors and should not be construed to be the official representation of any professional organization or group, any state Pharmacy and Therapeutics committee, any state Medicaid Agency, or any other clinical committee. This material is not intended to be relied upon as medical advice for specific medical cases and nothing contained herein should be relied upon by any patient, medical professional or layperson seeking information about a specific course of treatment for a specific medical condition. All readers of this material are responsible for independently obtaining medical advice and guidance from their own physician and/or other medical professional in regard to the best course of treatment for their specific medical condition. This publication, inclusive of all forms contained herein, is intended to be educational in nature and is intended to be used for informational purposes only. Send comments and suggestions to PSTCREditor@magellanhealth.com.

FDA-APPROVED INDICATIONS

Drug	Manufacturer	Indication
cyclosporine emulsion (Restasis®, Restasis Multidose®)[1,2]	Allergan; generic (Restasis only)	Increase tear production in patients whose tear production is presumed to be suppressed due to ocular inflammation associated with keratoconjunctivitis sicca
cyclosporine emulsion (Verkazia)[3]	Eyevance/Santen	Treatment of vernal keratoconjunctivitis (VKC) in adults and children 4 years of age and older
cyclosporine solution* (Cequa™)[4]	Sun	Increase tear production in patients with keratoconjunctivitis sicca (dry eye)
lifitegrast (Xiidra®)[5]	Novartis	Treatment of signs and symptoms of dry eye disease in adults
loteprednol (Eysuvis™)[6]	Kala	Short-term (up to 14 days) treatment of dry eye disease signs and symptoms
varenicline nasal spray (Tyrvaya)[7]	Oyster Point	Treatment of the signs and symptoms of dry eye disease in adults

* Cequa and Verkazia (cyclosporine), Eysuvis (loteprednol), and Tyrvaya (varenicline) nasal spray were approved under the United States (US) Food and Drug Administration (FDA) 505(b)(2) pathway that allows at least some data submitted for approval to be from studies not conducted by or for the applicant.[8, 9, 10, 11]

OVERVIEW

Dry eye disease (DED) is related to either decreased tear volume (aqueous deficient dry eyes) or rapid evaporative loss (evaporative dry eyes) due to poor tear quality.[12] The terms dry eye disease, dry eye syndrome, keratoconjunctivitis sicca (KCS), and keratitis sicca are often used interchangeably, with the term keratoconjunctivitis sicca being an older term.

DED affects approximately 10% to 30% of the United States (US) population and occurs more commonly in patients over 50 years of age. It is found more commonly in women, specifically those who are postmenopausal, pregnant, taking oral contraceptives, or are receiving hormone replacement therapy (particularly estrogen-only products). [13,14] Due to increased use of soft contact lenses and frequent smartphone and computer usage, the prevalence of DES is increasing among young adults aged 18 to 34 years. Patients with DED may have the following complaints: sensations of ocular dryness, grittiness, a foreign body, or irritation; hyperemia; mucoid discharge; excessive tearing; photophobia; and blurry vision. Some findings on examination consist of conjunctival hyperemia and fine, scattered loss of corneal or conjunctival epithelium.

Sjögren's syndrome, which can be a primary or secondary autoimmune disorder, often includes dry eye symptoms.[15] Aqueous tear deficient DED associated with Sjögren's syndrome affects approximately 1% to 2% of the US population. It also occurs more commonly in women. None of the agents in this review is indicated specifically for patients with Sjögren's syndrome.

In aqueous tear deficient DED, the inadequate tear production is typically idiopathic, but may also be secondary to a damaged or malfunctioning lacrimal gland or other autoimmune conditions (e.g., rheumatoid arthritis, systemic lupus erythematosus).[16] Evaporative DED is generally related to loss of the oily tear film, sometimes related to poor oil quality, such as in meibomian gland dysfunction or oil degradation (e.g., seborrheic blepharitis). Diagnosis is dependent on symptoms and clinical appearance. It may be further differentiated by the Schirmer test, which uses standardized strips of filter paper placed at the junction between the middle and lateral third of the lower lid. Five millimeters or less of wetting of the paper after 5 minutes on 2 successive occasions confirms the diagnosis of aqueous tear-deficient

dry eye. The tear breakup test (TBUT) helps identify evaporative DED and uses fluorescein installation to coat the eye. The patient stares and the time to the first dry spot is determined. Accelerated tear film breakup (< 10 seconds) indicates evaporative DED.

Drying of the eye can also result from inadequate closing of the eye during sleep, as seen with facial nerve palsy, or from insufficient blinking rate, as reported with conditions such as Parkinson's disease.[17]

In general, treatment is aimed to prevent corneal ulcers and scarring.[18] Symptomatic treatment of DED often includes the frequent application of viscous artificial tears and ointments. Multiple artificial tear products are available over-the-counter (OTC) and contain various formulations and strengths of cellulose to preserve viscosity, an agent to prevent evaporation (e.g., polyethylene glycol or an oil emulsion), and a preservative. Since there are various formulations, a patient may respond better to 1 agent than another, particularly if the patient is sensitive to certain preservatives or excipients. These products are available as drops, ointments, and gels and are dosed as needed based on symptoms. Preservative-free options are also available.[19,20] Prescription cyclosporine (Cequa, Restasis, Restasis Multidose), lifitegrast (Xiidra), loteprednol (Eysuvis), and varenicline (Tyrvaya) nasal spray provide treatment aimed at the cause of the dry eye symptoms rather than the symptomatic management.

