Supplement to
AOC
Advanced Ocular Care

November/December 2015

OCULAR THERAPEUTICS

CRITICAL UPDATES

THE STATE OF THE ART

THE STATE OF THE SCIENCE | 2.0

CE ACTIVITY

Supported by an unrestricted educational grant from Allergan, Inc.

evolve medical education

A CE activity jointly sponsored by Evolve Medical Education LLC and *Advanced Ocular Care*, and supported by an unrestricted educational grant from Allergan, Inc.

The State of the Art and the State of the Science 2.0

Ocular therapeutics in the treatment of ocular disease: critical updates.

Jointly sponsored by Evolve Medical Education LLC and Advanced Ocular Care.
Supported by an unrestricted educational grant from Allergan.

COPE Course ID: 47482-GO
Expiration Date: Dec. 9, 2018
This course is COPE approved for 2 credits.

CONTENT SOURCE

This COPE Accredited activity captures content from interviews with key opinion leaders in the field of optometry.

STATEMENT OF NEED

Identification of Educational Gap

Optometrists face increasing pressure to remain current in their clinical knowledge, diagnostic skills, and selection of therapeutic options due to a number of important factors. Shifts in population demographics, access to care, and the increasing number of aging patients will continue to have significant implications for the delivery of modern eye care for years to come. As population changes lead to shifts in ocular disease prevalence, ophthalmic development in pharmaceuticals and new medical device technology continues to change the treatment strategies available to optometrists. As an example, Tsontcho Ianchulev, MD, noted during the March 2010 Innovative Glaucoma Surgery Symposium that he had identified 548 ongoing clinical research studies, including 24 device studies and 198 studies in the active recruitment phase for glaucoma treatment.[1] The coordinated management of dry eye disease therapy, including preoperative and post-surgical attention to the ocular surface, can be a significant factor in patient satisfaction. Knowledge of the ocular surface impact of pharmaceuticals and surgical techniques is a continual process as new options are studied. Bielory and O'Brien also noted the importance of ocular allergy diagnosis and treatment in candidates for laser corneal refractive surgery.[2] Investigators have also found that ocular allergy is frequently underdiagnosed prior to elective eye surgery and perhaps underreported as the cause for poor outcomes in patients that suffer from dry eye following refractive surgery.[3] Key aspects in improving the effective delivery of ocular disease treatments include expanding the diagnostic skills of clinicians, as well as the awareness of patient symptoms and available treatment options.

Additionally, in a review of past Dulaney Foundation medical education activity feedback, fewer than 40% of glaucoma experts responding were aware of the prevalence of ocular surface disease among glaucoma patients being treated with topical IOP-lowering medications. Clearly, the ocular surface plays a key role in all areas of patient satisfaction when implementing other disease therapies or managing preoperative and postoperative surgical care.

Patient compliance with prescribed therapies remains a significant barrier to effective treatment in many areas of ocular disease, especially in glaucoma management, where failure can lead to the permanent loss of vision. In fact, new research in the journal *Ophthalmology* involving glaucoma medical therapy adherence and visual field defects demonstrated that patients "who were less than 80% adherent, according to the MEMS devices, were significantly more likely to have worse defect severity."[4]

The issue of patient adherence to medical therapy is a key aspect of improving patient outcomes in all areas of ocular disease management. Addressing these gaps in education relative to the burden of ocular disease is an important part of improving the delivery of effective care and improving the ocular health of the population.

Assessment of Educational Need

Due to the increased attention given to the medical needs of our aging population, the efforts to contain increasing medical costs, and the need to improve the efficient delivery of care, we continue to learn more about the current and future burden of ocular disease. According to several key papers[5,6] published in 2004 by the Eye Diseases Prevalence Research Group, the number of people in the United States with cataract is projected to rise to more than 30 million by the year 2020, and the number of open angle glaucoma cases will increase by 50%. Glaucoma is the leading cause of preventable blindness and at least 3 million Americans have the disease, according to the American Glaucoma Society.[7] Given the rapid increase in the aging population, as well as increases in groups at high risk for glaucoma, the burden of disease related to this condition becomes more significant each year.[8]

The Centers for Medicare & Medicaid Services (CMS) recognizes the following as high risk groups for glaucoma:[9]

- individuals with diabetes mellitus
- individuals with a family history of glaucoma
- African Americans aged 50 and older
- Hispanic Americans aged 65 and older

A report by Rosario and Bielory[10] determined that while the prevalence of allergic conjunctivitis in older population studies was 15% to 20%, current estimates may be as high as 40%. They also noted the high comorbidity of ocular allergy, rhinitis, and asthma. Similarly, ocular surface disease continues to be an increasing issue for many patients, especially in older patients that may have additional needs for ocular surgery for cataracts or retinal degenerative disease.[11,12] In August 2011, a poll by *Review of Ophthalmology* discussed how improved familiarity with clinical trials reporting and critical analysis of outcomes should improve the implementation of new techniques into clinical practice.[13] Understanding the near to market ocular therapeutics in the pipeline is a key element of coordinating the needs of a patient with the available clinical strategies. Possession of this knowledge can have a direct impact on optometrists' ability to more effectively communicate with patients and address their expectations. A thorough education program consisting of expert opinions and recent clinical evidence can serve as a valuable means of education for the target audience.

The use of current practice pattern reviews, ophthalmic therapeutic discussions, and clinical case examples that demonstrate treatment decision-making plans can effectively deliver key program learning points and take home messages designed to immediately impact patient care.

1. Ianchulev S. Clinical trial design. Paper presented at: The Innovative Glaucoma Surgery Symposium; March 3, 2010; Naples, FL.
2. Bielory BP, O'Brien TP. Allergic complications with laser-assisted in-situ keratomileusis. *Curr Opin Allergy Clin Immunol*. 2011;11(5):483-491.
3. Li XM, Hu L, Hu J, Wang W. Investigation of dry eye disease and analysis of the pathogenic factors in patients after cataract surgery. *Cornea*. 2007;26(9 suppl 1):S16-S20.
4. Sleath B, Blalock S, Covert D, et al. The relationship between glaucoma medication adherence, eye drop technique, and visual field defect severity. *Ophthalmology*. 2011;118(12):2398-2402.
5. Congdon N, Vingerling JR, Klein BE, et al; Eye Diseases Prevalence Research Group. Prevalence of cataract and pseudophakia/aphakia among adults in the United States. *Arch Ophthalmol*. 2004;122(4):487-494.
6. Friedman DS, Wolfs RC, O'Colmain BJ, et al; Eye Diseases Prevalence Research Group. Prevalence of open-angle glaucoma among adults in the United States. *Arch Ophthalmol*. 2004;122(4):532-538.
8. American Glaucoma Society. Frequently asked questions. Available at: http://www.americanglaucomasociety. net/patients/faqs. Accessed October 3, 2013.
9. Fiscella RG, Lee J, Davis EJ, et al. Cost of illness of glaucoma: a critical and systematic review. *Pharmacoeconomics*. 2009;27(3):189-198.
10. Centers for Medicare & Medicaid Servies (CMS). Available at: http://www.cms.gov/MLNProducts/downloads/ jan_glaucoma.pdf. Accessed October 3, 2013.
11. Rosario N, Bielory L. Epidemiology of allergic conjunctivitis. *Curr Opin Allergy Clin Immunol*. 2011;11(5):471- 476.
12. Galor A, Feuer W, Lee DJ, et al. Prevalence and risk factors of dry eye syndrome in a United States veterans affairs population. *Am J Ophthalmol*. 2011;152(3):377-384.e2.
13. Poll about clinical trials. *Review of Ophthalmology*. Available at: http://www.revophth.com/e-newsletters/rponlinenl/c/29982/. Accessed October 3, 2013.

TARGET AUDIENCE

This certified CE activity is designed for optometrists.

LEARNING OBJECTIVES

Upon completion of this activity, participants should be able to:

- properly diagnose external infectious and inflammatory eye disease
- discuss lid disease therapies and perioperative treatment strategies
- assess chronic conditions such as ocular surface disease and ocular allergies
- discuss current and emerging ocular allergy treatment options
- describe effective perioperative management of ocular surface disease
- interpret glaucoma diagnostic techniques
- incorporate current glaucoma therapeutics and address patient compliance
- explain effective combined surgical and medical glaucoma management
- describe key aspects of corneal and cataract surgery comanagement
- recognize new agents in the pipeline and off label indications for emerging agents.

METHOD OF INSTRUCTION

Participants should read the CE activity in its entirety. After reviewing the material, please complete the self-assessment test, which consists of a series of multiple-choice questions. To answer these questions online and receive real-time results, please visit www.evolvemeded.com and click "Online Courses." Upon completing the activity, and achieving a passing score of higher than 70% on the self-assessment test, you may print out a CE credit letter awarding. The estimated time to complete this activity is 1 hour.

FACULTY CREDENTIALS

Derek Cunningham, OD, Lead Faculty
Director of Optometry and Research
Dell Laser Consultants
Austin, Texas

Nicholas Colatarella, OD
Owner and Medical Director, PineCone Vision Center
Sartell, Minnesota

Mark Dunbar, OD, FAAO
Bascom Palmer Eye Institute
University of Miami, Miller School of Medicine
Miami, Florida

Whitney Hauser, OD
Founder,
Signal Ophthalmic Consulting
Memphis, Tennessee

Milton Hom, OD
Private practice
Azusa, California

Michael McFarland, OD
Vold Vision
Fayetteville, Arkansas

Justin Schweitzer, OD, FAAO
Cornea, Glaucoma, Cataract and Refractive Surgery Specialist
Vance Thompson Vision
Sioux Falls, South Dakota

Jeffrey Varanelli, OD, FAAO, Diplomate ABO, ABCMO
Optometrist
Simone Eye Center
Warren, Michigan

Walter O. Whitley, OD, MBA, FAAO
Director of Optometric Services, Virginia Eye Consultants
Norfolk, Virginia

FACULTY/STAFF DISCLOSURES

Nicholas Colatarella, OD, has had a financial agreement or affiliation during the past year with Allergan; Bio-Tissue; BioD LLC; and Katena/IOP Ophthalmics.

Derek Cunningham, OD, has had a financial agreement or affiliation during the past year with Abbott Medical Optics; Advanced Tear Diagnostics; Alcon Nutrition; Allergan; Artic Dx; Bausch + Lomb; Bio-Tissue; Glasses Off; Lumenis; Marco; Optovue; and TearLab.

Mark Dunbar, OD, has had a financial agreement or affiliation during the past year with Allergan; Alcon Nutrition; Artic DX; and Carl Zeis Meditec.

Whitney Hauser, OD, has had a financial agreement or affiliation during the past year with Allergan and Shire.

Milton Hom, OD, has had a financial agreement or affiliation during the past year with Allergan and Shire.

Michael McFarland, OD, has had no relevant financial agreements or affiliations during the past year.

Justin Schweitzer, OD, has had a financial agreement or affiliation during the past year with Allergan and Glaukos Corporation.

Jeffrey R. Varanelli, OD, FAAO, has had a financial agreement or affiliation during the past year with Allergan; Bio-Tissue; BioD LLC; Johnson & Johnson Vision Care; and Katena IOP Ophthalmics.

Walter O. Whitley, OD, MBA, FAAO, has had a financial agreement or affiliation during the past year with Alcon; Allergan; Beaver Visitec; Bio-Tissue; Shire; TearLab; TearScience; and Valeant.

All of those involved in the planning, editing, and peer review of this educational activity report no relevant financial relationships.

DISCLOSURE POLICY

In accordance with the disclosure policies of the Evolve Medical Education LLC and *Advanced Ocular Care*, anyone in a position to affect the content of a CE activity is required to disclose to the activity participants (1) the existence of any financial interest or other relationships with the manufacturers of any commercial products/devices or providers of commercial services, and (2) identification of a commercial product/device that is unlabeled for use or an investigational use of a product/device not yet approved.

DISCLAIMER

The views and opinions expressed in this educational activity are those of the faculty and do not necessarily represent the views of Allergan, Evolve Medical Education LLC, and *Advanced Ocular Care*. ■

Per a restructuring of The Dulaney Foundation, effective Nov. 30, 2015, all CE operations are being provided by Evolve Medical Education LLC, a Pennsylvania for-profit corporation.

OCULAR THERAPEUTICS

Welcome to *Ocular Therapeutics: The State of the Art and the State of the Science 2.0*. This supplement highlights critical new developments to the medical treatment of dry eye disease, ocular allergy, and recurrent corneal erosion syndrome. It also covers the use of perioperative pharmaceuticals, glaucoma agents, and retina therapies, as well as a dive into the pipeline of ophthalmic drugs in development.

This guide is an update to the original CE activity *Ocular Therapeutics: The State of the Art and the State of the Science* that was included as a supplement to the October 2013 edition of *Advanced Ocular Care*. Download the complete guide as an app, available for free from the iTunes app store and Google Play (search *Ocular Therapeutics Guide*).

Available on the App Store

Get it on Google play

CONTENTS

AOC
Advanced Ocular Care

Antiinflammatory Therapies in the Treatment of Dry Eye Disease

Established treatments and new approaches can aid patients.

