Toward Dropless Inflammation Control in Cataract Surgery

KENNETH A. BECKMAN, MD Developing novel pharmaceuticals and improving upon available agents have been of longstanding interest in ophthalmology. An exciting current trend is taking established drugs and delivering them to the eye by novel mechanisms in order to reduce the burden of drops on patients and improve pharmacodynamics, safety, and outcomes. Newly approved and pipeline agents are forwarding the universal trend toward dropless inflammation control post-cataract surgery.

Surgical techniques, while steadily evolving to become safer and less traumatic in recent decades, still remain traumatic to the eye, by inciting inflammation on molecular (eg, prostaglandin formation, chemokinase release), microvascular (eg, increased permeability, vasodilation), and tissue (eg, smooth muscle contraction, macular edema) level. When inflammation is poorly controlled, patients undergoing even routine ocular surgery are thought to be at increased risk for discomfort, impaired recovery, and complications including synecchia, cystoid macular edema (CME), and suboptimal visual outcomes.1

EVOLVING TOPICAL OPTIONS

Surgeons vary in their approach to reducing post surgical inflammation (Figure 1). Most prescribe a topical ocular corticosteroid, dosed multiple times per day for a period of several weeks following surgery. Corticosteroids' broad and reliable anti-inflammatory activity derives from blockade of phospholipase A and inhibition of prostaglandin formation early in the cascade. Progress has been made in recent years toward the development of safer alternatives to conventional high potency corticosteroids, such as difluprednate and prednisolone acetate. Loteprednol etabonate has intermediate potency and poses a lower risk for side effects due to a unique molecular structure that undergoes rapid metabolism and deactivation by ocular surface enzymes.2,3 While most corticosteroids approved for post-operative pain and inflammation control are dosed four times daily, a novel, recently US Food and Drug Administration (FDA)-approved formulation of loteprednol etabonate – InVeltys (loteprednol etabonate)

FIGURE 1 Slit lamp photo of a postop day one after cataract surgery. (Courtesy of Dr. Beckman.)
REFERENCES


8. Marguerite B. McDonald, MD, FACS, practices at the University of Florida College of Medicine. She is also a professor of ophthalmology at Tulane University Health Sciences Center. Dr. McDonald is a consultant for Alcon, Alcon, Bausch + Lomb, BlemphEx, FOCUS Laboratories, Shire, and J&J Vision.

9. Victor L. Perez, MD, is a professor of ophthalmology at the Duke University School of Medicine. He is also the director of Duke Eye Center’s Ocular Immunology Center and Ocular Surface Program. Dr. Perez is a consultant for Allergan, Shire, EyeGate, and TopiVert. He is also a stock shareholder for EyeGate.

10. Matthew J. Gray, MD, is an assistant professor in the Department of Ophthalmology at the University of Florida College of Medicine. He states that in the past 12 months, he has not had a financial relationship with any commercial organization that produces, markets, resells, or distributes healthcare goods or services consumed by or used on patients relevant to this manuscript.

11. Kenneth A. Beckman, MD, FACS, is Director of Corneal Services at Comprehensive EyeCare of Central Ohio and a clinical assistant professor of ophthalmology at The Ohio State University, Columbus, Ohio. Dr. Beckman is a consultant for Omeros and EyePoint Pharmaceuticals and is a stock shareholder for Ocular Science.

12. Joseph Tauber, MD, is the founder of Tauber Eye Center in Kansas City, MO where he specializes in anterior segment surgery, corneal transplantation, the treatment of corneal and external diseases, and laser vision correction procedures. He states that in the past 12 months, he has not had a financial relationship with any commercial organization that produces, markets, resells, or distributes healthcare goods or services consumed by or used on patients relevant to this manuscript.

13. Dr. Beckman reports no financial relationships with commercial organizations.

14. Dr. Tauber reports no financial relationships with commercial organizations.
ing multiple times per day for multiple weeks following their procedure. High dosing burden, confusing regimens, difficulty instilling drops (common in elderly populations), and medication costs all may contribute to reduced compliance with drops. Noncompliance with antiinflammatory and/or antibiotic prophylaxis places patients at increased risk for complications. Further, the use of drops introduces risks for ocular surface toxicity (related to active ingredient, preservatives or excipients) and infection due to the possible contamination of the medication. A dropl ess approach to inflammation control and infection prophylaxis around surgery holds considerable appeal to patients, surgeons, and surgical staff.