According to the 2018 Preferred Practice Parameter on dry eye syndrome and the 2021 Cornea/External Disease Summary Benchmark from the American Academy of Ophthalmology (AAO), specific treatment recommendations depend on the severity and source of the dry eye.[21,22] Aqueous enhancement using artificial tear substitutes are recommended for *mild* DED. Preservative-free versions are preferred, when available, particularly if preservative versions are not tolerated or when used frequently. Other recommendations for *mild* dry eye include elimination of offending topical or systemic medications (e.g., antihistamines, diuretics), cigarette smoking and exposure to second-hand smoke avoidance, eyelid therapy (e.g., warm compresses, eyelid hygiene), increased blinking, environmental changes (e.g., increasing humidity, avoiding air drafts), treatment of contributing ocular factors such as blepharitis or meibomianitis, and correction of eyelid abnormalities. Recommended measures for *moderate* dry eyes include use of anti-inflammatory agents, such as topical cyclosporine (Cequa, Restasis, Restasis Multidose), lifitegrast (Xiidra), topical corticosteroids, or systemic omega-3 fatty acids supplements, along with aqueous enhancement and other methods described above for mild disease. Other potential treatments for moderate dry eye include punctal plugs (lacrimal plugs) or spectacle side shields and moisture chambers. For *severe* dry eye, in addition to above mentioned treatments, systemic cholinergic agonists, systemic anti-inflammatories, mucolytic agents, autologous serum tears, contact lenses, permanent punctal occlusion, and tarsorrhaphy are recommended. Patient education is also an important part of successful management of DED.

Vernal keratoconjunctivitis (VKC), a chronic form of ocular allergy, can potentially lead to severe visual complications, including progressive corneal damage resulting in vision loss.[23,24,25] It is a fairly rare condition occurring more typically in temperate zones (e.g., Mediterranean area, Middle East, Africa, Central America, Indian subcontinent). It is more likely to affect males, and the onset or VKC typically occurs in the first decade of life, persisting throughout the first 2 decades (generally peaks near puberty, then subsides). Over 90% of patients with VKC have another atopic condition (e.g., asthma, eczema, allergic rhinitis). VKC is an IgE- and T cell-mediated disease, resulting in chronic inflammation involving eosinophils and lymphocytes. Symptoms include itching, photophobia, foreign body sensation, tearing, and blepharospasm. The 2018 American Academy of Ophthalmology (AAO) conjunctivitis guidelines state that general management should involve modifying the environment to minimize exposure to

allergens and irritants and using ocular lubricants and cool compresses. They further state that topical and oral antihistamines and topical mast cell stabilizers (e.g., cromolyn, lodoxamide [Alomide]) can be beneficial to maintain comfort. For acute exacerbations, the group states that topical corticosteroids are usually needed to control signs and symptoms. Regarding topical cyclosporine, they state that it has demonstrated effectiveness in more frequent dosing for severe VKC (I+ study evidence, Good quality, Strong recommendation) and preventing seasonal recurrence. This may limit unnecessary use of corticosteroids, and minimization of corticosteroids is a goal. Other topical agents (e.g., tacrolimus, pimecrolimus) have also been used. Rarely, systemic immunosuppressants may be utilized. Various surgical measures (e.g., superficial keratectomy) may also be used in select severe cases. Cyclosporine ophthalmic emulsion (Verkazia) offers the first FDA-approved topical immunomodulator treatment for VKC and provides a treatment option for those not responding to first-line therapies.

PHARMACOLOGY[26,27,28,29,30,31,32]

While cyclosporine is known to be an immunomodulator when administered systemically, the exact mechanism in the management of DED is unknown. Immunomodulating activity of cyclosporine is thought to reduce ocular inflammation. Topical cyclosporine (Cequa, Restasis, Restasis Multidose) and topical cyclosporine (Verkazia) may take up to 4 to 6 weeks to demonstrate benefit for DED[33,34] and up to 4 months for VKC[35,36], respectively.

The exact mechanism of lifitegrast (Xiidra), a lymphocyte function-associated antigen-1 (LFA-1) antagonist, in DED is unknown. Lifitegrast binds to LFA-1, blocking its interaction with its cognate ligand intercellular adhesion molecule-1 (ICAM-1). ICAM-1 is thought to be overexpressed in DED, and its interaction with LFA-1 may lead to T-cell activation and migration. Based on available clinical trials, lifitegrast has demonstrated this benefit at 12 weeks; however, a quicker onset of efficacy cannot be ruled out.

Loteprednol (Eysuvis) is a corticosteroid that inhibits the inflammatory responses, but the mechanisms associated with glucocorticoid/glucocorticoid receptor-dependent modulation of inflammation are not fully understood. However, corticosteroids are thought to play a role in inhibiting prostaglandin production.

The exact mechanism of action for varenicline nasal spray (Tyrvaya) is not known. However, the effectiveness of the agent in DED is thought to be due to activity at heteromeric sub-type(s) of the nicotinic acetylcholine (nACh) receptor where it acts as an agonist activating the trigeminal parasympathetic pathway which results in increased basal tear film production. Binding occurs with high affinity and selectivity at the following human neuronal nACh receptors: α4β2, α4α6β2, α3β4, α3α5β4 and α7.

PHARMACOKINETICS[37,38,39,40,41,42,43]

Blood cyclosporine (Restasis, Restasis Multidose) concentrations in all samples collected, after topical administration of cyclosporine 0.05% twice daily for 12 months, were below the quantitation limit of 0.1 ng/mL. Blood cyclosporine concentrations, after twice daily topical ocular administration of cyclosporine 0.09% (Cequa) into each eye of healthy subjects for up to 7 days and once on day 8, were either not detectable or were marginally above quantitation limit of 0.1 ng/mL. Blood levels of cyclosporine 0.1% (Verkazia) after administration of 1 drop 4 times daily at 2, 4, and 12 months had a maximum blood level of cyclosporine of 0.67 ng/mL.

Systemic exposure of lifitegrast (Xiidra) is minimal. Trough plasma concentrations at steady state were detectable in 19% of patients in a subset of patients with dry eyes who were on lifitegrast (range, 0.55 ng/mL to 3.74 ng/mL).

The plasma concentrations of loteprednol (Eysuvis) were below the quantitation limit of 1 ng/mL at all timepoints after bilateral topical ocular dosing of 2 drops administered 4 times daily for 14 days in 20 adult participants.