BY JEFFREY R. VARANELLI, OD, AND NICHOLAS COLATRELLA, OD


The term ocular surface disease can be used to describe any anomaly that affects the lids, conjunctiva, tear film, or cornea. It encompasses a variety of conditions including dry eye disease (DED), meibomian gland dysfunction (MGD), blepharitis, rosacea, allergies, and many others. This article focuses on anti-inflammatory therapies for the treatment of DED, briefly reviews a the mainstays of treatment, and touches on some future therapies.

DED can be as rewarding to treat as it is challenging to manage. The optometrist's role as a primary eye care provider should be to accurately diagnose, appropriately treat, and continually manage patients with DED. Inflammation is present in DED at all levels of severity.[1] In-office tests such as the TearLab Osmolarity System (TearLab) and InflammaDry (Rapid Pathogen Screening) can help detect and confirm the presence of inflammatory markers. The results of these objective diagnostic modalities, in addition to other clinical tests, can guide treatment choices.

According to recommendations from the 2014 Dry Eye Summit, basic management strategies should include ocular lubrication, lid hygiene, and nutrition, followed by antiinflammatories.[2]

NONTHERAPEUTIC TREATMENTS

Lid Hygiene, Environmental and Habitual Modifications

MGD is believed to be one of the leading cause of dry eyes, present in more than 80% of cases.[3] Use of lid scrubs and lid massage has been shown to improve tear breakup time.[4] When coupled with heat, these treatments may help clear and prevent clogging of the meibomian gland openings. Modification of home or work environments may also be useful in managing DED. Increasing moisture levels by using a humidifier at night and limiting exposure to forced or moving air (eg, ceiling fans, air conditioner vents) can also be beneficial.[1]

Essential Fatty Acids

Essential fatty acids are known to exhibit antiinflammatory properties; however, an appropriate ratio of omega-6 and omega-3 fatty acids is necessary to gain a benefit (a range of 1:1 to 5:1 is thought to be optimal). In a clinical trial, patients given oral linoleic and gamma-linoleic acids (both omega-6 fatty acids) showed significant improvement in symptoms of ocular irritation, as well as in lissamine green staining of the ocular surface, compared with patients receiving placebo.[5]

TOPICAL THERAPIES

Nonpreserved Artificial Tears

Artificial tears are the appropriate first-line agent for many patients with DED. The latest innovations include nanoemulsions, which are designed to adhere longer to the tear film to help reduce tear evaporation without impairing vision.6 These formulations help stabilize the tear film while still lubricating the corneal surface. Retaine (Ocusoft) is an example of a preservative-free artificial tear that contains a cationic oil-in-water nanoemulsion that helps to increase corneal residence time.[7]

Topical Cyclosporine

Topical cyclosporine (Restasis; Allergan) is a mainstay of DED treatment. Studies have shown a reduction in inflammatory cytokines and T-lymphocytes in treated eyes compared with those receiving vehicle.[8-10]

ADVANCED THERAPIES

Topical Corticosteroids

Corticosteroids are standard anti-inflammatory agents for reducing inflammation, including ocular surface disease associated with keratoconjunctivitis sicca (KCS). Studies confirm that topical corticosteroids reduce the signs and symptoms of KCS compared with vehicle.[11] The chronic nature of KCS warrants close monitoring due to the potential side effects associated with long-term steroid use. Numerous ophthalmic topical corticosteroids are commercially available in branded and generic formulations, including prednisolone acetate, dexamethasone, fluorometholone, and loteprednol etabonate.

Tetracyclines

Tetracycline antibiotics are known inhibitors of matrix metalloproteinases.[12] Low-dose doxycycline has been shown

to reduce the level of these inflammatory enzymes, levels of which are elevated in patients with DED. Although an optimal dosing schedule has yet to be established, common practice is to start at 20 to 50 mg twice a day.

Biologic Tear Substitutes

Both autologous serum and umbilical cord serum contain various growth factors and vitamins, as well as extracellular matrix proteins that help maintain the health of the ocular surface.[1] A study by Kojima et al showed significantly greater improvement in symptom scores, tear breakup time, and fluorescein and rose bengal staining in patients with DED receiving autologous serum eye drops compared to control patients using preservative-free artificial tears.[13]

Sutureless Amniotic Membrane

The avascular amniotic membrane tissue, harvested from consenting donors during planned Cesarean section, has inherent properties that make it effective in reducing inflammation and promoting growth factors. Sutureless amniotic membranes have been shown to improve the corneal surface in patients with KCS and in other types of ocular inflammatory conditions such as recurrent corneal erosions, chemical burns, and persistent epithelial defects.[14] Amniotic membrane products for ocular surface applications are available from several sources, including IOP Ophthalmics (AmbioDisk 2 and AmbioDisk5), Bio-Tissue (ProKera), and BioD (BioDOptix).

Secretagogues

Oral and topical secretagogues have been considered as potential therapies for DED patients. Oral cevimiline (Evoxac; Daiichi Sankyo) and pilocarpine (Salagen; Eisai) are indicated for the treatment of symptoms of dry mouth in patients with Sjögren syndrome. In sufficient dosages, these muscarinic agonists can increase secretions from exocrine glands, including the lacrimal gland. Both have been shown to improve ocular signs and symptoms in Sjögren syndrome KCS while improving aqueous tear production.[15-19]

NEW AND FUTURE THERAPIES

Anakinra (Kineret; Biovitrum AB), a recombinant interleukin-1 receptor antagonist (IL1-RA), is an injected drug approved for the treatment of moderate to severe rheumatoid arthritis. Topical 2.5% anakinra can be compounded and used off label for the treatment of DED. A prospective randomized clinical trial of topical 2.5% anakinra three times daily demonstrated a 30% decrease in staining in patients with evaporative DED at 6 weeks and a 46% decrease at 12 weeks.[20]

The systemic immunosuppressive drug tacrolimus is a calcineurin inhibitor that works by inhibiting T and B lymphocyte activation. It has been shown to be effective in improving DED associated with graft-versus-host disease.[21] Topical formulations are available as ointments or compounded eye drops.

Lifitegrast (Shire) is an integrin inhibitor that works by inhibiting T-cell activation. This is accomplished by preventing the binding of two important surface proteins: lymphocyte function-associated antigen-1, or LFA-1, on T cells and intercellular adhesion molecule-1, or ICAM-1, on antigen-presenting cells.[22] The drug's exact mechanism of action is unknown; however, early clinical trial data suggest that it is efficacious and safe in the treatment of DED. Lifitegrast was given priority review status by the US Food and Drug Administration earlier this year, and will have new information submitted to the agency in early 2016 with a potential launch that same year.[23]

CONCLUSION

Treatments for DED have evolved far beyond the use of artificial tears. Recently developed therapies and procedures can help patients achieve significant clinical improvements in both the signs and symptoms of the condition. Staying current on these treatments will allow eye care professionals to successfully manage their patients' OSD by helping to maintain a healthier ocular surface. ■

1. International Dry Eye WorkShop. 2007 report of the International Dry Eye WorkShop (DEWS). *Ocul Surf*. 2007;5:61-204.
2. Improving the screening, diagnosis, and treatment of dry eye disease: expert recommendations from the 2014 Dry Eye Summit. http://bt.e-ditionsbyfry.com/publication/?i=262605. Accessed September 23, 2015.
3. Nichols KK, Foulks GN, Bron AJ, et al. The international workshop on meibomian gland dysfunction: executive summary. *Invest Ophthalmol Vis Sci*. 2011 30;52(4):1922-1929.
4. Blackie C, Korb D. MGD: Getting to the root cause of dry eye. *Review of Optometry*. June 2012:30-39.
5. 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.
6. Lee SY, Tong L. Lipid-containing lubricants for dry eye: a systematic review. *Optom Vis Sci*. 2012;89(11):1654-1661.
7. Lallemand F, Daull P, Benita S, et al. Successfully improving ocular drug delivery using the cationic nanoemulsion, novasorb. *J Drug Deliv*. 2012;2012:604204.
8. 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;42:90-95.
9. Turner K, Pflugfelder SC, Ji Z, et al. Interleukin-6 levels in the conjunctival epithelium of patients with dry eye disease treated with cyclosporine ophthalmic emulsion. *Cornea*. 2000;19:492-496.
10. Kunert KS, Tisdale AS, Stern ME, Smith JA. Analysis of topical cyclosporine treatment of patients with dry eye syndrome: effect on conjunctival lymphocytes. *Arch Ophthalmol*. 2000;118:1489-1496.
11. 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;138:444-457.
12. Dursun D, Kim M, Solomon A, et al. Treatment of recalcitrant recurrent corneal erosions with inhibitors of matrix metalloproteinase-9, doxycycline and corticosteroids. *Am J Ophthalmol*. 2001;132:8-13.
13. 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;139:242-246.
14. Fernandes M, Sridhar MS, Sangwan VS, Rao GN. Amniotic membrane transplantation for ocular surface reconstruction. *Cornea*. 2005;24:643-653.
15. Takaya M, Ichikawa Y, Yamada C, et al. Treatment with pilocarpine hydrochloride for sicca symptoms in Sjogren's syndrome [article in Japanese]. *Ryumachi*. 1997;37(3):453-457.
16. Tsifetaki N, Kitsos G, Paschides CA, et al. Oral pilocarpine for the treatment of ocular symptoms in patients with Sjogren's syndrome: a randomised 12-week controlled study. *Ann Rheum Dis*. 2003;62:1204-1207.
17. Papas AS, Sherrer YS, Charney M, et al. Successful treatment of dry mouth and dry eye symptoms in Sjogren's syndrome patients with oral pilocarpine: a randomized, placebo-controlled, dose-adjustment study. *J Clin Rheumatol*. 2004;4:169-177
18. Petrone D, Condemi JJ, Fife R, et al. Double-blind randomized placebo-controlled study of cevimeline in Sjogren's syndrome patients with xerostomia and keratoconjunctivitis sicca. *Arthritis Rheum*. 2002;46:748-754.
19. Ono M, Takamura E, Shinozaki K, et al. Therapeutic effect of cevimeline on dry eye in patients with Sjogren's syndrome: a randomized, double-blind clinical study. *Am J Ophthalmol*. 2004;138:6-17.
20. Amparo F, Mohammad D, Okanobo A, et al. Topical interleukin 1 receptor antagonist for treatment of dry eye disease: a randomized clinical trial. *JAMA Ophthalmol*. 2013;131(6):715-723.
21. Aoki S, Mizote H, Minamoto A, et al. Systemic FK506 improved tear secretion in dry eye associated with chronic graft versus host disease. *Br J Ophthalmol*. 2005;89:243-244.
22. Sheppard JD, Torkildsen GL, Lonsdale JE, et al; OPUS-1 Study Group. Lifitegrast ophthalmic solution 5.0% for treatment of dry eye disease. Results of the OPUS-1 phase 3 study. *Ophthalmology*. 2014;121(2)475-483.
23. FDA Grants Priority Review to Lifitegrast NDA for Treatment of Dry Eye Disease in Adults [press release]. Lexington, MA: Shire PLC; April 9, 2015. https://www.shire.com/newsroom/2015/april/fda-grants-priority-review-to-lifitegrast-nda-for-treatment-of-dry-eye-disease-in-adults. Accessed September 23, 2015.

Promising DED Pipeline

Numerous agents are under study.

BY WHITNEY HAUSER, OD

Dry eye disease (DED) affects between 10% and 20% of the world's population.[1] Symptoms vary from innocuous to vision threatening, and management can be confounding for both doctors and patients. The multifactorial nature of DED compounds the disease's complexity and poses challenges for treatment.

Although the demand for treatments is high, only a handful of drugs are indicated for this condition. Research and development efforts are trending toward medications that decrease inflammation and increase the production of mucin and tears.[1] More than 20 medications for the treatment of DED are in various phases of clinical investigation. It is hoped that, as a result, many innovative pharmacotherapies will soon emerge to meet the needs of an expanding population of DED suffers.

SEEKING EXPANDED INDICATIONS

Some available drugs are being repurposed for DED care. For example, various topical antiinflammatory agents are routinely used off label to treat DED, and at least two are being investigated for use in this indication.