While the current trend toward dropl ess cataract surgery is in its infancy in the U.S., efforts to simplify the post-operative regimens for patients have gained traction. Combining drops reduces the number of bottles and drops that a patient must handle; for example, an antibiotic, NSAID, and corticosteroid can be placed in a single bottle by a compounding pharmacy. Use of more potent drugs and newer formulations allow for reduced dosing frequency. Intracameral injection of unsupervised cefuroxime or moxifloxacin (Vigamox), with or without adjunctive post-surgical topical antibiotics has been shown to reduce risk for endophthalmitis. Adverse events associated with intracameral antibiotics appear to be rare. Uveitis and retinal toxicity have been reported in conjunction with intracameral cefuroxime dosing error. In Europe, intracameral antibiotics are in routine use with cataract procedures. An approved, prepackaged single-use cefuroxime formulation for intraocular injection is available and indicated for endophthalmitis prophylaxis during surgery. Such intracameral agent is currently not available in the US (surgeons must mix their own preparation in the surgical suite), which likely contributes to lower rates of intracameral antibiotic use among US surgeons, although interest and use is growing.

A minority of cataract surgeons are already largely “dropl ess”, choosing to administer combination corticosteroid and antibiotic obtained from a compounding pharmacy for intracameral injection at the end of surgery. As with intracameral antibiotic injection, concerns regarding the lack of a branded, pre-prepared solution present a barrier for some surgeons as compounded products raise concerns about dilution error or contamination. Fortunately, several novel antiinflammatory delivery mechanisms are likely to hit the market soon, which are poised to partially bridge the gap until more comprehensively dropl ess technology becomes available.

**INTRACAMERAL CORTICOSTEROID**

DEXYCU™ (dexamethasone intraocular suspension) 9% (EyePoint Pharma, Watertown MA) is a novel, unpreserved, long-acting formulation of dexamethasone indicated for the treatment of postoperative inflammation. Dexycu, which contains dexamethasone 517 mcg in a proprietary biodegradable liquid drug delivery vehicle called Verisome R, is injected as a single 0.005 mL dose into the posterior chamber inferiorly behind the iris at the end of ocular surgery, and medication is released over about 21 days. With its approval by the FDA in February 2018 and transitional pass-through and reimbursement approval by the Centers for Medicare and Medicaid Services (CMS) in October 2018, Dexycu will soon be a new option for surgeons in the U.S., paving the way for an at least partially dropl ess approach to cataract surgery.

**Clinical trials**

A multicenter randomized, double-masked, placebo-controlled phase 3 clinical study compared 342 mcg and 517 mcg of IBI-10090 (intraocular dexamethasone) to placebo intraocular injection in 394 eyes undergoing cataract surgery by phacoemulsification. The primary efficacy endpoint was anterior chamber cell (ACC) clearing (zero cells) at day 8, and patients were followed for safety and adverse events for 90 days postoperatively. The proportion of eyes treated with the higher dose of IBI-10090 (Dexycu) that had ACC clearing at day 8 was 66%, compared with 25% among placebo-treated eyes (P < 0.001). Need for rescue anti-inflammator y medication on post-operative day (POD) 7 was 16.3% and 1.9% among placebo-treated and Dexycu-treated patients, respectively.

Adverse events were similar between treatment groups overall; no serious adverse events were reported through POD 90. Intraocular pressure (IOP) increase of at least 10 mmHg from baseline was observed among 29% of Dexycu-treated eyes vs. 13% in placebo-treated eyes. IOP did not exceed 21 mmHg at any measurement in any group. Other treatment-emergent adverse events, including corneal edema, pain, inflammation in the anterior chamber, and dry eye, occurred in < 15% of eyes. Inflammatory adverse events including macular edema, eye inflammation, and iritis were more common in placebo-treated eyes. CME as diagnosed by OCT was seen in 3.8% of placebo-treated and 3.2% of Dexycu-treated eyes.

In a separate multicenter, randomized, open-label study, Dexycu (dexamethasone intraocular suspension) 9% administered intracamerally at the end of surgery was compared to prednisolone acetate 1.0% drops administered four times daily for 3 weeks following surgery in patients undergoing cataract surgery (N = 194). Safety through POD 90 was the primary endpoint. Overall, safety of the two treatment groups were similar. Three serious adverse events were reported in the Dexycu group, one related to diabetic retinopathy and two that were systemic; all were considered unre-
lated to study medication. Change in endothelial cell density was not significantly different between groups.