Varenicline nasal spray (Tyrvaya) can be detected in plasma with a mean C_{max} of 0.34 ng/mL and an AUC_{0-inf} of 7.46 h*ng/mL after administration of 0.12 mg (0.06 mg per 50-µL spray in each nostril; higher than the approved concentration); detection of varenicline occurred within 5 minutes and peak levels were achieved within 2 hours. These systemic levels, as measured by $AUC_{0-inf,}$ from this intranasal dose was approximately 7.5% of that seen with a 1 mg oral dose of varenicline.

CONTRAINDICATIONS/WARNINGS[44,45,46,47,48,49,50]

Both cyclosporine 0.05% (Restasis, Restasis Multidose) and lifitegrast (Xiidra) are contraindicated in patients with known hypersensitivity to the active ingredient or any excipient ingredient; however, no contraindications are listed in the product labeling for cyclosporine 0.09% solution (Cequa). Cyclosporine 0.1% (Verkazia) has no contraindications, but carries a warning regarding the potential for eye injury and contamination; patients should be advised to avoid touching the vial tip to the eye or other surfaces.

Loteprednol (Eysuvis) is contraindicated in the presence of most viral diseases of the cornea and conjunctiva including epithelial herpes simplex keratitis, vaccinia, and varicella. It is also contraindicated in patients with mycobacterial infection of the eye or fungal diseases of ocular structures.

Cyclosporine ophthalmic emulsions (0.05% and 0.09%), lifitegrast, and loteprednol should not be administered while wearing contact lenses. Patients should wait 15 minutes following drug administration to insert contact lenses. In addition, care should be taken not to touch the vial tip to the eye or other surfaces to avoid eye injury and contamination.

Loteprednol may delay healing and cause corneal and scleral thinning. Use of loteprednol in the presence of thin corneal or scleral tissue may lead to perforation. Thorough examination and assessment should be made prior to the initial and each subsequent renewal of the loteprednol prescription.

Prolonged use of loteprednol may result in glaucoma with optic nerve damage, as well as defects in visual acuity and fields of vision. Loteprednol may also result in formation of posterior subcapsular cataract.

Loteprednol may increase the hazard of secondary ocular infections by suppressing the immune response. Loteprednol may mask infection or enhance existing infection during acute eye purulent eye conditions. In addition, caution should be exercised when using loteprednol in patients with a history of herpes simplex. Loteprednol may prolong the course and may exacerbate the severity of viral eye infections (including herpes simplex). Long-term loteprednol use may cause fungal infections of the cornea.

Varenicline nasal spray (Tyrvaya) has no contraindications or warnings listed in its product labeling.

DRUG INTERACTIONS[51,52,53,54,55,56,57]

No information is available in the prescribing information regarding drug interactions with cyclosporine (Cequa, Restasis, Restasis Multidose, Verkazia), lifitegrast (Xiidra), loteprednol (Eysuvis), or varenicline nasal spray (Tyrvaya).

ADVERSE EFFECTS[58,59,60,61,62,63,64]

The most common adverse effect with cyclosporine 0.05% (Restasis, Restasis Multidose) is ocular burning (17%). Other reported adverse effects (incidence of 1% to 5%) include conjunctival hyperemia, discharge, epiphora, eye pain, foreign body sensation, pruritus, stinging, and visual disturbances (e.g., blurring). Postmarketing adverse effects that have been reported with cyclosporine 0.05% include hypersensitivity (e.g., eye swelling, urticaria, angioedema, face and/or tongue swelling, pharyngeal edema, allergic conjunctivitis, and dyspnea) and superficial eye injury secondary to the vial tip touching the eye during administration. The most common adverse reactions (incidence of 1% to 5%) reported for cyclosporine 0.09% (Cequa) include pain on instillation of drops (22%) and conjunctival hyperemia (6%). Adverse reactions reported in ≥ 1% of patients receiving cyclosporine 0.1% (Verkazia) included eye pain and instillation site pain (12%), eye pruritus and instillation site pruritus (8%), foreign body sensation and ocular discomfort (6%), reduced visual acuity (5%), cough (5%), ocular hyperemia (4%), headache (4%), and upper respiratory tract infection (2%).

The most common adverse reactions occurring in 5% to 25% of patients during clinical trials with lifitegrast (Xiidra) were instillation site irritation, dysgeusia, and decreased visual acuity. Rare cases of hypersensitivity have been reported following product use with various symptoms, including anaphylaxis, bronchospasm, respiratory distress, tongue swelling, pharyngeal edema, and urticaria. Postmarketing cases of eye swelling and rash have also been reported.

The most common adverse drug reaction reported with loteprednol use was instillation site pain, which occurred in 5% of patients in clinical trials.

The most common adverse effects reported in clinical trials for varenicline nasal spray (Tyrvaya) were sneezing (82%), cough (16%), throat irritation (13%), and instillation-site irritation (8%).

SPECIAL POPULATIONS[65,66,67,68,69,70,71]

Pediatrics

Safety and efficacy of cyclosporine 0.05% (Restasis, Restasis Multidose) have not been established in children < 16 years old. Safety and efficacy of cyclosporine 0.09% (Cequa), loteprednol (Eysuvis), and varenicline nasal spray (Tyrvaya) have not been established in patients < 18 years of age. Safety and efficacy of lifitegrast (Xiidra) have not been established in pediatric patients < 17 years old. Safety and efficacy of cyclosporine 0.1% (Verkazia) have been established in children from 4 through 18 years of age.

Pregnancy

Previously, cyclosporine 0.05% (Restasis in single-use containers) was assigned Pregnancy Category C, but its labeling was updated in compliance with the Pregnancy and Lactation Labeling Rule (PLLR) and now includes descriptive text. Cyclosporine 0.05% (Restasis Multidose), lifitegrast (Xiidra), and

loteprednol (Eysuvis) have not been assigned a Pregnancy Category based on the PLLR. Clinical administration of cyclosporine 0.05% ophthalmic emulsion is not detected systemically; maternal use is not expected to result in fetal drug exposure. No human data are available on the use of cyclosporine 0.09% (Cequa), cyclosporine 0.1% (Verkazia), lifitegrast (Xiidra), loteprednol (Eysuvis), or varenicline nasal spray (Tyrvaya) in pregnant women to provide insight into drug-associated risks.