A phase 2 trial was recently completed evaluating the effectiveness of difluprednate 0.05% (Durezol; Alcon) for reducing ocular symptoms of DED. Difluprednate was dosed twice daily to 726 patients, and the efficacy of this antiinflammatory agent was gauged by measuring ocular discomfort on the visual analog scale.1 There was a low incidence of adverse events and an acceptable safety profile in the phase 2 study.[2]

Similarly, a phase 2 clinical trial of loteprednol etabonate 0.5% (Lotemax; Bausch + Lomb) for the treatment of DED was recently completed. The 4-week, single-center, randomized, double-masked trial compared this topical corticosteroid, dosed three or four times a day, with placebo. Primary endpoints were ocular comfort during controlled adverse environment exposure. Corneal and conjunctival staining and conjunctival redness were also evaluated after exposure. The safety and efficacy study has completed phase 2, but no results have been reported.[3]

NEW CANDIDATES IN THE PIPELINE

Lifitegrast 5% ophthalmic solution (Shire) offers a novel mechanism of action for the treatment of DED. The drug is a small-molecule integrin antagonist that interrupts binding of intercellular adhesion molecule-1, or ICAM-1, to lymphocyte-function associated antigen-1, which is an important step in the activation, recruitment, and migration of T-cells. The drug also abates cytokine release, which causes a decrease in inflammation. Studies show that ICAM-1 is overexpressed in DED patients.4 Unlike Restasis (cyclosporine 0.05%; Allergan), which functions on newly formed T cells, lifitegrast may be effective against existing cells. In a phase 3 clinical trial, statistically significant improvement in signs and symptoms of DEDwere seen with lifitegrast compared with placebo.[5] More adverse events were noted with drug compared with placebo, although none posed a threat to vision. Most commonly noted adverse events were dysgeusia and instillation site irritation. Shire announced in April 2015 that the drug has received priority review designation from the US Food and Drug Administration (FDA). If approved, lifitegrast would be the first drug indicated for treatment of both signs and symptoms of DED.[6]

Sjögren syndrome is a systemic autoimmune disease with ocular symptoms that parallel those of DED. Approximately 4 million Americans have Sjögren syndrome, but only 25% of cases are diagnosed.[7] Symptoms often mirror other autoimmune conditions such as rheumatoid arthritis, lupus, and fibromyalgia. Diagnosis can be further confounded by systemic medications taken by the patient, resulting in an average of 4.7 years for a patient to be properly diagnosed.[7] Sjögren syndrome is characterized by elevated levels of serum B-cell activation factor and consequential B-cell hyperactivity.[1,8] Belimumab (Benlysta; GlaxoSmithKline) is an FDA-approved B lymphocyte stimulator indicated for the treatment of lupus. A 52-week phase 2 trial evaluating the efficacy and safety of belimumab in primary Sjögren syndrome patients reported favorable initial results.[9]

Rituximab (Rituxan; Genentech/Biogen) is another drug FDA approved for systemic diseases that has been investigated in Sjögren patients. Rituxmab targets the origin of B cells and thereby reduces their numbers. The injectable drug was evaluated in an interventional, randomized 24-week study. Global scores of disease, joint pain, fatigue, and dryness (ocular, tracheal, vaginal, and cutaneous) were rated. The primary outcome measure was a reported 30% improvement in two of four assessments.[10] Rituximab is in phase 3 clinical trials for use in DED.[1]

Two monoclonal antibodies FDA approved for treatment of systemic diseases have been compared to each other in DED patients.[11] Secukinumab (Cosentyx; Novartis), approved for the treatment of psoriasis, and canakinumab (Ilarus; Novartis), approved to treat juvenile idiopathic arthritis and other conditions, each selectively inhibit interleukins, the cytokines at the root of many inflammatory diseases. In a randomized, double-masked

interventional study, patients with DED received a single 10-mg/kg intravenous dose of either secukinumab, canakinumab, or placebo. The primary outcome measure was corneal staining at 4 weeks. The cornea was assessed in five zones, central and four quadrants. Secondary assessments included production of tears, tear breakup time, conjunctival redness, Ocular Surface Disease Index (OSDI) changes, the desire to use an artificial tear, and best corrected visual acuity. The study was completed in 2012, but no outcome measures results have been reported.[11]

Another interleukin inhibitor, a topical interleukin-1 receptor blocker (EBI-005; Eleven Biotherapeutics) failed to meet the primary efficacy endpoints in a phase 3 trial in patients with moderate to severe DED.[12] In the trial's coprimary endpoints of total corneal fluorescein staining score and patient-reported discomfort, there were no significant differences between treated patients and those receiving vehicle placebo; however, patients in both groups showed statistically significant improvement from baseline in both measures. The company does not plan to initiate a second phase 3 study in DED but will continue to develop EBI-005 as a treatment for allergic conjunctivitis, based on scientific rationale and positive results seen in a previous phase 2 study for that indication.

Omega-3 and omega-6 polyunsaturated fatty acids act as precursors to eicosanoids. Eicosanoids originating from omega-6 produce proinflammatory effects, whereas those from omega-3 have antiinflammatory functions.[13] Over-the-counter supplements are often recommended for patients with meibomian gland dysfunction and associated decreased lipid layer thickness. An investigation sponsored by the American Society of Cataract and Refractive Surgery Foundation and GlaxoSmithKline evaluated the effects of oral omega-3 ethyl esters (Lovaza; GlaxoSmithKline) on relief of signs and symptoms among patients with DED. The primary outcome measure of this randomized, double-masked, interventional study was subjective relief as measured by OSDI. Secondary outcome measures included tear production (Schimer 1 test), ocular surface irregularity (lissamine green staining), and tear film stability (fluorescein tear breakup time). The initial results confirm the improvemement in DED symptoms with supplementation.[14]

Nerve growth factor is a protein secreted to maintain the development and survival of neurons. Research is focused on its use in treating Alzheimer disease, multiple sclerosis, glaucoma, and other conditions. MIM-D3 (Mimetogen Pharmaceuticals) has demonstrated similar activities to nerve growth factor, and it is being evaluated as an agent to improve the ocular surface and corneal wound healing.[1] In a phase 3 clinical trial, 1% MIM-D3 demonstrated significant improvements in signs and symptoms of DED compared with placebo. In the endpoints of central and total corneal fluorescein staining at week 8, MIM-D3 was superior to placebo. The drug also improved common vision-related symptoms of DED as measured by OSDI. The compound was comfortable and well tolerated. The company has met with the FDA to confirm requirements for the rest of its clinical development plan.[15]

Autologous serum eye drops have been used to improve the health of the ocular surface in patients with severe DED.[16] Now an ophthalmic solution containing recombinant human serum albumin is being assessed in clinical studies for treatment of DED.17 In a phase 1/2 randomized safety and initial efficacy trial, RU-101 (R-Tech Ueno) significantly improved corneal staining score, time-dependently and statistically, at 12 weeks after starting instillation, the primary endpoint of the study. However, no significant difference in the primary endpoint was seen at 12 weeks between patients receiving drug and placebo because the placebo patients improved as well. Results of the study suggested that the compound may be particularly effective in patients with more severe disease. Clinical evaluation is continuing.[17]

There is widespread interest in technologies for sustained release of drugs in ophthalmology, especially in the treatment of chronic conditions such as glaucoma or macular degeneration. A sustained-release drug-eluting dexamethasone punctal plug (OTX-DP; Ocular Therapeutix) is being evaluated in an exploratory phase 2 trial in patients with inflammatory DED. The trial, which started in January, follows on successful results with the drug product in a phase 3 trial in patients after cataract surgery; the sustained-release corticosteroid reduced pain and signs of inflammation significantly better than a placebo punctal plug in postoperative patients.[18]

Another novel formulation of a steroid, a nanotechnology-based formulation of loteprednol etabonate (KP-121; Kala Pharmaceuticals), showed positive results in a phase 2 trial in patients with DED.[19] The company's mucus-penetrating particle is designed to enhance drug exposure to ocular tissue by facilitating penetration through the mucus layer of the tear film. Patients receiving 0.25% KP-121 had significantly better improvement in the primary endpoint of bulbar conjunctival hyperemia at 1 month than those receiving placebo. No statistically significant differences were seen in symptom endpoints, although promising trends were noted. The drug was generally well tolerated. Last year, Kala announced plans to evaluate KP-121 in a phase 2 clinical trial in patients with meibomian gland dysfunction. No results of that trial has been announced.[19]

CONCLUSION

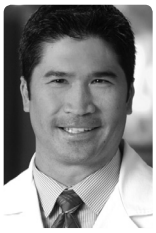
Patients and doctors await innovative therapies offering relief from DED. Although a single magic bullet is unlikely, it is hoped that one or more of the agents described will yield improvements in signs and symptoms of this ocular surface condition. ■

1. Colligris B, Crooke A, Huete-Toral F, Pintor J. An update on dry eye disease molecular treatment: advances in drug pipelines. *Expert Opin Pharmacother.* 2014;15(10):1371-1390.
2. https://clinicaltrials.gov/ct2/show/results/NCT01276223. Accessed September 18, 2015.
3. https://clinicaltrials.gov/ct2/show/NCT00560638. Accessed September 18, 2015.
4. Chen YT, Lazarev S, Bahrami AF, et al. Interleukin-1 receptor mediates the interplay between CD4+ T cells and ocular resident cells to promote keratinizing squamous metaplasia in Sjögren's syndrome. *Lab Invest.* 2012;92(4):556-570.
5. Gebhart F. Lifitegrast promising for patients using artificial tears. *Ophthalmology Times.* June 2014.
6. Salerni T. Lifitegrast heads up dry eye pipeline. Presented at: Ophthalmology Innovation Summit; April 8, 2015; San Diego, CA.
7. Nichols K, Epstein A, Devries D, Mastrota K. Are you missing the early signs of Sjögren's Syndrome? *Optometric Management.* February 2014.
8. Mackay F, Groom JR, Tangye SG. An important role for B-cell activation factor and B cells in the pathogenesis of Sjögren's syndrome. *Curr Opin Rheumatol.* 2007;19(5):406-413.
9. Mariette X, Seror R, Quartuccio L, et al. Efficacy and safety of belimumab in primary Sjögren's syndrome: results of the BELISS open-label phase II study. *Ann Rheum Dis.* 2015;74(3):526-531.
10. Gottenberg JE, Cinquetti G, Larroche C, et al. Efficacy of rituximab in systemic manifestations of primary Sjogren's syndrome: results in 78 patients of the AutoImmune and Rituximab registry. *Ann Rheum Dis.* 2013;72(6):1026-1031.
11. https://clinicaltrials.gov/ct2/show/NCT01250171. Accessed September 18, 2015.
12. Eleven Biotherapeutics Announces Top-Line Results from Pivotal Phase 3 Study of EBI-005 in Patients with Moderate to Severe Dry Eye Disease [press release]. Cambridge, MA: Eleven Biotherapeutics; May 18, 2015.
13. Wall R, Ross RP, Fitzgerald GF, Stanton C. Fatty acids from fish: the anti-inflammatory potential of long-chain omega-3 fatty acids. *Nutr Rev.* 2010;68(5):280-289.
14. https://clinicaltrials.gov/ct2/show/NCT01107964. Accessed September 18, 2015.
15. Mimetogen Pharmaceuticals announces topline results of its second clinical study with MIM-D3 for the treatment of dry eye syndrome [press release]. Gloucester, MA: Mimetogen Pharmaceuticals; September 9, 2014.
16. 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;139:242-246.
17. Completion of a Phase I/II clinical study of recombinant human serum albumin-containing ophthalmic solution (development code: RU-101) in the US for the treatment of severe dry eye [press release]. Tokyo: R-Tech Ueno; November 10, 2014.
18. Ocular Therapeutix reports positive topline clinical data for the first of two phase 3 clinical trials evaluating OTX-DP for the treatment of post-surgical ocular inflammation and pain. [press release]. Bedford, MA: Ocular Therapeutix; March 10, 2015.
19. Kala Pharmaceuticals announces positive results from phase 2 trial of KPI-121 in dry eye disease [press release]. Waltham, MA: Kala Pharmaceuticals Inc.; April 1, 2015.

Current State of the Science in Ocular Allergies

There are many effective agents for this prevalent condition.

BY WALTER O. WHITLEY, OD, MBA, FAAO



Ocular allergies are extremely prevalent. It is estimated that up to 60 million Americans have allergies, and 24 million have ocular symptoms suggestive of ocular allergies.[1] It is the fifth leading chronic disease in the United States and may account for up to 8 million office visits per year and about $5.9 billion in direct costs.[1]

Fortunately for patients, there are very effective agents for the local treatment of ocular allergies. Yet, the management of ocular allergies should not rely solely on empirical treatment, as many of the signs and symptoms crossover with those of common ocular surface disease states, such as dry eye disease (DED) and blepharitis. In fact, the correct management of ocular allergy starts with the proper diagnosis, which includes an appropriate use of testing and encompasses a graduated approach to therapy that is inclusive of avoidance and palliative care measures.

DIAGNOSIS

When considering ocular allergy, the patient's history is essential for proper diagnosis, specifically, practitioners should ask direct questions aimed at identifying how the patient's eyes feel. Separate from the reason for the patient's office visit, it is almost universally relevant to ask about itching, burning, fluctuation of vision throughout the day, does the patient need to use drops, is there bothersome redness, etc. Of these, ocular itching is the hallmark of ocular allergy.

If there is itching, the next steps in the examination should be directed toward determining its location; is it nasal and associated with the nasal canthus (more typical of allergy) or is it along the lids (suggestive of blepharitis). Another question to ask is whether the symptoms appear unilaterally or bilaterally; the latter is more typical of allergy—however, it is important to note that not all ocular allergy is necessarily bilateral in presentation.

Common ocular signs of allergic conjunctivitis include chemosis, eyelid swelling, conjunctival papillae, and no preauricular lymphadenopathy. An ancillary bit of information that may be useful in making the diagnosis is the current season. Although the concept of an "allergy season" is becoming less relevant, pollen is more typical in the spring, grasses in the summer, and weeds in the fall.