IOP elevation was observed in 11.1% of patients in the Dexycu group compared with 3.6% of the topical prednisolone group; iritis (6.3%) and anterior segment inflammation (9.5%) were also higher among Dexycu-treated eyes. Proportion of eyes with anterior chamber cell clearing on POD 8 was 51.6% and 50.9% in Dexycu- and prednisolone-treated eyes, respectively (P = NS). Among Dexycu-treated patients, 68.7% strongly agreed that not having to use drops was “very convenient”; and 39.2% of patients who received drops stated a strong preference to a dropless approach.

**New Considerations**

Convenience and direct action at the site of inflammation are advantages of a single-dose, intracameral medication delivery mechanism; but there are also potential disadvantages. For example, it remains unclear whether a single-dose injectable corticosteroid like Dexycu would provide sufficient anti-inflammatory activity for patients with a baseline inflammatory conditions, such as iritis, or autoimmune conditions, such as rheumatoid arthritis. Such patients might require additional corticosteroid drops in the post-operative period. In addition, some patients might benefit from more finely controlled dosing made possible by topical therapy. For example, should a patient with history of herpetic keratitis experience a recurrence post-operatively, or patient with glaucoma experience an IOP spike, one would want the ability to taper a topical corticosteroid. While there are no contraindications to Dexycu as per the label, the potential for IOP elevation, delayed healing, infection exacerbation, and cataract progression are included as warnings.

**INTRACANALICULAR CORTICOSTEROID**

Another mode for dropless, sustained delivery of dexamethasone (or other topical ocular medication) is via drug-eluting intracameral delivery device. A leading device in this category is Dextenza (dexamethasone insert) 0.4mg for intracameral use; (Ocular Therapeutix, Bedford, MA), which is currently under FDA review for treatment of postoperative ocular inflammation and pain.

With Dextenza, active drug is housed in a polyethylene glycol (PEG) hydrogel vehicle that has been conjugated with fluorescein, making it visible by blue light for easy confirmation of placement and retention. Once in place in the canaliculus, the device provides sustained and tapered release of unpreserved dexamethasone over 30 days, after which time the vehicle softens and is cleared or reabsorbed though the nasolacrimal duct. One advantage a drug-eluting intracameral device has over an intracameral injection, as discussed above, is the option to access the device in the event of IOP elevation or other corticosteroid-related adverse event. Also, placement of a drug-eluting intracameral device can be performed in the office, making it more flexible to use. Thus, surgeons who opt for something like Dextenza would provide their patients with a dropless option while retaining the ability to withdraw corticosteroid if a need arose.

A theoretical disadvantage (relative to intracameral injection) is that, like drops, the drug is topical and must penetrate several tissue layers to reach the site of inflammation; whereas intracameral injection places the drug directly at the site of inflammation. Further, some patients, such as those with stenotic or congenitally small puncta, might theoretically have difficulty with placement or retention of the device and may be poor candidates.

**Clinical Trials**

A multicenter, randomized, double-masked, vehicle-controlled phase 3 clinical trial aimed to demonstrate efficacy and safety of Dextenza placed in the inferior distal canaliculus at the end of surgery in patients who underwent unilateral phacoemulsification (N = 60). Primary endpoints were the absence of pain at day 8 and absence of ACC at day 14. Other endpoints included ACC, anterior chamber flare (ACF), retention of device at various time points. Patients who met designated criteria for inflammation were given rescue anti-inflammatory treatment.

On POD 8, ACC clearing among Dextenza-treated patients was 20.7%, compared with 10% among patients with sham device (P = 0.15). Although this endpoint was not met with statistical significance, ACC clearing at POD 14 (34.5% vs. 3.4%; P = 0.0027) and POD 30 (62.1% vs. 13.8%; P = 0.0002) was significantly more common among patients in the intracameral dexamethasone group vs. placebo. The proportion of pain-free patients on POD 8 and all other time points was significantly higher with intracameral dexamethasone treatment vs. placebo (P < 0.002). Further, ACC and ACF were markedly reduced with intracameral dexamethasone through day 30 (P < 0.0251). Need for rescue medication was significantly lower with intracameral dexamethasone.