Geriatrics

No overall differences in safety or effectiveness were observed between geriatric and younger adults in clinical trials with cyclosporine (Cequa, Restasis, Restasis Multidose), lifitegrast (Xiidra), loteprednol (Eysuvis), or varenicline nasal spray (Tyrvaya). The safety and effectiveness of cyclosporine 0.1% (Verkazia) have not been studied in geriatric patients.

DOSAGES[72,73,74,75,76,77,78,79]

Drug	Dosage	Comment	Availability
cyclosporine emulsion (Restasis, Restasis Multidose)	1 drop in each eye twice daily (12 hours apart)	Restasis Multidose: contains unidirectional valve and air filter; prime by squeezing 2 drops onto a tissue before initial use	0.05% ophthalmic emulsion in 0.4 mL single-use, preservative-free containers (trays of 30 or 60) Restasis Multidose: 5.5 mL of 0.05% ophthalmic emulsion in a 10 mL bottle (preservative-free) (brand only)
cyclosporine emulsion (Verkazia)	1 drop 4 times daily into each affected eye Treatment can be discontinued when signs and symptoms are resolved and can be reinitiated if recurrence occurs	Gently shake the vial several times before use Contact lenses should be removed before application and may be reinserted 15 minutes following administration If more than 1 topical ophthalmic product is being used, administer at least 10 minutes apart; administer 10 minutes prior to using any eye ointment, gel, or other viscous eye drops	0.1% ophthalmic emulsion in low-density polyethylene single-dose vials Each vial contains 0.3 mL 5 vials are packaged in an aluminum pouch 6, 12, or 24 pouches are packaged in a box
cyclosporine solution (Cequa)	1 drop in each eye twice daily (12 hours apart)	If used concomitantly, administer artificial tear products at least 15 minutes apart from cyclosporine ophthalmic emulsion	0.09% ophthalmic solution in 0.25 mL single-use, preservative-free container vials (cartons of 60 vials)
lifitegrast (Xiidra)	1 drop in each eye twice daily (12 hours apart)	--	5% ophthalmic emulsion in 0.2 mL single-use, preservative-free containers (carton of 60 single-use containers stored in foil pouches of 5 containers/pouch)

Dosages (continued)

Drug	Dosage	Comment	Availability
loteprednol (Eysuvis)	1 to 2 drops into each eye 4 times a day	Shake bottle for 2 to 3 seconds prior to each use. If other eye drops are used concurrently, wait at least 5 minutes between instillation of loteprednol. This product should only be renewed after examination under magnification such as a slit lamp and evaluation of the intraocular pressure	0.25% sterile suspension in a 8.3 mL multi-dose bottle
varenicline nasal spray (Tyrvaya)	1 spray in each nostril twice daily (approximately 12 hours apart)	Prime with 7 actuations before first use, re-prime with 1 actuation if not used for > 5 days; do not shake	Nasal solution: 0.03 mg (0.05 mL)/spray; supplied as a carton containing 2 bottles of nasal spray; each bottle delivers 15 day supply (60 sprays)

The single-use containers should be discarded immediately after use.

CLINICAL TRIALS

Search Strategy

Studies were identified through searches performed on PubMed and review of information sent by manufacturers. Search strategy included the FDA-approved use of all drugs in this class. Randomized, comparative, controlled trials comparing agents within this class for the approved indications are considered the most relevant in this category. Studies included for analysis in the review were published in English, performed with human participants, and randomly allocated participants to comparison groups. In addition, studies must contain clearly stated, predetermined outcome measure(s) of known or probable clinical importance, use data analysis techniques consistent with the study question, and include follow-up (endpoint assessment) of at least 80% of participants entering the investigation. Despite some inherent bias found in all studies, including those sponsored and/or funded by pharmaceutical manufacturers, the studies in this therapeutic class review were determined to have results or conclusions that do not suggest systematic error in their experimental study design. While the potential influence of manufacturer sponsorship and/or funding must be considered, the studies in this review have also been evaluated for validity and importance.

cyclosporine 0.05% emulsion (Restasis) versus vehicle

Four randomized, vehicle-controlled, multicenter, clinical trials assessed the efficacy and safety of cyclosporine in approximately 1,200 patients with moderate to severe KCS whose tear production was suppressed due to ocular inflammation.[80] In these trials, cyclosporine demonstrated superiority over vehicle in Schirmer wetting of 10 mm at 6 months (approximately 15% with cyclosporine versus 5% with vehicle). Notably, increased tear production did not occur in patients using topical anti-inflammatory drugs or punctal plugs.

Cyclosporine 0.05% and 0.1% ophthalmic emulsions were compared to vehicle for efficacy and safety in 877 patients with moderate to severe DED over 6 months.[81] In these 2 identical, randomized, double-blind, multicenter trials, patients were administered treatment twice daily and evaluated based on

corneal dye staining, Schirmer test, tear break-up time, ocular surface disease index, patient subjective rating scale, symptoms of dry eyes, use of artificial tears, and investigator's evaluation of global response to treatment. Both cyclosporine arms provided significantly greater improvement on the corneal staining and Schirmer values than the vehicle group (p≤0.05). Subjective measures including blurred vision, need for artificial tears, and investigator's global assessment were greatly improved with cyclosporine 0.05% (p≤0.05). No dose-response relationship was observed. All therapies were well tolerated.

cyclosporine 0.1% emulsion (Verkazia) versus vehicle

VEKTIS (Vernal KeratoconjunctiviTIs Study) and NOVATIVE were randomized, multicenter, double-masked, vehicle-controlled clinical trials.[82,83,84,85] In both studies, most patients had limbal or tarsal forms of VKC (65% VEKTIS, 74% NOVATIVE) and a history of VKC for a mean of about 3 years. Results of NOVATIVE (NCT00328653), which was used as additional supporting evidence for the approval, are not detailed in the product labeling.