Role of Testing

Because the signs and symptoms of DED, allergy, and blepharitis overlap (and because they can be present at the same time), differentiating the exact etiology of ocular inflammation is crucial for directing therapy. Therefore, point-of-care testing is becoming increasingly relevant in eye care, and several companies either have tests or are developing them for use in differentiating ocular disease (InflammaDry [RPS], TearLab Osmolarity System, Sjo and Doctor's Allergy Formula [both from Bausch + Lomb]).

There are only two currently available tests for ocular allergy. One test measures both the quantity and quality of the tears via levels of lactoferrin and immunoglobulin E (IgE) levels (TearScan; Advanced Tear Diagnostics). Lactoferrin is a protein that exhibits a unique combination of antimicrobial, antiviral, and antiinflammatory properties. Low lactoferrin levels directly correlate to dry eye syndrome caused by aqueous deficiency; as such, low lactoferrin levels indicate dry eye syndrome and depressed ocular immunity.[2] In the allergic cascade, IgE binds to allergens and triggers the degranulation of mast cells that cause inflammation.[3] When IgE is present, it indicates a diagnosis of allergic conjunctivitis with levels of IgE increase corresponding with the severity of the allergic response.

The US Food and Drug Administration-approved TearScan test takes about 2 to 3 minutes to perform, and its results can help differentiate the etiology of ocular surface disease, including aqueous deficient versus evaporative DED and/or ocular allergy. In addition to the diagnostic capabilities, the technology allows you to monitor efficacy of treatment as well as patient compliance to treatment measures. In the near future, there is likely to be additional objective point of care allergy tests to improve our diagnostic accuracy as in the case of DED.

Serum and skin testing may have a role for certain patients, especially to help guide patients' education regarding allergen avoidance. Such testing can also help shore up the diagnosis so that appropriate therapy can be selected. Serum

and skin testing have relative pros and cons that should be understood.

Testing may be an underappreciated aspect of managing ocular allergy. As important as it is to rule in allergies, it is equally useful to be able to rule out the condition as a potential cause of ocular surface irritation. One diagnostic allergy test that we have found beneficial is the Doctor's Allergy Formula (Bausch + Lomb) which improves our diagnosis and management of allergies. In this allergy test, patients are exposed to 60 of the most common allergens specific to our area (regional profiles vary). If positive, we discuss the importance of avoiding/modifying the environment to minimize their symptoms. Also, we prescribe appropriate topical/nasal/systemic therapies as indicated. There are occasions where patients test negative to any of the allergens. Although patients may still have an allergy, they are more likely suffering from other ocular surface diseases such as blepharitis or DED. In these cases, we have patients discontinue their systemic allergy medication which is exacerbating their symptoms while aggressively treat their ocular surface.

TREATMENT

The treatment of ocular allergy truly starts with its identification, because counseling patients to avoid triggers is essential: If you remove the trigger, the allergic cascade never starts. Unfortunately, full avoidance may not be possible. In terms of active treatment, most therapeutic plans progress in a stepwise fashion, with the need to graduate to more sophisticated measures determined by a lack of response to previous therapy.

Therapy for ocular allergy centers on use of combination mast cell-antihistamine agents because of their proven efficacy, safety and convenience. The newest agent to the market is Pazeo (olopatadine HCl 0.7%; Alcon) which can be used once a day and is approved for the treatment of itch for 24 hours. One popular strategy for more severe allergic responses is to start the patient on steroidal agents such as Alrex (loteprednol etabonate 0.2%; Bausch + Lomb), either alone or concurrently with combination drops, to quiet the inflammation, and then to taper off and add the combination agent for longer-term maintenance.

In some situations it may be advantageous for the eye care provider to consult with an allergist to coordinate the comanagement of allergic conditions. For example, patients with sinus and throat symptoms with or without headaches may require systemic immunotherapy to address what may be a serious underlying condition.

CONCLUSION

Although it is useful to know what to do in more severe manifestations of ocular allergy, by and large, most patients with likely ocular allergies are treatable with combination agents. All patients, however, should be counseled on palliative and preventive care measures. Here are 12 allergy tips that I learned from John Sheppard, MD, MMsc which should be shared with patients diagnosed with ocular allergies:

- never rub your eyes
- wash your hands
- use allergy-free pillows
- stay indoors
- use drops for eyes, sprays for nose
- avoid vasoconstrictors
- chill your drops
- use cool compresses
- apply allergy drops proactively
- keep the pets out of house or bedroom
- know and avoid your personal allergens
- be aware of resources such as pollen.com, weather.com, and webmd.com, which are useful for knowing what the pollen counts are in your area, as well as what is the most predominant pollen type

It may not always be possible for patients to follow all 12 steps, however, it is a basic fact that if the allergen is removed, the allergic cascade never begins. As a result, managing ocular allergy really does begin with recognition and proper diagnosis. ■

1. Raizman M, Luchs J, Shovlin J, Wolf R. Ocular allergy: a scientific review and expert case debate. *Rev Ophthalmol*. May 2012. http://www.reviewofophthalmology.com/continuing_education/tabviewtest/lessonid/108270.
2. Ohashi Y, Ishida R, Kojima T, et al. Abnormal protein profiles in tears with dry eye syndrome. *Am J Ophthalmol*. 2003;136:2:291-299.
3. Broide DH. Molecular and cellular mechanisms of allergic disease. *J Allergy Clin Immunol*. 2001;108(2):S65-S71.

Important Developments in Ocular Allergy

The one airway philosophy.

BY MILTON HOM, OD

Many optometrists are concerned only with the ocular surface manifestations of allergy; however, the totality of the problem with respect to allergies is not visible through the slit lamp.

Patients with ocular allergies deserve an approach to treatment that considers their entire health, including the systemic manifestations as well as the ocular signs and symptoms. Remember, although the patient is presenting for an ocular surface condition, allergy is a systemic disease, and it should be treated as such. There is a high correlation between allergic rhinitis and ocular allergy, and there is a correlation between asthma and rhinitis, because it is all one large mucus membrane. This concept, the one airway philosophy, recognizes that the ocular surface is connected via nasal lacrimal duct to the nose, the eustachian tubes to the ears, down to the bottom of the throat, down into the lungs, and into the peripheral bronchial.

This emerging concept radically changes the way optometrists are taught to think about allergy when patients present with itchy eyes. Yet, this and other changing trends are important to be aware of so that eye care providers can help patients with allergies.

E-CIGARETTES

Electronic cigarettes (e-cigarettes) have been introduced as an alternative to smoking. They are presumed to be safer, and insofar as they do not contain near the level of carcinogenic toxins that are in the average cigarette, this is true. Yet, the ingredients of some of these products is, frankly, concerning, and the side effects from their use are troubling.

The perception that e-cigarettes are a 100% safe alternative to smoking is false, and patients should be counseled properly about their use. E-cigarettes typically contain propylene glycol, glycol, or both, as well as nicotine and flavor chemicals.[1] During the vaporization of these chemicals, glycol breaks down into formaldehyde, which, when inhaled, is associated with decreased pulmonary function as well as being carcinogenic—and in fact, the risk of pulmonary dysfunction associated with e-cigarettes may be 5 to 15 times higher than that of traditional smoking.[1]

One of the more upsetting aspects of these products is that they are available to minors, and they often contain flavors that appeal to younger individuals. Yet, they contain things like dyethylene glycol, which is often used in antifreeze.[2] There have been reports of cartridge leaks in some products, which yields a risk for massive nicotine exposure.[2]

Rather than being a safe alternative to smoking, e-cigarettes may be a burgeoning public health crisis all their own.

RISING POLLEN COUNTS

Global warming has changed the environment in which we all live and breathe. It is causing unquestionably higher pollen counts secondary to warmer temperatures. Seasons are getting longer, and therefore plants pollinate longer. As a result, the concept of "allergy season" is largely forgotten in modern allergy practice. Where I practice in Southern California, we do not have a true winter. We are in severe drought situations most of the year, and, thus, we have high pollen counts year-round. Of course, pollen counts are going to be highest in the springtime, but it is foolhardy to dismiss the plausibility of ocular allergies simply because of the calendar month.

Another misconception I hear frequently is the belief that ocular allergies cannot occur during winter months or when snow is present. Yet, mold allergies are a prevalent and common malady that may affect untold numbers of patients. Whenever dark and wet environs exist, there is potential for mold to grow, release spores, and induce an allergic response in a susceptible individual.

EMERGING TREATMENT

Fortunately, there is also good news in the world of allergy, as new, stronger formulations of ocular allergy treatments are now available. For many years, olopatadine HCl ophthalmic solution 0.2% (Pataday; Alcon) has been the preferred treatment for ocular allergy, as it is available for once-a-day use. This combination mast-cell stabilizer and antihistamine has high affinity for most ocular allergen and is proven safe and effective.

Now a stronger formulation of this agent available: Pazeo (Alcon) has a concentration of 0.7%. It is a highly viscous solution, offering very good ocular surface adherence, but that comes with a slight trade off in terms of issues with blurring of vision.

PIPELINE

Some interesting products in the pipeline warrant attention. Eleven Biotherapeutics has an agent that was originally being tested for dry eye that it is now being investigated for the treatment of ocular allergies. The company announced earlier this year that the first patients are being dosed in a phase 3 trial of EBI-005 in patients with moderate to severe allergic conjunctivitis.

When Shire recently purchased Foresight, it acquired the rights to the latter's ocular allergy portfolio. Likewise, Valeant bought Nicox and received its interests in ocular allergy as part of the deal. There is also some early stage work being done to investigate whether a topical formulation of cetirizine, the active ingredient in Zyrtec (McNeil-PPC), might be relevant for allergic conjunctivitis.

An interesting and compelling area of research deals with immunotherapy tablets, which may be a way to avoid immunotherapy vaccines. Merck has developed a product called Ragwitek, which is a tablet with low levels of ragweed allergen. Patients take the pill and it trains the immune system to react—but not overreact to—the ragweed allergen.

The tablet is an interesting concept, although one surrounded by a fair amount of controversy. For immunotherapy to work, it has to be given at high enough dose to induce an immunologic response; yet, too high and it could induce an anaphylactic reaction. Because there is no way for the treating physician to titrate the dose, the tablet may be of questionable utility.

I am involved in some research looking at whether the caruncle might be a reservoir in which allergens nestle. My colleagues and I are learning that, as allergens drain from the puncta, they may collect in the caruncle. It is the source of the highest concentration of immunological factors, and this appears to correlate with the fact that patients with ocular allergies associate their itch to the nasal part of the eye.

CONCLUSION

Optometry is increasingly positioning itself as a source of primary eye care. In some ways, the eye care practitioner's role in managing ocular allergy may be the perfect manifestation of this concept. Changing environmental factors and evolving understanding of allergy in terms of a whole airway concept may grow the role of eye care providers in managing patients' allergic disease. ■

1. Jensen RP. Luo W. Pankow JF, et al. Hidden formaldehyde in e-cigarette aerosols. *N Eng J Med.* 2015;372:392–394.
2. Foggs MB. E-cigarette controversy. *ACAAI News*. American College of Allergy, Asthma and Immunology. 2013.

Simplifying Patient Care in the Perioperative Period

New delivery modalities may have an impact on patients' ability to afford and comply with postoperative protocols.

BY JUSTIN SCHWEITZER, OD

There is every indication that optometrists will become increasingly involved in the care of surgical patients. Therefore, it is incumbent on optometrists to be familiar with protocols for the perioperative management of cataract and refractive surgery patients. Even optometrists who do not work in collaborative or integrated care models may wish to keep current on this information, as it is relevant for educating patients referred outside the practice for surgical care.

This article outlines standard care in pre- and postoperative management of cataract and refractive surgery patients and examines how recently available drugs may change management practices.

TOPICAL THERAPY FOR CATARACT SURGERY

Pre- and postoperative care of patients undergoing cataract surgery typically involves the use of some combination of topical antibiotics, nonsteroidal antiinflammatory drugs (NSAIDs), and steroids.

No topical antibiotics are approved by the US Food and Drug Administration (FDA) for use in the perioperative period of cataract surgery. Most surgery centers use a fourth-generation fluoroquinolone because these newer agents offer coverage of Gram-negative and Gram-positive bacteria, whereas older antibiotics have less broad-spectrum coverage. For example, vancomycin is very effective against Gram-positive bacteria but covers only those bacteria. Vancomycin is also effective against the increasingly prevalent methicillin-resistant *Staphylococcus aureus.* Cefuroxime, similarly to vancomycin, has excellent Gram-positive coverage, as well as moderate Gram-negative coverage.

The fourth-generation fluoroquinolones available include gatifloxacin 0.3% and 0.5% (Zymar and Zymaxid; Allergan) and moxifloxacin HCl 0.5% (Vigamox; Alcon). Besifloxacin 0.6% (Besivance; Baush + Lomb) may also be considered in this class. These agents are typically prescribed four times a day for 3 days before surgery and four times a day for 1 week after surgery. Some ophthalmic surgeons use an antibiotic drop the day of surgery. In my colleagues and my practice, we use polymyxin B sulfate for patients with fluoroquinolone allergies.