There was no difference in IOP elevations as adverse events (one patient in each group). Overall adverse events were more common among placebo-treated vs. Dextenza-treated eyes (43.3% vs. 13.8%). Ninety-three percent of physicians reported that the device was “easy” or “very easy” to insert; 100% reported that it was “easy” or “very easy” to visualize. Among participants who responded to a post-study interview, 96% rated the convenience of Dextenza treatment as “very convenient” or “extremely convenient”; and 84% reported that they would be willing to pay more for the insert if they could forego drops.

A second phase 3 clinical trial of similar design compared dexamethasone 0.4mg intracameral insert to vehicular control in patients who underwent phacoemulsification in 21 centers in the US (N = 438). In addition to the much larger patient sample, differences in study design included placement of the device on POD 1 (instead of intraoperatively) and primary endpoints of percent of patients ocular pain-free at POD 8 (same as Walters et al) and percent of patients with ACC clearing at POD 14. Primary endpoints were met: the proportion of patients with ACC clearing on POD 14 was 52.3% vs 31.1% (P < 0.0001); and the proportion pain-free on POD 8 was 79.6% vs. 61.3% (P < 0.0001) among Dextenza-treated and placebo-treated groups, respectively. Ocular inflammation was diminished as early as day 4 and pain as early as day 2 with Dextenza relative to placebo. Adverse events were similar between the two groups.

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BECKMAN continues on page 8
Essential Fatty Acids in Antiinflammatory Therapy for Dry Eye Disease

JOSEPH TAUBER, MD

Dietary supplementation of essential fatty acids (EFA) for the treatment of dry eye disease (DED) remains controversial based on conflicting data, although significant anecdotal experience among ophthalmologists supports its use in patients. The goal of EFA supplementation is to alter the corneal surface of the DED patient from a proinflammatory to an antiinflammatory state and to supplement the inadequate lipid milieu of the tear film caused by meibomian gland dysfunction and excess tear evaporation. Omega-3 fatty acid is considered to play an important role in this regard and may well be as critical to ocular health as it has proven to be in reducing the risk of several other diseases, including cardiovascular and autoimmune disease.

CORE CONCEPTS

- Maintaining a normal lipid milieu in the eye reduces ocular surface inflammation and prevents the pathologic mechanisms that lead to DED.
- Both “essential” fatty acids (omega-6 and omega-3 fatty acid) and “conditional” fatty acids (eicosapentaenoic acid, docosahexaenoic acid and gamma-linoleic acid) are important for maintaining ocular health.
- Omega-6 fatty acids can be proinflammatory while omega-3 fatty acids are antiinflammatory thus the correct ratio of dietary consumption and/or supplementation is important.
- Conflicting data exist as to whether omega-3 fatty acid supplementation is beneficial in treating DED.
- EFA supplementation is beneficial in older patients, who typically present with DED, for reducing hypertension, risk of heart attack, arthritis and Alzheimer’s disease.

RISK FACTORS FOR DEVELOPING DED

DED is a common yet complex condition that is characterized by an impaired or dysfunctional tear film for which there are two major clinical forms: an aqueous deficient form due to insufficient production of tears from the lacrimal gland and an evaporative form due to excessive tear loss, most often due to deficient or abnormal tear lipids in the tear film. Often both clinical manifestations are present simultaneously, though to variable degrees in patients.

Increased tear osmolarity and ensuing epithelial cell desiccation, loss of the glycocalyx that surrounds cell membranes, inflammation and cell apoptosis occur in both manifestations and lead to the frequent signs and symptoms experienced by DED patients. These include eye redness, itching, foreign-body sensation, contact lens intolerance, tearing, pain, blurred vision and, if left untreated, visual loss.

Women and individuals aged 65 years or older are at highest risk of developing DED mostly due to hormonal changes (believed to be reduced androgen levels, either age-related or due to surgical/chemical castration for the treatment of cancer). However, other risk factors include having autoimmune forms of arthritis, osteoporosis, allergies, thyroid disease, severe headaches, migraines and head injury, and the use of certain medications including antihistamines, benzodiazepine, anti-depressants and steroids. The prevalence of symptomatic DED among adults in the US is approximately 14% with an estimated 3.23 million women suffering from the condition. The annual cost of medical care and productivity loss combined equate to more than US$55 billion.