VEKTIS, NCT01751126, a multinational phase 3 study, included 169 patients 4 to 17 years old (mean, 9.2 years; 78.6% male; 70.8% White) with active severe VKC (grade 3 or 4 on Bonini scale) and severe keratitis (corneal fluorescein staining [CFS] score of grade 4 or 5 on the modified Oxford scale), ≥ 1 recurrence of VKC in the prior year, and a mean score ≥ 60 mm using a 100 mm Visual Analogue Scale (VAS) measuring symptoms (photophobia, tearing, itching, and mucous discharge). Patients were randomized 1:1:1 to cyclosporine 0.1% ophthalmic suspension 1 drop in affected eye(s) 4 times daily (high-dose), cyclosporine 0.1% ophthalmic suspension 1 drop in affected eye(s) 2 times daily plus twice daily vehicle (low-dose), or vehicle 4 times daily for 4 months (Period 1). Rescue medication using dexamethasone 0.1% 4 times daily for up to 5 days was permitted in patients meeting study-defined criteria for keratitis and/or symptom worsening. Patients were then switched to cyclosporine 0.1% 4 or 2 times daily during month 4 through 12 (Period 2). Efficacy was defined as improvement in a composite score assessing keratitis (assessed by CFS and scored via the modified Oxford scale), need for rescue medication, and occurrence of corneal ulceration with detailed scoring described. Across Period 1, the mean composite score was 2.06 (95% confidence interval [CI], 1.67 to 2.45) in the high-dose group, 1.93 (95% CI, 1.56 to 2.3) in the low-dose group, and 1.34 (95% CI, 1.02 to 1.67) in the vehicle group, with between-group comparisons favoring both active treatments over vehicle (high-dose least squares mean difference versus vehicle, 0.76 [95% CI, 0.26 to 1.27; p=0.007]; low-dose least squares mean difference versus vehicle, 0.67 ([95% CI, 0.16 to 1.18; p=0.01]). The CFS score was determined to be the main driver of changes in the composite score, with much of the remaining impact driven by use of rescue medication. At baseline, the mean CFS was 4.1 in the vehicle group and 4.3 in the 4 times daily group. At month 4, the mean change in CFS score was -1.2 in the vehicle group compared to -2.3 in the 4 times daily, resulting in a treatment difference between the 4 times daily group and vehicle of -1.1. At baseline, the mean itching score was near or at 78 in both groups. At month 4, the mean change in itching score was -25.4 in the vehicle groups compared to -44.1 in the 4 times daily, resulting in a treatment difference between the 4 times daily group and vehicle of -18.7. In general, improvements remained stable during Period 2.

cyclosporine 0.09% solution (Cequa) versus vehicle

Two clinical trials compared cyclosporine 0.09% ophthalmic solution to vehicle for efficacy and safety in 304 patients with keratoconjunctivitis sicca.[86,87,88] Patients were treated with 1 drop in both eyes twice daily. After 84 days in both studies, approximately 17% of cyclosporine-treated patients experienced

increases of ≥ 10 mm from baseline in Schirmer wetting compared to about 9% of vehicle-treated patients (Study 1: treatment difference, 8.2%; 95% confidence interval [CI], 1.9 to 14.6; p<0.01; and Study 2: treatment difference, 7.3%; 95% CI, 3.3 to 11.3; p<0.01).

lifitegrast (Xiidra) versus vehicle

Four, 12-week, randomized, double-masked, vehicle-controlled, multicenter trials demonstrated the efficacy and safety of lifitegrast in DED (n = 1,181).[89,90,91,92] Study 1, a dose-finding study, also included additional concentrations that are not commercially available; Study 1, which is a phase 2 trial, is not included in this review.[93] Study 2 (OPUS-1) and Study 3 (OPUS-2), both phase 3 trials, have also been published, but Study 4 has not been published. In all trials, patients with DED were randomized 1:1 to lifitegrast or vehicle twice daily. Use of artificial tears was not allowed. The mean age in all trials was 59 years (range, 19 to 97) and 76% were female. At each visit, patients rated their Eye Dryness Score (EDS) using a visual analog scale (VAS; 0 = no discomfort, 100 = maximum discomfort). Inferior Fluorescein Corneal Staining Score (ICSS) was also recorded at each visit (range, 0 [no staining] to 4 [coalescent]). At baseline, EDS scores ranged from 40 to 70 while mean ICSS scores ranged from 1.8 to 2.4. In Study 2, the difference in EDS at day 84 between vehicle and lifitegrast was -4.7 (95% CI, -8.9 to -0.4) and the difference in ICSS at day 84 between vehicle and lifitegrast was -0.23 (95% CI, -0.36 to -0.1). In Study 3, the difference in EDS at day 84 between vehicle and lifitegrast was -12.3 (95% CI, -16.4 to -8.3) and the difference in ICSS at day 84 between vehicle and lifitegrast was -0.03 (95% CI, -0.16 to 0.1). In Study 4, the difference in EDS at day 84 between vehicle and lifitegrast was -7.5 (95% CI, -11.6 to -3.5) and the difference in ICSS at day 84 between vehicle and lifitegrast was -0.17 (95% CI, -0.3 to -0.03). Thus, a statistically significant difference was found between vehicle and lifitegrast in EDS in all 3 trials and in ICSS in 2 of 3 trials.

loteprednol (Eysuvis) versus vehicle

Safety and efficacy of loteprednol were evaluated in 4 double-masked, placebo-controlled trials that enrolled approximately 2,900 patients with dry eye disease.[94] Patients were randomized 1:1 to loteprednol 0.25% administered 4 times daily or placebo for 2 weeks. The primary endpoint of daily ocular discomfort severity (ODS) was assessed using a patient-rated visual analog scale (0 = very mild, 100 = very severe). At day 15, patients who received loteprednol experienced a greater reduction from baseline in ocular discomfort (ODS) compared to those given placebo (ODS difference based on least square means and 2-sided confidence intervals [95% CI]: Study 1, -5.27 [-10.52 to -0.03]; Study 2, -5.43 [-7.92 to -2.95]; Study 3, -1.87 [-4.3 to +0.55]; Study 4, -4.67 (-7.08 to -2.26]). In addition, in all 4 trials, a larger reduction in conjunctival hyperemia from baseline, measured using the Cornea and Contact Lens Research Unit (CCLRU) grading scale (0=none, 4=severe) at day 15, was report with loteprednol compared to placebo (hyperemia difference based on least square means and 2-sided confidence interval [95% CI]: Study 1, -0.26 [-0.45 to -0.07]; Study 2, -0.25 [-0.33 to -0.18]; Study 3, -0.16 [-0.23 to -0.09]; Study 4, -0.18 [-0.24 to -0.12]).