Steroid drops are commonly used in the pre- and postoperative period. Again, there is no topical steroid FDA approved for this indication. Generic prednisolone acetate is often prescribed four times a day for 3 days before the surgery and one drop on the morning of surgery. After surgery the steroid is prescribed four times per day for the first week, then two times per day for 3 weeks. Some surgeons prefer the use of difluprednate (Durezol) prescribed two times per day for one week, then one time per day for one week.

In our practice, we do not use generic NSAIDs, as these have been associated with corneal melts.[1] Branded NSAIDs include ketorolac tromethamine ophthalmic solution 0.5%, 0.45%, and 0.4% (Acular, Acuvail, and Acular LS, respectively; all Allergan), as well as a nonpreserved formulation of ketorolac tromethamine 0.5% (Acular PF; Allergan); flurbiprofen 0.3% (Ocufen; Allergan); diclofenac (Voltaren, Novartis) bromfenac 0.09% (Bromday, Bausch + Lomb); and nepafenac 0.1% (Nevanac; Alcon). The last two drugs and the 0.45% formulation of ketorolac are specifically FDA approved for the treatment of pain and inflammation associated with cataract surgery. Regardless of agent, NSAIDs are typically prescribed for as little as once-daily up to four times daily for one month after surgery.

Two relatively recent introductions in the NSAID category are new formulations of existing drugs: nepafenac 0.3% (Ilevro; Alcon) and bromfenac 0.07% (Prolensa, Bausch + Lomb). These two formulations are labeled for once-daily dosing starting 3 day before cataract surgery and continuing postoperatively for one month.

PERIOPERATIVE MANAGEMENT

Dropless Therapy

The cost, confusion, and difficulty of following postoperative drop regimens has driven an interest in developing alternative strategies to reduce the potential for inflammation, endophthalmitis, and cystoid macular edema (CME). Studies have noted poor patient compliance with postoperative protocols; one study showed that 50% of patients took only half the number of recommended drops and 20% took less than a quarter of their prescribed medications after cataract surgery.[2] Vision-threatening endophthalmitis remains a rare but real concern, occurring in about one in 1,000 to one in 5,000 cases.[3,4]

Recently, simplified options for perioperative management of cataract patients have become available in the form of compounded injections: Tri-Moxi (Imprimis Pharmaceuticals) is a combination of the antibiotic moxifloxacin and the steroid triamcinolone acetonide, and Tri-Moxi-Vanc (Imprimis Pharmaceuticals) adds the antibiotic vancomycin to the combination. These drugs can be injected directly behind the IOL through the zonules and into the vitreous cavity at the time of cataract surgery.

Although this has not been studied, it is believed that many intraocular infections begin in the vitreous, so the mechanism of delivery of these injectables may be advantageous. These drugs also help control postoperative inflammation and protect against surgically induced CME. It is proposed that, with the use of one intraoperative injection, patients would no longer need postoperative eye drops or, depending on surgeon preference, an NSAID alone could be prescribed postoperatively.

Injectable therapy may represent a new paradigm in cataract surgery, but it is to be used with important caveats. Although the formulation was safe and effective in clinical trials, Tri-Moxi-Vanc is a viscous substance, and it may induce blurred vision in the 48 hours after it is injected. Patients may also experience floaters or dark shadows for up to 72 hours. There is also a chance that some of the injected material can pass through the pupil and settle into the anterior chamber, giving the appearance of a hypopyon, one sign of endophthalmitis; however, patients will not have the hallmark red and painful eyes associated with endophthalmitis.

In a retrospective study, patients taking Tri-Moxi experienced mean intraocular pressure of 21.8 mm Hg on the day of surgery and 14.5 mm Hg at 3 weeks postoperative; no eyes required ocular hypotensive treatment due to steroid response.[5]

Intraoperative Mydriasis

Another injectable option in cataract surgery is the recently approved combination of phenylephrine 1% and ketorolac 0.3% (Omidria; Omeros), which is added to the balanced salt solution infused during cataract surgery. The main advantage of this formulation is that it is FDA approved to maintain pupil dilation and reduce postoperative inflammation, so it can replace off-label and compounded medications used for similar purposes.

In two phase 3 clinical trials, 4% of patients in the group receiving the drug had a pupil diameter less than 6.0 mm at the start of lens implantation, compared with 23% of those receiving placebo. The use of the combination infusion was associated with maintenance of consistent pupil dilation throughout surgery.6 Patients in the active treatment group also reported significantly lower pain scores than those in the placebo group.

The cost of this medication has been cited as a barrier to its adoption. However, the product has been granted temporary pass-through status under Medicare, meaning it is reimbursed at drug cost plus 4% through December 2017; at that time, a decision will be made as to whether it will be included in routine reimbursement for cataract surgery.

REFRACTIVE SURGERY

The trend in perioperative management of ophthalmic surgery patients in general is to reduce the number of drops required so as to improve adherence to drug regimens. In my estimation, this trend applies equally to management of surgical patients.

The standard of care in the postoperative management of LASIK patients is prescription of fourth-generation fluoroquinolone every two hours on the day of surgery, six times daily for the next 2 days, then four times daily for the next 4 days. Patients also typically get a steroid drop, to be used six times on days 1 through 3, four times on days 4 through 7, twice a day during week 2, and then stopped.

Recently, we have started using the compounded prednisolone-moxifloxacin combination off label for LASIK patients. It is prescribed for use four times a day for 1 week, then twice a day for 1 week. The advantage of this approach is that it greatly simplifies the patient's protocol down to a single bottle.

The standard of care in postoperative management of PRK and phototherapeutic keratectomy patients is prescription of a fourth-generation fluoroquinolone six times per day until removal of the bandage contact lens on day 4, then four times on days 5 through 7. These patients also get a steroid to be taken four times a day for the first week and twice a day for the second week. Patients are also prescribed ketorolac 0.45% but given instructions to fill the prescription and use the medication only as needed for discomfort, up to two times per day for a maximum of three days; this is done out of concern for the possibility of corneal melt, especially in the presence of the corneal defect induced by the surgery.

As with LASIK patients, we recently have started using compounded prednisolone-moxifloxacin combination off label for PRK patients. It is prescribed for use four times a day for 1 week, then twice a day for 1 week. These patients are also given a prescription for ketorolac 0.45% and given the same instructions previously discussed in regards to PRK and phototherapeutic keratectomy.

CONCLUSION

There are new options in the perioperative management of ocular surgical patients that have potential to simplify therapy and thereby improve compliance. Looking to the future, there are other drugs in development that could continue this theme. For example, our center is involved in a clinical trial with the company Xigen to test an NSAID that is delivered subconjunctivally. Envisia Therapeutics is studying a nanotechnology platform for anterior chamber deployment that may help to address postoperative inflammation.

What these new entities really promise are ways to simplify our patients' pre- and postoperative protocols and reduce the cost burden while still giving them the best chances to achieve excellent outcomes. ■

1. Flach AJ. Corneal melts associated with topically applied nonsteroidal anti-inflammatory drugs. *Trans Am Ophthalmol Soc.* 2001;99:205–212.
2. Hermann MM, Ustundag C, Diestelhorst M. Compliance with topical therapy after cataract surgery using a new microprocessor-controlled eye drop monitor. *Invest Ophthalmol Vis Sci.* 2005;46: e-abstract 3832.
3. Javitt JC, Vitale S, Canner JK, et al. National outcomes of cataract extraction: endophthalmitis following inpatient surgery. *Arch Ophthalmol.* 1991;109(8):1085–1089.
4. West ES, Behrens A, McDonnell PJ, et al. The incidence of endophthalmitis after cataract surgery among the US Medicare population increased between 1994 and 2001. *Ophthalmology.* 2005;112(8):1388–1394.
5. Shorstein NH, Winthrop KL, Herrinton LJ. Decreased postoperative endophthalmitis rate after institution of intracameral antibiotics in a Northern California eye department. *J Cataract Refract Surg.* 2013;39:8–14.
6. Hovanesian JA, Sheppard JD, Trattler WB, et al. Intracameral phenylephrine and ketorolac (OMS302) during cataract surgery maintains intraoperative mydriasis and reduces postoperative ocular pain – integrated results from two pivotal phase 3 studies. *J Cataract Refract Surg.* [submitted for publication 2015]

Management of Recurrent Corneal Erosion Syndrome

Combined therapies are associated with the best outcomes.

BY NICHOLAS COLATRELLA, OD, AND JEFFREY R. VARANELLI, OD


Although recurrent corneal erosion syndrome (RCE) has been recognized as a disease entity for more than 100 years, there have been no long-term studies to define a specific treatment paradigm.[1-4] In the few trials that have been performed in patients with RCE, success was obtained when multiple treatments were used together.[5-7]

In RCE, the reattachment of the corneal epithelium after an abrasion appears faulty due to a variety of adhesion-complex defects. There can be a reduplication of the basement membrane, loculation of connective tissue, or a complete absence of the basement membrane and hemidesmosomes.[8] The corneal epithelium then develops pale, swollen basal cells, along with pseudocystic collections of cellular and amorphous debris. This leads to elevation of the epithelium and an accumulation of underlying debris, with further formation of abnormal basement membrane and the continuation of this self-perpetuating cycle.[9]

Matrix metalloproteinases (MMP) are a group of enzymes that break down the structure of the extracellular matrix (collagenase). Elevated levels of gelatinase, a specific MMP composed of MMP-9 and MMP-2, have been observed in the tears of patients with RCE. Gelatinase degrades collagen types IV and VII and laminin, all of which are major components of the basement membrane.[10,11]

The main goals of treatment and management in RCE are to control inflammation, promote epithelial regeneration, and allow basement membrane complexes to form properly. To aid in those processes, we recommended using a minimum of four different individual treatments that work synergistically to greatly improve the chance of reducing and preventing RCE exacerbations.

TREATMENT ELEMENTS

Several of the following individual treatment strategies should be combined to create a treatment plan for RCE.

Artificial Tears

One of the main goals of medical management is to promote epithelial health and regeneration. Therefore, treatment typically starts with increasing lubrication and optimizing the health of the tear film,[8,10] allowing a reduction in friction and decreasing the adherence of the eyelids to the epithelium. Multiple formulations of preserved and unpreserved artificial tears, with numerous types of vehicle, are commercially available.

Hyperosmotics

Sodium chloride solutions and ointments create an osmotic gradient that is useful in reducing corneal edema. These hypertonic agents also promote epithelial adherence.[8]

Tetracyclines

Members of the tetracycline family of antibiotics inhibit MMP. Low dose doxycycline has been shown to reduce the level of these inflammatory enzymes and reduce recurrences. Typically prescribed at 20 to 50 mg twice a day for a minimum of 2 months, doxycycline also lessens meibomian gland dysfunction by regulating lipases from colonizing bacteria that create an abnormal tear composition.[6,8,9,12]

Topical Azithromycin

AzaSite (azithromycin ophthalmic solution 1%; Akorn), a topical macrolide indicated for the treatment of bacterial conjunctivitis, has also been shown to reduce levels of MMP-9.[13,14]

Corticosteroids

Topical corticosteroids have been shown to be effective in reducing MMP activity.[6] Multiple topical ophthalmic formulations of corticosteroids are commercially available. All corticosteroids can delay epithelial healing, and these agents should be used with caution.

Cyclosporine Ophthalmic Emulsion

Cyclosporine ophthalmic emulsion 0.05% (Restasis, Allergan) is a topical immunomodulator with anti-inflammatory effects. It works by reducing inflammation and producing a more stable tear film to help epithelial cells to anchor properly.

Autologous Serum

Autologous serum replaces individualized antibodies and gives an extra supply of glucose, proteins, and calcium neces-

sary for the epithelium to migrate rapidly. It contains vitamin A and fibronectin, both of which help speed up the first phase of wound healing. It also affects the final phases of wound healing by supplying growth factors that activate keratocytes to produce extracellular matrix components.[15,16]

N-acetylcysteine

A study in 2012 found that N-acetylcysteine reduced MMP-9 production in human corneal epithelial cells and inhibited cell migration, suggesting that this may be a viable therapeutic option for RCE.[11]

Bandage Contact Lenses

Bandage contact lenses are a useful adjunct for treatment. A study by Fraunfelder and Cabezas showed that extended-wear bandage contact lenses (worn for 3 months, replaced every 2 weeks) offered immediate relief of symptoms and provided long-term resolution in most of their recalcitrant RCE patients.[1,17]

Punctal Plugs

Punctal plugs help thicken the tear film and prevent tear evaporation at night, thereby helping to prevent epithelial avulsion.