THE ROLE OF EFA IN MAINTAINING HEALTH OF THE OCULAR SURFACE

Maintaining a normal lipid milieu in the tear film that has a balance of the fundamental components of water, oils and mucins/lipids reduces ocular surface dehydration and inflammation and prevents the pathologic mechanisms that lead to DED. This composition is altered in DED and is characterized by elevations in tear osmolarity, increased numbers of proinflammatory cells, a higher expression of cytokines (including interleukin [IL]-1β, IL-6 and IL-10) and matrix metalloproteinase-9 (MMP-9), a proteolytic enzyme that is produced by stressed ocular epithelial cells. Since the body is not able to synthesize adequate levels of EFA to meet all its physiological needs, dietary sources of EFAs are critical to maintaining both ocular and general health.

There are two “essential” fatty acids that are important in maintaining ocular health, namely omega-6 fatty acid (linoleic acid; LA) which is the precursor to the “conditional” fatty acids gamma-linoleic acid (GLA), dihomo-gamma-linoleic acid (DGLA) and arachidonic acid (AA), and omega-3 fatty acid (alpha-linoleic acid; ALA) which is the precursor to the “conditional” fatty acid eicosapentaenoic acid (EPA) which then gives rise to docosahexaenoic acid (DHA). The “conditional” fatty acids are those that may be required under disease conditions when the body is unable to synthesize quantities sufficient to meet pathophysiologic needs. While both omega-6 fatty acids and omega-3 fatty acids are essential for general optimal health, the ratio of consumption is important due to differences in their proinflammatory (omega-6 fatty acid) versus antiinflammatory (omega-3 fatty acid) nature.

Common dietary sources of omega-6 fatty acids are plant-based oils from nuts and seeds, such as safflower oil, corn oil, soybean oil and sesame oil. Both omega-6 and omega-3 fatty acids are present in walnut oil, sunflower seeds and flaxseed, while fish is a common source of omega-3 fatty acid. GLA is present in less commonly consumed foods like borage oil, black currant oil and hemp oil. Overall, Mediterranean diets, which are olive oil-based, and far-east Asian diets show higher consumption of EFA than the typical Western diet.
OMEGA-3 FATTY ACID SUPPLEMENTATION FOR TREATING DED

The rationale for EFA supplementation in the treatment of DED is based on the finding that omega-3 fatty acid catabolism results in generation of antiinflammatory molecules that suppress the inflammatory pathways found in meibomian gland disease. Secondly, omega-3 fatty acids change the fatty acid composition of the meibomian gland secretion so that it contains increased levels of unsaturated fatty acids, which prevent blockage of the meibomian gland ducts and meibum stagnation. This increases the quality of meibomian gland secretions and reduces tear film evaporation.6

Research in animal models suggests that supplementation with omega-3 fatty acid has potential to produce significant therapeutic benefits for treating dry eye.7 These benefits have been shown also in prospective clinical studies in humans.8,10 One study of 32,470 women showed that tuna consumption was inversely associated with dry eye symptoms with 2–4 servings/week and 5–6 servings/week versus ≤ 1 serving/week (P = 0.005, for both comparisons) and that a higher ratio of omega-6 to omega-3 fatty acid consumption was associated with significantly increased risk of dry eye symptoms (P = 0.01).11 Further, a meta-analysis of 790 subjects from 7 independent studies investigating