varenicline nasal spray (Tyrvaya) versus vehicle

ONSET-1 (n=182; NCT03636061; phase 2) and ONSET-2 (n=758; NCT04036292; phase 3) were multicenter, randomized, double-blind, vehicle-controlled trials that supported efficacy of varenicline nasal spray for approval for DED. [95,96,97] In ONSET-1, patients were randomized 1:1:1:1 to varenicline 0.006 mg, varenicline 0.03 mg, varenicline 0.06 mg, or vehicle as 1 spray in each nostril twice daily. In

ONSET-2, patients were randomized 1:1:1 to varenicline 0.03 mg, varenicline 0.06 mg, or vehicle as 1 spray in each nostril twice daily. In both trials, the majority of patients (74%) were female, the mean age was 61 years, the mean baseline anesthetized Schirmer's core was 5 mm (ONSET-1) and 5.1 mm (ONSET-2), and the mean baseline eye dryness score (EDS) in the combined group was 59.3. The primary endpoint was the percentage of patients who achieved ≥ 10 mm increase in Schirmer's score from baseline. At 28 days in ONSET-1, 52% of patients treated with varenicline 0.03 mg in each nostril twice daily compared to 14% of those treated with placebo achieved the primary endpoint (proportion difference, 38%; 95% confidence interval [CI], 21 to 56; p<0.01). At 28 days in ONSET-2, 47% of those treated with varenicline 0.03 mg in each nostril twice daily compared to 28% of those treated with placebo achieved the primary endpoint (proportion difference, 20%; 95% CI, 11 to 28; p<0.01). At 28 days in ONSET-1, the mean change in Schirmer's score in those treated with varenicline 0.03 mg in each nostril twice daily was 11.7 mm compared to 3.2 mm in those treated with placebo. At 28 days in ONSET-2, the mean change in Schirmer's score in those treated with varenicline 0.03 mg in each nostril twice daily was 11.3 mm compared to 6.3 mm in those treated with placebo.

SUMMARY

Dry eye disease (DED), also known as dry eye syndrome and keratoconjunctivitis sicca, is related to either decreased tear volume (aqueous deficient dry eyes) or rapid evaporative loss (evaporative dry eyes) due to poor tear quality. Both of these conditions may be present as well. The role in therapy, or indication, of lifitegrast (Xiidra) is highly similar to that of topical cyclosporine 0.05% emulsion (Restasis, Restasis Multidose) and cyclosporine 0.09% solution (Cequa). However, lifitegrast is approved for both the signs and symptoms of DED, while both cyclosporine formulations are approved to enhance tear production and cyclosporine 0.05% emulsion (Restasis, Restasis Multidose) is also indicated to treat inflammation associated with DED. Loteprednol (Eysuvis) is an ocular corticosteroid approved specifically for the short-term (up to 2 weeks) treatment of the signs and symptoms of DED. Varenicline nasal spray (Tyrvaya) is a partial nicotinic acetylcholine receptor agonist approved for treatment of the signs and symptoms of DED in adults. It offers an alternative mechanism of action and route of administration from other products approved for DED.

Vernal keratoconjunctivitis (VKC) is a type of ocular allergy that causes chronic bilateral conjunctivitis and is frequently associated with significant risk of progressive corneal damage, which can result in vision loss. Cyclosporine ophthalmic emulsion (Verkazia) is the first FDA-approved topical immunomodulator treatment for VKC and provides a treatment option for those not responding to first-line therapies (e.g., topical and oral antihistamines, topical mast cell stabilizers, topical corticosteroids).

Significant adverse effects are similar between cyclosporine (Cequa, Restasis, Restasis Multidose, Verkazia), lifitegrast (Xiidra), and loteprednol (Eysuvis). These adverse effects primarily include ocular burning, irritation, or pain upon instillation. In contrast, adverse effects of varenicline nasal spray (Tyrvaya) include sneezing, cough, throat irritation, and instillation-site irritation. No clinical trials have been published comparing any of the agents in this review, but all have demonstrated efficacy against vehicle. Topical cyclosporine (Cequa, Restasis, Restasis Multidose) may take up to 4 to 6 weeks to demonstrate benefit. Published clinical trials of lifitegrast, varenicline nasal spray (Tyrvaya), and topical cyclosporine (Verkazia) evaluated outcomes primarily at 12 weeks, 4 weeks, and 4 months, respectively; it is unknown if clinically significant improvements may occur sooner. In clinical trials, improvement in DED with loteprednol was reported at day 15.

Clinical practice guidelines recommend topical cyclosporine or lifitegrast for moderate and severe dry eye syndrome, in addition to other treatment measures. Loteprednol (Eysuvis), varenicline nasal spray (Tyrvaya), and cyclosporine (Verkazia) were not available at the time of the clinical practice guidelines publishing.