Epithelial Debridement

Removal of the dystrophic epithelium and basement membrane can be performed with the goal of creating a smooth Bowman's layer and a clean, more regular surface for new basement membrane to form, resulting in stronger adhesions of the basal epithelial cells to the basement membrane.[1,9,18,19]

Amniotic Membrane

Amniotic membrane is an avascular, acellular tissue that promotes epithelialization, suppresses inflammation, inhibits scarring, inhibits angiogenesis, and contains neurotrophic factors. Placement of self-retained (ie, sutureless) cryopreserved (Prokera; Bio-Tissue) or dehydrated (AmbioDisk; IOP Ophthalmics) amniotic membranes, can be performed in the office to aid in wound healing and prevent RCE.[20]

Anterior Stromal Puncture

In anterior stromal puncture, a hypodermic needle is used at the slit lamp to make multiple punctures through loose epithelium and Bowman's layer into the anterior half of the stroma. It is believed that the breaching of Bowman's membrane stimulates more secure bonding of the epithelium to the underlying basement membrane, Bowman's layer, and stroma.[1,9,10,19,21-23]

Phototherapeutic Keratectomy

In phototherapeutic keratectomy, excimer laser ablation is applied after the epithelium is removed to help smooth Bowman's layer and permit the formation of a new basement membrane with adhesion complexes. Typically there is no refractive effect.[9,19]

Alcohol Delamination

In alcohol delamination, 20% ethanol is applied for 30 seconds to split the basement membrane epithelium from the stroma at the level of the lamina lucida (which is removed) and lamina densa (which remains), taking away proteinaceous and cellular debris but leaving collagen types IV and VII to allow formation of new anchoring fibrils.[10,19,24]

Superficial Keratectomy

Superficial keratectomy can be performed with a blade, diamond knife, or Amoils epithelial scrubber (Innovative Excimer Solutions). The benefit of this technique is that the dystrophic epithelium and basement membrane are peeled off in one continuous sheet, leaving undisturbed Bowman's layer and a clean surface for new basement membrane to form.[1,10,19]

CONCLUSION

The goals of treatment in a patient with RCE are to restore the normal ocular surface anatomy, control inflammation, and prevent epithelial avulsion. With today's understanding of RCE, and utilizing a combined treatment modality, it is possible to maintain vision and prevent recurrences in the large majority of RCE patients. ■

1. Watson SL, Lee MH, Barker NH. Interventions for recurrent corneal erosions. *Cochrane Database Syst Rev*. 2012 Sep 12;9:CD001861.
2. Hansen E. Om den intermitterende keratitis vesicularis neuralgica af traumatisk opindelse. *Hospitalis-Tidene.* 1872;51:201-203.
3. Von Arlt F. Ueber die Verletzungen des Auges in gerichtsaerztlicher Bexiehung. *Wien Medizin Wochenshr*. 1874;23:447-449.
4. Stood W. Ueber rezidivierende Blasenbildungen aufeder Hornhaut des Auges und Keratalgien nach Verletzungen der Hornhautoberflaeche. *Arch Augenheilkd.* 1901;43:220-228.
5. Yoon K, Choi W, You I, Choi J. Application of umbilical cord serum eyedrops for recurrent corneal erosions. *Cornea*. 2011;30:744-748.
6. Dursun D, Kim M, Solomon A, et al. Treatment of recalcitrant recurrent corneal erosions with inhibitors of matrix metalloproteinase-9, doxycycline and corticosteroids. *Am J Ophthalmol.* 2001;132:8-13.
7. Reidy JJ, Paulus MP, Gona S. Recurrent erosions of the cornea: epidemiology and treatment. *Cornea*. 2000;19:767-771.
8. Das S, Seitz B. Recurrent corneal ersosion syndrome. *Surv Ophthalmol.* 2008;53:3-15.
9. Ramamurthi S, Rahman MQ, Dutton GN, Ramaesh K. Pathogenesis, clinical features and management of recurrent corneal erosions. *Eye* (Lond). 2006;20:635-644.
10. Ewald M, Hammersmith KM. Review of diagnosis and management of recurrent erosion syndrome. *Curr Opin Ophthalmol.* 2009;20:287-291.
11. Ramaesh T, Ramaesh K, Riley SC, et al. Effects of N-acetylcysteine on matrix metalloproteinase-9 secretion and cell migration of human corneal epithelial cells. *Eye* (Lond). 2012;26:1138-1144.
12. Wang L, Tsang H, Coroneo M. Treatment of recurrent corneal erosion syndrome using combination of oral doxycycline and topical corticosteroid. *Clin Exp Ophthalmol.* 2007;36:8-12.
13. Foulks GN, Borchman D, Yappert M, et al. Topical azithromycin and oral doxycycline therapy of meibomian gland dysfunction: a comparative clinical and spectroscopic pilot study. *Cornea*. 2013;32:4-53.
14. Jacot JL, Jacot TA, Sheppard JD, et al. Evaluation of MMP 2/9 modulation by AzaSite and DuraSite in human corneal epithelial cells and bovine corneal endothelial cells in vitro. Presented at: Association for Research in Vision and Ophthalmology; April 28, 2008; Ft. Lauderdale, FL.
15. Fox RI, Chan R, Michelson JB, et al. Beneficial effect of artificial tears made with autologous serum in patients with keratoconjunctivitis sicca. *Arthritis Rheum*. 1984;27:459-461.
16. Ziakas N, Boboridis K, Terzidou C, et al. Long-term follow up of autologous serum treatment for recurrent corneal erosions. *Clin Exp Ophthalmol.* 2010;38:683-687.
17. Fraunfelder F, Cabezas M. Treatment of recurrent corneal erosion by extended-wear bandage contact lens. *Cornea*. 2011;30:164-166.
18. Aldave A, Kamal KM, Vo, RC, et al. Epithelial debridement and Bowman's layer polishing for visually significant epithelial irregularity and recurrent corneal erosions. *Cornea*. 2009;28:1085-1090.
19. McGrath LA, Lee GA. Techniques, indications and complications of corneal debridement. *Surv Ophthalmol.* 2014;59:47-63.
20. Huang Y, Sheha H, Tseng SCG. Self-retained amniotic membrane for recurrent corneal erosion. *J Clin Exp Ophthalmol.* 2013;4:272.
21. McLean EN, MacRae SM, Rich LF. Recurrent erosion, treatment by anterior stromal puncture. *Ophthalmology*. 1986;93:784-788.
22. Malecha M. Anterior stromal puncture for recurrent corneal erosion after laser in situ keratomileusis. *J Cataract Refract Surg.* 2004;30:496-498.
23. Avni Zauberman, Noa. Anterior stromal puncture for the treatment of recurrent corneal erosion syndrome: patient clinical features and outcomes. *Am J Ophthalmol*. 2014;157:273-279.
24. Mencucci R, Paladini I, Brahimi B, et al. Alcohol delamination in the treatment of recurrent corneal erosion: an electron microscopic study. *Br J Ophthalmol.* 2010;94:933-939.

Evolving Trends in Topical Glaucoma Therapy

The introduction of preservative-free agents continues to be of keen interest.

BY MICHAEL MCFARLAND, OD

The understanding of how topical medications may contribute to ocular surface disease continues to evolve. As a result of growing concern in this area, pharmaceutical manufacturers have begun producing topical formulations meant to be less toxic to the eye while retaining their effectiveness.

Medical management is usually the first treatment in patients newly diagnosed with glaucoma, and the long-term use of topical medications is often needed for these patients. Because glaucoma is a chronic disease and therefore requires chronic treatment, a glaucoma patient may be exposed to thousands upon thousands of drops over his or her lifetime. Glaucoma surgery may reduce the burden of medications, but this is not always an option, as some patients may not be good candidates or may fail traditional surgical methods.

PRESERVATIVES

A major area of interest has been the introduction of preservative-free and oxidizing preservatives that may have a less deleterious effect on the ocular surface. Preservatives serve a very important purpose: specifically, they keep multidose bottles free of biologic contaminants. It may not be realistic to completely eliminate preservatives from all glaucoma medications, unless the medication is supplied in a truly preservative-free single-dose vial. This, of course, would raise costs and might be inconvenient for the patient.

Benzalkonium chloride (BAK) has historically been the most commonly used preservative, but it has been shown in multiple studies to have a negative effect on ocular surface health.[1-4] Fortunately, for clinicians (and patients) who would like to avoid BAK, there are several options.

BAK-FREE OPTIONS

There are three types of preservative-free topical glaucoma medications on the market. Timoptic 0.25% and 0.5% (timolol maleate ophthalmic solution) in Ocudose (Bausch + Lomb) are beta-blockers. Zioptan (tafluprost ophthalmic solution 0.0015%; Akorn) is a prostaglandin. A preservative-free formulation of Cosopt, Cosopt PF (dorzolamide HCl-timolol maleate ophthalmic solution; Akorn) is a fixed-combination beta-blocker-carbonic anhydrase inhibitor. All three medications have side effect profiles typical of their active ingredients but are excellent options for patients who have concurrent ocular surface disease or who are sensitive to preservatives.

There are two medications with what may be considered a "disappearing preservative" that inactivates once it touches the ocular surface. The SofZia preservative system in Travatan Z (travoprost 0.004%; Alcon) is an ionic buffer containing borate, propylene glycol, sorbitol, and zinc. When applied to the eye, it breaks down into its individual components, which are considered to be gentler on the ocular surface than BAK.[5] Alphagan P (brimonidine 0.1%; Allergan) contains the preservative Purite. When exposed to light, Purite dissociates into water, sodium and chloride ions, and oxygen.[6] These preservatives may be better options for patients with ocular surface concerns.

SYSTEMIC CONSIDERATIONS IN TOPICAL THERAPY

The typical glaucoma patient is an older individual who is often taking concurrent medications for systemic diseases. In terms of systemic side effects in these patients, most doctors are concerned about beta-blockers. Furthermore, topical beta-blockers are less effective in patients already taking systemic beta-blockers.[7] In 2013, the fixed combination Simbrinza (Alcon), containing brimonidine 0.2% and brinzolamide 1%, was approved. This drug allows practitioners to prescribe a combination therapy to patients who may be susceptible to side effects of beta-blockers.

GENERICS

When generic latanoprost became available several years ago, it was heralded as a major milestone in glaucoma therapeutics because it was believed that its lower cost would improve compliance. Has the generic formulation of the original drug, Xalatan (Pfizer), lived up to its promise?

Generic formulations are required to show bioequivalence to the branded product but are not required to undergo the extensive testing and human trials that a branded product is subject to. In a recent study, Myers and colleagues found that a significant percentage of patients who did not reach target

intraocular pressure (IOP) on generic latanoprost achieved additional IOP lowering when switching to branded Lumigan (bimatoprost ophthalmic solution 0.01%; Allergan).[8] Other potential concerns with generic equivalents include variation in bottle design, drop size, pH level, the preservative used, and drug stability.[9]

Cost is most often the driving factor when considering a generic option. Depending on the patient's insurance plan and formulary, however, a generic is not always the least expensive option. All factors, including potential safety and efficacy issues, should be considered when evaluating the use of generic medications. In my colleagues and my clinic, we feel more comfortable using branded medications as often as possible because there is less variability and better quality control.

FUTURE DIRECTIONS OF MEDICAL THERAPY

Several promising therapeutics are being investigated for use in glaucoma.

Rhopressa

This agent from Aerie Pharmaceuticals) is a novel topical medication designed to inhibit both Rho kinase, or ROCK, and the norepinephrine transporter, or NET. It is believed to lower IOP by a triple action of reducing aqueous production, increasing trabecular outflow, and decreasing episcleral venous pressure.[10] In a phase 2 trial, Rhopressa dosed once daily lowered IOP by 5.7 mm Hg from unmedicated baseline.[11]

Roclatan

Also from Aerie, this is a combination of Rhopressa and latanoprost. Theoretically, this would be a quadruple-action medication, as it will have all the effects of Rhopressa with the addition of increased uveoscleral outflow secondary to the effect of latanoprost.[10]

Latanoprostene Bunod

Vesneo, from Bausch + Lomb, is a novel nitrous oxide–donating prostaglandin agonist with a dual mechanism of action, increasing both uveoscleral and trabecular outflow. In a phase 2 trial, once-daily latanoprostene bunod 0.024% reduced IOP to a significantly greater degree than latanoprost with comparable side effects. The manufacturer of this drug recently submitted a new drug application to the US Food and Drug Administration.[12]

INJECTABLES

Injectable medications represent another way of getting active drug to its target tissue. This strategy is popular in general medicine, and ophthalmology has taken advantage of this route of administration with injectable steroids and antivascular endothelial growth factor formulations, among other things. Thus, it is no surprise that injectable glaucoma medications will likely be available in the not-too-distant future.

Allergan is evaluating a sustained-release bioerodible implant injected into the anterior chamber. Phase 2 data suggest that the implant lasts for 4 to 6 months and is comparable to daily topical installation of bimatoprost.[13] Several other companies are also evaluating injectable delivery devices, targeting both the anterior chamber and the subconjunctival space.[14]

MICROINVASIVE GLAUCOMA SURGERY

Although this article focuses on medical glaucoma therapy, surgical options should always be on the mind of the complete practitioner. Microinvasive glaucoma surgery (MIGS) has been a hot topic in the glaucoma world over the past several years. The beauty of MIGS lies in its superior safety profile compared with that of traditional surgery such as a trabeculectomy or tube shunt. FDA-approved MIGS options include the Trabectome (NeoMedix) and the iStent Trabecular Micro-Bypass Stent (Glaukos). With improved safety profiles, these options may be considered earlier in the course of the disease and may reduce the burden of topical medications.