| TABLE 1 A comparison of the study design for the Epitropoulos et al study and DREAM study |
|------------------------------------------|------------------------------------------|
| **Epitropoulos et al Study**             | **DREAM Study Research Group**           |
| **Design**                               | **Design**                               |
| Prospective, randomized, interventional, | Prospective, randomized, interventional, |
| double-masked                            | double-masked                            |
| **Number of sites**                      | **Number of sites**                      |
| Multicenter (number of sites not stated | 27                                       |
| in primary publication)                  |                                           |
| **Treatment and sample size (N = patients** | **Treatment and sample size (N = patients** |
| completing primary endpoint assessment)  | completing primary endpoint assessment)  |
| Active treatment (1,680 mg EPA / 560 mg | Active treatment (2,000 mg EPA / 1,000 mg DHA): N=329 |
| DHA): N=54 vs. Control (3,136 mg LA): | vs. Placebo (refined olive oil [68% oleic acid, 13% palmitic acid, 11% LA): N=170 |
| N=51                                     |                                           |
| **Inclusion criteria**                   | **Inclusion criteria**                   |
| ≥18 years of age                         | ≥18 years of age                         |
| Previously confirmed diagnosis of DED    | Symptomatic moderate to severe DED ≥6 months |
| MGD stage 1 or 2                         | Use/desire to use artificial tears ≥2 times per day prior to screening |
| Tear osmolarity of ≥312 mOsm/L in at least one eye | OSDI score 25-80 at time of screening and 21-80 at eligibility confirmation visit |
|                                          | ≥2 of 4 signs in at least one eye:      |
|                                          | Conjunctival lissamine-green staining score: ≥1 (scale 0-6) |
|                                          | Corneal fluorescein staining score: ≥4 (scale 0-15) |
|                                          | TBUT: ≤7 seconds                         |
|                                          | Schirmer’s test: 1–7 mm in 5 minutes    |
|                                          |                                           |
| **Exclusion criteria**                   | **Exclusion criteria**                   |
| MGD stage 3                               | Not taking ≥90% of run-in supplements (5/day) |
| Use of topical cyclosporine 0.05%, corticosteroids, | Contact lenses worn 30 days prior to screening |
| nonsteroidal anti-inflammatory drugs, glaucoma medications, or oral omega-3 fatty acids 3 weeks prior to screening | LASIK or recent ocular surgery (within past 6 months) |
| LASIK or PRK surgery within 1 year of screening | Ocular infection |
| Use of systemic medication that might affect the ocular surface | Regular use of DED treatments including omega-3 fatty acid supplements |
| Subjects instructed to discontinue contact lenses within 12 hours of study visits. | EPA plus DHA at <1200 mg daily |
|                                           | Systemic medications known to cause ocular dryness |
|                                           | Systemic glucocorticoids or other immunosuppressive agents allowed if patient committed to continued use for next 12 months |
|                                           | Medical history of thyroid disease, Sjogren’s syndrome, rheumatoid arthritis or inflammatory diseases could be included. |
| **Length of exposure to treatment**      | **Length of exposure to treatment**      |
| 12 weeks                                  | 52 weeks                                 |
| **Key assessments**                      | **Key assessments**                      |
| Mean change in tear osmolarity, TBUT, OSDI, fluorescein corneal staining, Schirmer test, MMP-9 and omega-3 index at 12 weeks | Mean change from baseline in the OSDI score at 52 weeks (primary endpoint). |
| Percent of patients with a decrease from baseline in the OSDI score of ≥10 points, changes in the percentages of EPA and DHA in total fatty acids in red cells, changes in signs of DED (assessed by conjunctival staining score, corneal staining score, TBUT, Schirmer’s test), changes in Medical Outcomes Study 36-Item Short Form Health Survey (SF-36) scores, changes in Brief Ocular Discomfort Index (BODI) scores, changes in treatments used for DED, changes in visual acuity and intraocular pressure, incidence of adverse events (key secondary endpoints). |

EPA: eicosapentaenoic acid; DHA: docosahexaenoic acid; LA: linoleic acid (omega-3 fatty acid)

the effect of omega-3 fatty acids on dry eye symptoms found an improvement in Schirmer scores and TBUT although not Ocular Surface Disease Index (OSDI).12

Recognising the risks associated with omega-3 fatty acid supplementation through fish due to the bioaccumulation of mercury and carcinogens; a multicenter, prospective, interventional, placebo-controlled, double-masked study in 105 subjects investigated the effects of commercial re-esterified fish oil (developed through a process of detoxifying the oil) in subjects with DED. Results showed that relative to controls, oral consumption of re-esterified omega-3 fatty acids was associated with a significant improvement in tear osmolarity and increased omega-3 index levels and tear break up time (TBUT; P = 0.002), a significant reduction in MMP-9 positivity (P = 0.024) and decreased OSDI symptom scores (P = 0.002) by 12 weeks (and as early as 6 weeks).13 In contrast, a more recent prospective, randomized study in 535 patients with DED (the DREAM study) showed there was no benefit in patients receiving supplements containing 3,000 mg of omega-3 fatty acids for 12 months relative to those patients receiving a placebo as demonstrated by no difference between the groups in OSDI score, conjunctival staining score, corneal staining score, TBUT and Schirmer’s test.13

Differences in outcomes between the Epitropoulos et al study and the DREAM study may be explained by differences in sample size, patient eligibility criteria, dose of omega-3 fatty acid and length of treatment exposure (Table 1). The DREAM study was a much larger and longer study that reflected a real-world patient population, however potential limitations include that the placebo was not completely inactive since it contained olive oil (although amounts were well below what would be consumed as a part of a Mediterranean diet). Potentially more problematic was the fact that patients could change their DED treatment during the study. The Epitropoulos et al study was more focused on assessing dry eye associated with inadequate tear production as opposed to the evaporative type, while both clinical types were addressed in the DREAM study. In general, for all studies investigating the impact of EFA supplementation in treating DED, the imprecision and irreproducibility of the metrics used for measuring the signs and symptoms of DED remains a barrier and often patient-reported quality of life measures are the true metric of whether supplementation is beneficial.