REFERENCES

1 Restasis [package insert]. Irvine, CA; Allergan; July 2017.
2 Restasis Multidose [package insert]. Irvine, CA; Allergan; October 2016.
3 Verkazia [package insert]. Emeryville, CA; Santen; June 2021.
4 Cequa [package insert]. Cranbury, NJ; Sun; September 2019.
5 Xiidra [package insert]. Lexington, MA; Shire; June 2020.
5 Eysuvis [package insert]. Watertown, MA; Kala; October 2020.
7 Tyrvaya [package insert]. Princeton, NJ; Oyster Point Pharma; October 2021.
8 Cequa FDA approval letter. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/210913Orig1s000Approv.pdf. Accessed April 8, 2022
9 Eysuvis FDA approval letter. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2020/210933Orig1s000ltr.pdf. Accessed April 8, 2022.
10 Department of Health and Human Services. FDA. Abbreviated new drug applications and 505(b)(2) applications. September 2016. Available at: https://www.fda.gov/downloads/Drugs/Guidances/ucm079345.pdf. Accessed April 8, 2022..
11 Verkazia FDA approval letter. Available at: https://www.verkazia.com/pdf/Verkazia-Press-Release.pdf. Accessed April 11, 2022.
12 Foster S, Dahl AA. Dry Eye Disease (Keratoconjunctivitis Sicca). Practice Essentials. Updated January 3, 2022. Available at: http://emedicine.medscape.com/article/1210417-overview. Accessed April 8, 2022.
13 Foster S, Dahl AA. Dry Eye Disease (Keratoconjunctivitis Sicca). Epidemiology. Updated January 3, 2022. Available at: http://emedicine.medscape.com/article/1210417-overview. Accessed April 8, 2022.
14 Keratoconjunctivitis Sicca. Available at: https://www.merckmanuals.com/professional/eye-disorders/corneal-disorders/keratoconjunctivitis-sicca. Accessed April 8, 2022.
15 Keratoconjunctivitis Sicca. Updated May 2020. Available at: https://www.merckmanuals.com/professional/eye-disorders/corneal-disorders/keratoconjunctivitis-sicca. Accessed April 8, 2022.
16 Keratoconjunctivitis Sicca. Updated May 2020. Available at: https://www.merckmanuals.com/professional/eye-disorders/corneal-disorders/keratoconjunctivitis-sicca. Accessed April 8, 2022.
17 Keratoconjunctivitis Sicca. Updated May 2020. Available at: https://www.merckmanuals.com/professional/eye-disorders/corneal-disorders/keratoconjunctivitis-sicca. Accessed April 8, 2022.
18 Foster S, Dahl AA. Dry Eye Disease (Keratoconjunctivitis Sicca). Treatment. Updated January 3, 2022. Available at: http://emedicine.medscape.com/article/1210417-overview. Accessed April 8, 2022.
19 Drugs for some common eye disorders. The Medical Letter. 2019; 61(1586): 187-194.
20 Lifitegrast (Xiidra) for dry eye disease. Med Lett Drugs Ther. 2016; 58(1502): 110-111.
21 American Academy of Ophthalmology Cornea/External Disease Panel. Preferred Practice Pattern Guidelines. Dry eye syndrome. San Francisco, CA: American Academy of Ophthalmology (AAO); 2018. Available at: https://www.aao.org/guidelines-browse. Accessed April 8, 2022.
22 American Academy of Ophthalmology Cornea/External Disease Panel. Cornea/External Disease Summary Benchmark. San Francisco, CA: American Academy of Ophthalmology (AAO); 2021. Available at: https://www.aao.org/guidelines-browse. Accessed April 8, 2022.
23 Leonardi A. Management of vernal keratoconjunctivitis. Ophthalmol Ther. 2013 Dec;2(2):73-88. Available at: https://pubmed.ncbi.nlm.nih.gov/25135808. Accessed April 11, 2022.
24 P Vichyanond, PPacharn, U Pleyer, et al. Vernal keratoconjunctivitis: A severe allergic eye disease with remodeling changes. Pediatric Allergy and Immunology Volume 25, Issue 4 p. 314-322. Available at: https://doi.org/10.1111/pai.12197. Accessed April 11, 2022.
25 Allergic conjunctivitis. Updated October 8, 2019. Available at: https://emedicine.medscape.com/article/1191467-overview. Accessed April 12, 2022.
26 Cequa [package insert]. Cranbury, NJ; Sun; September 2019.
27 Restasis [package insert]. Irvine, CA; Allergan; July 2017.
28 Restasis Multidose [package insert]. Irvine, CA; Allergan; October 2016.
29 Xiidra [package insert]. Lexington, MA; Shire; June 2020.
30 Eysuvis [package insert]. Watertown, MA; Kala; October 2020.
31 Tyrvaya [package insert]. Princeton, NJ; Oyster Point Pharma; October 2021.
32 Verkazia [package insert]. Emeryville, CA; Santen; June 2021.
33 Drugs for some common eye disorders. The Medical Letter. 2019; 61(1586): 187-194.
34 Lifitegrast (Xiidra) for dry eye disease. Med Lett Drugs Ther. 2016; 58(1502): 110-111.
35 NCT01751126. ClinicalTrials.gov. Available at: https://clinicaltrials.gov/ct2/home. Accessed April 12, 2022.
36 NCT00328653. ClinicalTrials.gov. Available at: https://clinicaltrials.gov/ct2/home. Accessed April 12, 2022.
37 Cequa [package insert]. Cranbury, NJ; Sun; September 2019.
38 Restasis [package insert]. Irvine, CA; Allergan; July 2017.
39 Restasis Multidose [package insert]. Irvine, CA; Allergan; October 2016.
40 Xiidra [package insert]. Lexington, MA; Shire; June 2020.
41 Eysuvis [package insert]. Watertown, MA; Kala; October 2020.