CONCLUSION

As our understanding of glaucoma continues to evolve, so does our appreciation of its comorbidities and the complications associated with its treatments. Future glaucoma medications will have simpler dosing regimens and greater efficacy, and will work through multiple mechanisms with reduced side effects. Surgical options will continue to improve. Generics are not going away any time soon, and patients will continue to request switches to other medications based solely on their formularies. Thus, eye care practitioners must work diligently to stay up to date with new and current treatments and to always do what is best for patients. In the end, making glaucoma treatment as simple and effective as possible for patients, while maintaining their quality of life, is paramount. ■

1. Epstein SP, Chen D, Asbell PA. Evaluation of biomarkers of inflammation in response to benzalkonium chloride on corneal and conjunctival epithelial cells. *J Ocul Pharmacol Ther*. 2009;25(5):415-424.
2. Epstein SP, Ahdoot M, Marcus E, Asbell PA. Comparative toxicity of preservatives on immortalized corneal and conjunctival epithelial cells. *J Ocul Pharmacol Ther*. 2009;25(2):113-119.
3. Ammar DA, Noecker RJ, Kahook MY. Effects of benzalkonium chloride-preserved, polyquad-preserved, and sofZia-preserved topical glaucoma medications on human ocular epithelial cells. *Adv Ther*. 2010;27(11):837-845.
4. De saint jean M, Brignole F, Bringuier AF, et al. Effects of benzalkonium chloride on growth and survival of Chang conjunctival cells. *Invest Ophthalmol Vis Sci*. 1999;40(3):619-630.
5. Kahook MY. Travoprost Z ophthalmic solution with sofZia: clinical safety and efficacy. *Expert Rev Ophthalmol*. 2007;2:363-368.
6. Masschelein WJ. *Chlorine Dioxide, Chemistry and Environmental Impact of Oxychlorine Compounds*. Ann Arbor, MI: Ann Arbor Science Publishers; 1979: 50-55.
7. Schuman JS. Effects of systemic beta-blocker therapy on the efficacy and safety of topical brimonidine and timolol. Brimonidine Study Groups 1 and 2. *Ophthalmology*. 2000;107(6):1171-1177.
8. Myers JS, Vold S, Zaman F, et al. Bimatoprost 0.01% or 0.03% in patients with glaucoma or ocular hypertension previously treated with latanoprost: two randomized 12-week trials. *Clin Ophthalmol*. 2014;8:643-652.
9. Kahook MY, Fechtner RD, Katz LJ, et al. A comparison of active ingredients and preservatives between brand name and generic topical glaucoma medications using liquid chromatography-tandem mass spectrometry. *Curr Eye Res*. 2012;37(2):101-108.
10. Aerie Pharmaceuticals. Our Product Portfolio. http://www.aeriepharma.com/aerietech.html. Accessed August 24, 2015.
11. Bacharach J, Dubiner HB, Lew B, et al. Double-masked, randomized, dose-response study of AR-13324 versus latanoprost in patients with elevated intraocular pressure. *Ophthalmology*. 2015:122:302-307.
12. Weinreb RN, Ong T, Scassellati Sforzolini B, et al. A randomized controlled comparison of latanoprostene bunod and latanoprost 0.005% in the treatment of ocular hypertension and open angle glaucoma: the VOYAGER study. *Br J Ophthalmol*. 2015;99(6):738-745.
13. Allergan.com. Allergan Investor Presentation. 2015. http://www.allergan.com/miscellaneous-pages/allergan-pdf-files/rd_investor_presentation_jun30_2014. Accessed September 5, 2015.
14. Novak GD. New Horizons in Glaucoma Drug Delivery. *Glaucoma Today*. July/August 2014.

Retina in the Future: Emerging Data and a Burgeoning Pipeline

The pace of innovation in the posterior segment shows no signs of slowing.

BY MARK DUNBAR, OD

During the past decade, the posterior segment has seen a tremendous amount of innovation in drug and device development. The genesis for this work was the release of optical coherence tomography (OCT) in the early 1990s, a technology that singularly improved the diagnostic ability of posterior segment practitioners. OCT offered the ability to image, and thus study, the structures of the retina and macula. From that point of origin sprang new understandings of retinal architecture and the disease states seen in clinical practice. What followed from this knowledge has been a veritable avalanche of new products and technologies in the ensuing decades.

ONGOING INNOVATION

The pace of innovation in retina has not slowed, and there is no sign it will in the foreseeable future. Indeed, these are exciting times, as new drugs and devices proffer the ability to help patients maintain or regain visual ability in the face of retinal pathologies that once were blinding conditions. In disease states such as age-related macular degeneration (AMD) and diabetic macular edema (DME), there has been a shift away from slowing vision loss to preserving visual ability to now potentially restoring some vision by accessing intact visual pathways not yet affected by the disease. A quick look to the future reveals products and drugs in development—agents such as genetic modifiers and stem cell therapies—that may actually restore visual ability.

It would not be possible to review all of the developments in the posterior segment, therefore this article focuses on important data on the use of vascular endothelial growth factor (VEGF)-inhibiting agents that have emerged in the past few years, and it highlights several potentially important drugs in development.

NEW DATA ON ANTI-VEGF AGENTS

Agents that inhibit VEGF have had a tremendous impact on our ability to treat posterior segment diseases such as AMD, DME, and retinal vein occlusions, as well as a number of other posterior and anterior segment pathologies. In the past few years, research on anti-VEGF agents has focused largely on how to use them more effectively in clinical practice. The prevailing wisdom in today's retina practice is that, although these agents may be most effective when used in a monthly regimen, that frequency may be impractical and unsustainable. Therefore, it may be incumbent on the treating physician to use an as-needed or treat-and-extend (TAE) protocols. In the former, patients are monitored monthly with OCT imaging and given an anti-VEGF injection when fluid is present in the macula. In a TAE regimen, patients are started on monthly injections, usually for 3 months, but then the physician increases the interval between doses (to 4 weeks, then 6 weeks, and then 8 weeks, etc.) until the fluid returns, indicating the longest interdose interval that may be used before disease activity returns. There is no consensus on which is better, but most physicians now use TAE in regular practice.[1]

In the past year, two anti-VEGF agents, aflibercept (Eylea, Regeneron) and ranibizumab (Lucentis, Genentech), have gained approval from the US Food and Drug Administration for use in treating diabetic retinopathy (DR) in the presence of DME. In addition, aflibercept gained approval for treating central and branch retinal vein occlusion, indications for which ranibizumab already had approval.

The literature suggests there may be subtle differences in the activity of these agents. Any discussion of anti-VEGF agents must also include the off-label use of bevacizumab (Avastin, Genentech). Briefly, ranibizumab is a monoclonal antibody fragment of bevacizumab; the latter is approved for use in several solid tumors, and the former was specifically developed for use in ophthalmic settings. However, when compounded to ophthalmic portions, bevacizumab is considerably cheaper, and, therefore, it has become common practice to have bevacizumab prepared in single-use vials. This practice is rife with controversy due to potential safety issues with compounding and the unregulated nature of compounding pharmacies; however, in today's cost-conscious health care environment, whether physicians should be using this off-label agent as a front-line approach has become a hot topic of debate.

A number of landmark studies have attempted to settle this debate. First came data from CATT, which compared ranibizumab and bevacizumab in patients with AMD. The study found no difference in efficacy between the two drugs.[2]

A similar study in Europe, IVAN, noted similar outcomes.[3] However, there is controversy regarding whether these agents are similar in safety. In the CATT population, a significantly higher proportion of patients in the bevacizumab group experienced systemic serious adverse events compared with the ranibizumab group at 1 and 2 years.[2,4] A meta-analysis of six major AMD trials that compared the two drugs found a similarly increased risk,[5] but another analysis did not.[6] Needless to say, this remains an important and unresolved question that pertains not only to AMD but to every disease state in which anti-VEGF agents are used. No guidelines on preferred usage patterns for anti-VEGF agents exist, and it should be noted that these safety concerns have not significantly affected usage patterns. However, it has been suggested that certain patients may be at higher risk for systemic sequelae, notably those with preexisting cardiovascular conditions.

Another landmark study involving anti-VEGF agents was published earlier this year. The Protocol T study by the Diabetic Retinopathy Clinical Research Network, or DRCR.net, compared ranibizumab, bevacizumab, and aflibercept in eyes with DME.[7] In the overall patient population there were no differences among the drugs in safety or efficacy, but there were important differences in patients with poorer baseline visual acuity. In patients with 20/50 or worse vision, aflibercept demonstrated a significantly better effect than the other drugs. In an accompanying editorial, Daniel Martin, MD, the principal investigator in CATT and a leading anti-VEGF researcher, argued that the results of Protocol T should guide treatment strategy: That is, due to cost concerns, the lowest-price agent (bevacizumab) should be used for patients with 20/40 or better vision (accounting for 75% of patients), while aflibercept should be the treatment of choice for patients with 20/50 or worse presenting visual acuity.[8]

The fundamental truth behind all these questions, however, is that there is more than enough room in the marketplace for multiple anti-VEGF agents, even as a fourth anti-VEGF agent (conbercept; Lumitin, Chengdu Kang Hong Biotech) may come to market. Conbercept, approved in China for use in AMD, has a slightly different structure from other agents; whereas ranibizumab and bevacizumab block VEGF-A isoforms, conbercept and aflibercept block VEGF-A, VEGF-B, and placental growth factor. Conbercept, like aflibercept, contains the extracellular domain 2 of VEGF receptor 1 and extracellular domains 3 and 4 of VEGF receptor 2 combined with the Fc portion of the human immunoglobulin G1. These attributes may impart a longer-half life than ranibizumab or bevacizumab.[9]

On a practical level, all of this research on anti-VEGF agents may be of great interest and importance, but it does not help answer how we should educate patients. To my way of thinking, not much has changed, except that there is added confidence that bevacizumab may be used safely and effectively for a variety of indications, albeit in an off-label fashion. Also, recent studies have suggested that aflibercept may have important advantages as far as higher affinity for VEGF receptors and longer duration of action.

THE DME/DR PIPELINE

In addition to the noted recent DR indications for anti-VEGF agents, two intravitreal steroid implants have emerged as viable options for treatment of diabetic eye disease. The dexamethasone intravitreal implant (Ozurdex, Allergan) releases steroid for about 3 to 4 months, and the fluocinolone acetonide 0.19 mg implant (Iluvien, Alimera) lasts around 36 months.

In the pivotal MEAD trial, more patients gained 15 or more letters of BCVA with the dexamethasone implant than with sham treatment (22% vs 12.0%, respectively; $P \leq .018$), and there was greater reduction of central retinal thickness with the steroid than with sham (-111.6 µm vs -41.9 µm, respectively; $P < .001$).[10] In FAME, the fluocinolone implant was associated with more ETDRS 15-letter gains (28.7% vs 16.2 with sham treatment; $P = .002$) and greater mean gain in BCVA (4.4 letters vs 1.7 with sham treatment; $P = .016$).[11]

The importance of these durable steroid agents is that they offer a potential paradigm shift in how diabetic eye disease is managed. Although anti-VEGF agents are the gold-standard therapy for DME, it is becoming increasingly apparent that patients' compliance with monthly (or as needed or even TAE) injections is less than optimal; thus, sustained-release steroid implants offer an option to improve compliance and also to provide constant antiinflammatory efficacy for extended periods of time.

There is a significant amount of work being done on diabetic eye disease because there is an impending diabetes crisis in the United States. Obesity is on the rise, and the number of people diagnosed with type 2 diabetes has increased from 5.6 million in 1980 to 20.9 million in 2011.[12]

Among the agents being investigated in this category, a drug under development by Aerpio Therapeutics (AKB-9778) seems particularly promising. The drug works by inhibiting human protein tyrosine phosphate, which in turn ensures that the Tie2 enzyme remains active; Tie2, which helps ensure the health of the vascuature, is dysregulated in diabetes. The company recently announced positive results in a phase 2 study of AKB-9778 combined with ranibizumab in patients with DME.[13]

AMD PIPELINE

As noted earlier, the most significant development in the treatment of AMD over the past couple of years has been a refinement in how particular anti-VEGF agents are used in clinical practice. Much of the ongoing or planned research in AMD involves mechanisms to extend drug delivery and prolong anti-VEGF effect. There are also agents in development that may one day function as complements to anti-VEGF therapy.

There is activity in development of drug delivery mechanisms both for AMD and for other retinal diseases. One strategy involves the use of gene therapy, or viral vectors manufactured to contain genetic sequences that alter local ocular tissue to produce anti-VEGF activity. Several research groups and companies are investigating this approach, including pioneering work by Jean Bennett, MD, PhD, of the University of Pennsylvania, (who was involved in the Leber congential

amaurosis gene therapy trials in collaboration with the National Eye Institute) and Avalanche Biotechnologies. That company's lead candidate, AVA-101, is being evaluated in a phase 2a single-center, investigator-sponsored trial outside the United States. AVA-101 is an adeno-associated virus serotype 2—AAV-2—that transduces retinal pigment epithelium (RPE) cells in the outer retina, leading to continuous expression of the protein sFlt-1, which blocks local VEGF signaling.[14] The companies AGTC and Hemera Biosciences are also investigating promising gene therapies involving AAV-2 and other viral vectors.[15]

Among agents that could be used in combination therapy for AMD are some platelet-derived growth factor or PDGF inhibitors. Of a number of companies working on PDGF-inhibiting drugs, Ophthotech is furthest along with Fovista. The company recently completed a phase 2b study of Fovista combined with ranibizumab; in the trial, patients receiving a combination of 1.5 mg of Fovista and ranibizumab gained a mean of 10.6 letters from baseline on a standardized vision chart, compared with a mean gain of 6.5 letters from baseline in patients receiving ranibizumab monotherapy, according to the company.[16]

Genentech, in partnership with Roche, is developing lampalizumab, an antigen-binding fragment (Fab) of a humanized monoclonal antibody that inhibits complement D from binding to complement B. In the natural disease course of geographic atrophy (GA), binding of complement D to B activates the complement immune pathway and subsequent release of inflammatory factors. In the phase 2 MAHALO study, there was a 20% reduction in mean GA area growth among patients treated with lampalizumab monthly compared with sham treatment.17 In patients that had specific genetic biomarkers for geographic atrophy, lampilizumab treated eyes more then doubled the treatment response with an overall reduction in geographic atrophy area of 44% compared to 20% in the study cohort.

There are now two phase 3 trials under way—Chroma (NCT02247479) and Spectri (NCT02247531)—that will investigate the safety and efficacy of lampalizumab 10 mg as treatment for GA.

At the core of all this activity is the belief that AMD therapy must be individualized. Even within the phase 3 programs for lampalizumab, the investigators are looking studying whether patients with a certain genetic profile may derive greater benefit from treatment. More important, however, data are emerging indicating that patients have variable and individualized responses to anti-VEGF therapy. At the same time, research on AMD disease features in the peripheral retina (the study of which only became possible in the past 2 to 3 years) suggests that there may be several distinct AMD subtypes.[18]

Taken together, these recent understandings—that genetic factors potentially affect response to therapy, that there are individualized responses to therapy, and that potentially several AMD subtypes exist—suggest that, although AMD therapy has advanced by leaps and bounds, we may only be scratching the surface.

CONCLUSION

Just a few years ago, the use of slow-release steroid implants and of genetic medicine in practice were scant possibilities on the horizon. Today, however, these are realities, and we are looking toward a future in which stem cell therapy and regenerative medicine may be possible. In the end, it is patients who will ultimately continue to benefit from our enhanced abilities to treat and cure retinal pathologies. ■

1. American Society of Retina Specialists preferences and trends survey. Presented at: The American Society of Retina Specialists annual meeting; August 24-28, 2013; Ontario, Canada.
2. Martin DF, Maguire MG, Fine SL, et al; Comparison of Age-related Macular Degeneration Treatments Trials (CATT) Research Group. Ranibizumab and bevacizumab for treatment of neovascular age-related macular degeneration: two-year results. *Ophthalmology*. 2012;119(7):1388-1398. doi: 10.1016/j.ophtha.2012.03.053.
3. Chakravarthy U, Harding SP, Rogers CA, et al; IVAN Study Investigators. Ranibizumab versus bevacizumab to treat neovascular age-related macular degeneration: one-year findings from the IVAN randomized trial. *Ophthalmology*. 2012;119(7):1399-1411. doi: 10.1016/j.ophtha.2012.04.015.
4. CATT Research Group; Martin DF, Maguire MG, Ying GS, et al. Ranibizumab and bevacizumab for neovascular age-related macular degeneration. *N Engl J Med*. 2011;364(20):1897-1908.
5. Solomon SD, Lindsley K, Vedula SS, et al. Anti-vascular endothelial growth factor for neovascular age-related macular degeneration. *Cochrane Database Syst Rev*. 2014;8:CD005139.
6. Moja L, Lucenterforte E, Kwag KH, et al. Systemic safety of bevacizumab versus ranibizumab for neovascular age-related macular degeneration. *Cochrane Database Syst Rev*. 2014;9:CD011230. doi:10.1002/14651858.CD011230.pub2.
7. Wells JA, Glassman AR, Ayala AR, et al. Aflibercept, bevacizumab, or ranibizumab for diabetic macular edema [published online ahead of print February 18, 2015]. *N Engl J Med*. doi:10.1056/NEJMoa1414264.
8. Martin DF, Maguire MG. Treatment choice for diabetic macular edema [published online ahead of print February 18, 2015]. *N Engl J Med*. doi:10.1056/NEJMe1500351.
9. Li X, Xu G, Wang Y, et al. Safety and efficacy of conbercept in neovascular age-related macular degeneration: results from a 12-month randomized phase 2 study: AURORA study. *Ophthalmology*. 2014;121(9):1740-1747.
10. Boyer DS, Yoon YH, Belfort R Jr, et al. Three-year, randomized, sham-controlled trial of dexamethasone intravitreal implant in patients with diabetic macular edema. *Ophthalmology*. 2014;121(10):1904-1914.
11. Campochiaro PA, Brown DM, Pearson A, et al; FAME Study Group. Long-term benefit of sustained-delivery fluocinolone acetonide vitreous inserts for diabetic macular edema. *Ophthalmology*. 2011;118(4):626-635.e2.
12. US Centers for Disease Control and Prevention. Diabetes Public Health Resource. Number (in Millions) of Civilian, Noninstitutionalized Persons with Diagnosed Diabetes, United States, 1980–2011. http://www.cdc.gov/diabetes/statistics/prev/national/figpersons.htm. Accessed November 3, 2015.
13. Aerpio Therapeutics Announces Positive Results of a Phase 2a Study of AKB-9778 in Diabetic Macular Edema: The TIME-2 Trial. July 15, 2015. http://www.aerpio.com/news/Positive-Results-Phase-2a. Accessed Nov 5, 2015.
14. Bennett J, Ashtari M, Wellman J, et al. AAV2 gene therapy readministration in three adults with congenital blindness. *Sci Transl Med*. 2012;4(120):120ra15. doi: 10.1126/scitranslmed.3002865.
15. Taney LS, Reichel E. Gene therapy for treatment of retinal disease. *Retina Today*. March 17, 2015. http://retinatoday.com/2015/03/gene-therapy-for-treatment-of-retinal-disease/
16. Fovista Anti-PDGF Therapy Clinical Development. http://www.ophthotech.com/product-candidates/fovista/. Accessed October 7, 2015.
17. Basel, Switzerland: Roche; November 16, 2013. www.roche.com/investors/updates/inv-update-2013-11-16.htm. Accessed October 7, 2015.
18. Witmer MT, Kozbial A, Daniel S, Kiss S. Peripheral autofluorescence findings in age-related macular degeneration. *Acta Ophthalmol*. 2012;90:e428-e433.

INSTRUCTIONS FOR CE CREDIT

Cope Course ID: 47482-GO
COPE approved for 2 credits

Expiration Date: Dec. 9, 2018
CE credit is available electronically via evolvemeded.com.

To receive credit, you must complete the Post Test and Activity Evaluation and mail or fax to Evolve Medical Education LLC; PO Box 358; Pine Brook, NJ 07058; Fax: (610) 771-4443. To answer these questions online and receive real-time results, please visit www.evolvemeded.com and click "Online Courses." Certificates are issued electronically, please provide your email address below.

Please type or print clearly, or we will be unable to issue your certificate.

Name _____

Phone (required) _____ Email (required) _____

City _____ State _____

CE QUESTIONS

1. The term ocular surface disease can be used to describe any anomaly that affects:
a. The tear film alone
b. The cornea and conjunctiva
c. The cornea, conjunctiva, and tear film
d. The cornea, conjunctiva, tear film, and lids

2. Corneal inflammation related to DED presents at which levels of disease?
a. Levels 2, 3, and 4
b. Levels 3 and 4
c. Level 4 only
d. All levels

3. Meibomian gland disease has been shown to be present in what percentage of DED cases?
a. 80%
b. 70%
c. 60%
d. 50%

4. What has been shown to help dry eye patients by reducing the levels of matrix metalloproteinases in the tear film?
a. Oral secretagogues
b. Tetracycline antibiotics
c. Corticosteroids
d. All of the above

5. What would be the most appropriate ratio of omega-6 essential fatty acids to omega-3 essential fatty acids?
a. 3:1
b. 10:1
c. 15:1
d. 20:1

6. All of the following may be classified as ocular surface disease except:
a. Dry eye disease
b. Blepharitis
c. Iritis
d. Allergies

7. Liftegrast works by:
a. Interrupting the binding on intracellular adhesion molecule-1 (ICAM1) to lymphocyte function associated antigen-1(LFA-1)
b. Interrupts the binding of intracellular adhesion molecule-1 (ICAM1) to cytokines
c. Promotes the binding of intracellular adhesion molecule-1 (ICAM1) to lymphocyte function associated antigen-1 (LFA-1)
d. Promotes the binding of intracellular adhesion molecule-1 (ICAM1) to cytokines

8. Rituximab, a systemic drug, investigated for Sjogren's Syndrome, targets:
a. A Cells
b. C Cells
c. C Cells
d. D Cells

9. Approximately what percentage of cases of Sjogren's Syndrome is diagnosed?
a. 20%
b. 25%
c. 30%
d. 35%

10. Dry eye disease affects what percentage of the population?
a. Between 30% and 40%
b. Between 20% and 30%
c. Between 10% and 20%
d. Between 10% and 15%

11. What type of cytokines did Dr. Hauser's article states is at the root of many inflammatory diseases?
a. Chemokines
b. Lymphokines
c. Interleukins
d. Interferons

12. What is the estimated number of Americans who have allergies?
a. 40 million
b. 50 million
c. 60 million
d. 70 million

A CE activity jointly sponsored by Evolve Medical Education LLC and *Advanced Ocular Care*, and supported by an unrestricted educational grant from Allergan, Inc.

13. Taking a proper patient history, according to Dr. Whitley, includes:
a. Direct questions aimed at identifying how the patient's eyes feel
b. A thorough dietary history
c. Questions about sleep habits
d. None of the above

14. What does Dr. Whitley state is the hallmark of ocular allergy?
a. Ocular redness
b. Tearing
c. Blurred vision
d. Itching

15. After asking about ocular itching, the next question the examining physician should ask is:
a. The location of itching
b. Is the itching unilateral or bilateral
c. In what season the itching is worse
d. All of the above

16. Most patients who undergo phototherapeutic keratectomy (PTK) for recurrent corneal erosion experience what type of shift?
a. Hyperopic
b. Myopic
c. There is an equal risk of either hyperopic or myopic shift
d. Typically there is no refractive effect

17. Which of the following statements regarding doxycycline and recurrent corneal erosion syndrome is true:
a. It is typically dosed at the sub antimicrobial dose
b. It will reduce the level of matrix metalloproteinases
c. It is typically dosed at 20 to 50 mg twice a day
d. All of the above

18. Autologous serum has been shown to benefit recurrent corneal erosion syndrome patients by all but:
a. Being a source of glucose, proteins and calcium to help epithelial migration
b. Being a valuable source of vitamin A and fibronectin, to help speed healing
c. Decreasing the levels of matrix metalloproteinase 2 and 9
d. Supplying growth factors to activate stromal keratocytes

19. Fourth-generation fluoroquinolones offer coverage against
a. Gram-positive bacteria
b. Gram-negative bacteria
c. Both Gram-positive and Gram-negative bacteria
d. None of the above

The risk of pulmonary dysfunction associated with e-cigarettes may be how many times higher than that of traditional smoking?
a. 2 to 12 times
b. 5 to 15 times
c. 7 to 17 times
d. 10 to 20 times

ACTIVITY EVALUATION

Did the program meet the following educational objectives?	Agree	Neutral	Disagree
Properly diagnose external infectious and inflammatory eye disease	_____	_____	_____
Discuss lid disease therapies and perioperative treatment strategies	_____	_____	_____
Assess chronic conditions such as ocular surface disease and ocular allergies	_____	_____	_____
Discuss current and emerging ocular allergy treatment options	_____	_____	_____
Describe effective perioperative management of ocular surface disease	_____	_____	_____
Interpret glaucoma diagnostic techniques	_____	_____	_____
Incorporate current glaucoma therapeutics and address patient compliance	_____	_____	_____
Explain effective combined surgical and medical glaucoma management	_____	_____	_____
Describe key aspects of corneal and cataract surgery comanagement	_____	_____	_____
Recognize new agents in the pipeline and off-label indications for emerging agents	_____	_____	_____

Your responses to the questions below will help us evaluate this CE activity. They will provide us with evidence that improvements were made in patient care as a result of this activity.
Do you feel the program was educationally sound and commercially balanced? ___ Yes ___ No
Comments regarding commercial bias:
_____
_____
Rate your knowledge/skill level prior to participating in this course: 5 = High, 1 = Low _____
Rate your knowledge/skill level after participating in this course: 5 = High, 1 = Low _____
Would you recommend this program to a colleague? ___Yes ___No
Do you feel the information presented will change your patient care? ___Yes ___No
If yes, please specify. We will contact you by email in 1 to 2 months to see if you have made this change.
_____
_____
If no, please identify the barriers to change.
_____
_____

Please list any additional topics you would like to have covered in future Evolve Medical Education LLC activities or other suggestions or comments.
_____