42 Tyrvaya [package insert]. Princeton, NJ; Oyster Point Pharma; October 2021.
43 Verkazia [package insert]. Emeryville, CA; Santen; June 2021.
44 Cequa [package insert]. Cranbury, NJ; Sun; September 2019.
45 Restasis [package insert]. Irvine, CA; Allergan; July 2017.
46 Restasis Multidose [package insert]. Irvine, CA; Allergan; October 2016.
47 Xiidra [package insert]. Lexington, MA; Shire; June 2020.
48 Eysuvis [package insert]. Watertown, MA; Kala; October 2020.
49 Tyrvaya [package insert]. Princeton, NJ; Oyster Point Pharma; October 2021.
50 Verkazia [package insert]. Emeryville, CA; Santen; June 2021.
51 Cequa [package insert]. Cranbury, NJ; Sun; September 2019.
52 Restasis [package insert]. Irvine, CA; Allergan; July 2017.
53 Restasis Multidose [package insert]. Irvine, CA; Allergan; October 2016.
54 Xiidra [package insert]. Lexington, MA; Shire; June 2020.
55 Eysuvis [package insert]. Watertown, MA; Kala; October 2020.
56 Tyrvaya [package insert]. Princeton, NJ; Oyster Point Pharma; October 2021.
57 Verkazia [package insert]. Emeryville, CA; Santen; June 2021.
58 Cequa [package insert]. Cranbury, NJ; Sun; September 2019.
59 Restasis [package insert]. Irvine, CA; Allergan; July 2017.
60 Restasis Multidose [package insert]. Irvine, CA; Allergan; October 2016.
61 Xiidra [package insert]. Lexington, MA; Shire; June 2020.
62 Eysuvis [package insert]. Watertown, MA; Kala; October 2020.
63 Tyrvaya [package insert]. Princeton, NJ; Oyster Point Pharma; October 2021
64 Verkazia [package insert]. Emeryville, CA; Santen; June 2021.
65 Cequa [package insert]. Cranbury, NJ; Sun; September 2019.
66 Restasis [package insert]. Irvine, CA; Allergan; July 2017.
67 Restasis Multidose [package insert]. Irvine, CA; Allergan; October 2016.
68 Xiidra [package insert]. Lexington, MA; Shire; June 2020.
69 Eysuvis [package insert]. Watertown, MA; Kala; October 2020.
70 Tyrvaya [package insert]. Princeton, NJ; Oyster Point Pharma; October 2021.
71 Verkazia [package insert]. Emeryville, CA; Santen; June 2021.
72 Cequa [package insert]. Cranbury, NJ; Sun; September 2019.
73 Restasis [package insert]. Irvine, CA; Allergan; July 2017.
74 Restasis Multidose [package insert]. Irvine, CA; Allergan; October 2016.
75 Available at: http://www.clinicalpharmacology-ip.com/default.aspx. Accessed April 8, 2022.
76 Xiidra [package insert]. Lexington, MA; Shire; June 2020.
77 Eysuvis [package insert]. Watertown, MA; Kala; 2020.
78 Tyrvaya [package insert]. Princeton, NJ; Oyster Point Pharma; October 2021.
79 Verkazia [package insert]. Emeryville, CA; Santen; June 2021.
80 Restasis [package insert]. Irvine, CA; Allergan; July 2017.
81 Sall K, Stevenson OD, Mundorf TK, et al. Two multicenter, randomized studies of the efficacy and safety of cyclosporine ophthalmic emulsion in moderate to severe dry eye disease. CsA Phase 3 Study Group. Ophthalmology. 2000; 107(4):631-639.
82 NCT01751126. ClinicalTrials.gov. Available at: https://clinicaltrials.gov/ct2/home. Accessed April 12, 2022.
83 NCT00328653. ClinicalTrials.gov. Available at: https://clinicaltrials.gov/ct2/home. Accessed April 12, 2022.
84 Leonardi A, Doan S, Amrane M, et al for the VEKTIS Study Group. A randomized, controlled trial of cyclosporine A cationic emulsion in pediatric vernal keratoconjunctivitis: the VEKTIS study. Ophthalmology. 2019;126(5):671-681. DOI: 10.1016/j.ophtha.2018.12.027.
85 Bremond-Gignac D, Doan S, Amrane M, et al for the VEKTIS study group. Twelve-month results of cyclosporine A cationic emulsion in a randomized study in patients with pediatric vernal keratoconjunctivitis. Am J Ophthalmol. 2020;212:116-126. DOI: 10.1016/j.ajo.2019.11.020.
86 Cequa [package insert]. Cranbury, NJ; Sun; September 2019.
87 Clinical trial NCT 02254265. Available at: https://clinicaltrials.gov/ct2/show/results/NCT02254265. Accessed April 8, 2022.
88 Clinical trial NCT 02688556. Available at: https://clinicaltrials.gov/ct2/show/record/NCT02688556. Accessed April 8, 2022.
89 Xiidra [package insert]. Lexington, MA; Shire; June 2020.
90 Semba CP, Torkildsen GL, Lonsdale JD, et al. A phase 2 randomized, double-masked, placebo-controlled study of a novel integrin antagonist (SAR 1118) for the treatment of dry eye. Am J Ophthalmol. 2012; 153(6): 1050-1060. DOI: 10.1016/j.ajo.2011.11.003.
91 Sheppard JD, Torkildsen GL, Lonsdale JD, et al. Lifitegrast ophthalmic solution 5.0% for treatment of dry eye disease: results of the OPUS-1 phase 3 study. Ophthalmology. 2014; 121(20: 475-483. DOI: 10.1016/j.ophtha.2013.09.015.
92 Tauber J, Karpecki P, Latkany R, et al. Lifitegrast ophthalmic solution 5.0% versus placebo for treatment of dry eye disease: results of the randomized, phase III OPUS-2 study. Ophthalmology. 2015; 122(12): 2423-2431. DOI: 10.1016/j.ophtha.2015.08.001.
93 Semba CP, Torkildsen GL, Lonsdale JD, et al. A phase 2 randomized, double-masked, placebo-controlled study of a novel integrin antagonist (SAR 1118) for the treatment of dry eye. Am J Ophthalmol. 2012; 153(6): 1050-1060. DOI: 10.1016/j.ajo.2011.11.003.
94 Eysuvis [package insert]. Watertown, MA; Kala; 2020.
95 Tyrvaya [package insert]. Princeton, NJ; Oyster Point Pharma; October 2021
96 NCT03636061. ClinicalTrials.gov. Available at: https://clinicaltrials.gov/ct2/home. Accessed April 8, 2022.
97 NCT04036292. ClinicalTrials.gov. Available at: https://clinicaltrials.gov/ct2/home. Accessed April 8, 2022.