ADVISING PATIENTS REGARDING BENEFITS OF EFA SUPPLEMENTATION FOR DED

The question as to whether omega-3 fatty acid supplementation provides any benefit for DED remains controversial. The International Dry Eye Workshop and International Workshop on Meibomian Gland Dysfunction both recommended dietary supplementation with omega-3 fatty acids as a primary therapy.14 In contrast, the most recent American Academy of Ophthalmology Preferred Practice Pattern guidelines noted that omega-3 fatty acids without ethyl esters have been recommended and widely used although the current evidence does not establish a benefit.15

In terms of advising patients, there is much data showing the benefit of omega-3 fatty acid supplementation for reducing arthritis, coronary heart disease and Alzheimer’s disease.16-18 As such, there is no harm in ophthalmologists recommending supplementation for DED patients, particularly since DED patients are older and at a higher risk of the above-stated diseases. It is not uncommon for DED patients to consider increasing their dietary consumption of EFA without taking supplements. However, it is important they understand the vast quantities of foods, such as fish, they would need to consume to provide adequate EFAs to address the pathophysiological needs associated with DED beyond the normal physiological needs. This is where therapeutic supplementation is advantageous.

One issue relating to patients achieving adequate EFA supplementation is patient compliance, which is difficult to measure and mandate in real clinical practice. While it is possible to measure objectively concentrations of omega-3 fatty acid in blood relative to other fatty acids (typically 8-9%), such tests are expensive and there is significant inter-laboratory variation (3-4-fold).19 Until there is a greater use of commercially available tests in clinics, it is difficult to know their accuracy for assessing omega-3 fatty acid levels in DED patients in supporting supplementation compliance.

THE FUTURE OF TREATING DED WITH LIPID-BASED THERAPIES

Currently, there are a plethora of over-the-counter oral omega-3 fatty acid supplements available for DED patients, however few are prescription-grade. The differential benefits of triglyceride-based formulations versus ester-based or re-esterified formulations remain to be determined, although the former are better absorbed and potentially more bio-available.20 Many topical artificial tears are available yet a paucity of lipid-containing artificial tears.21 There exist differences in viscosity in artificial tears with the thicker formulations conferring better outcomes for patients who present with lipid-deficient tear films, although visual blurring is reported. As regards lipid-containing artificial tears, mouse studies have demonstrated a significant decrease in corneal fluorescein staining, CD11b(+) cell number and expression of corneal IL-1a and TNF-a22 and significant improvements in corneal irregularity scores, corneal fluorescein staining and IL-17, IL-10 and 4-hydroxy nonenal (HNE) concentrations23 in response to topical administration of omega-3 fatty acid. These studies indicate the potential role of topical EFA in reducing inflammatory mediators associated with dry eye. There is only one commercially available preparation of topical EFA (RX-10045; Resolvyx, Celtic Pharma, Hamilton Bermuda), which has been shown to increase tear film stability and improve ocular surface signs of the cornea.22-24

New therapies currently under investigation include anti-inflammatory agents, secretory stimulants and tear film stabilizers. Lifitegrast is a recently approved integrin blocker for the treatment of DED that has anti-inflammatory effects by preventing LFA-1/ICAM-1 interaction preventing T cell activation and recruitment. Further, low dose brimonidine and lacixin supplementation are under clinical study, as are water-free, antivehaporative eye drops.25,26

Joseph Tauber, MD is the founder of Tauber Eye Center in Kansas City, MO where he specializes in anterior segment surgery, corneal transplantation, the treatment of corneal and external diseases, and laser vision correction procedures. He states that in the past 12 months, he has not had a financial relationship with any commercial organization that produces, markets, resells, or distributes healthcare goods or services consumed by or used on patients relevant to this manuscript. Medical writer Caroline Markey, PhD, of Markey Medical Consulting Pty Ltd, assisted in the preparation of this manuscript.

The full reference list for this article is available online at: http://cme.ufl.edu/ed/self-study/toai/
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1. Which of the following statements is accurate reading the newly approved product Dexycu (dexamethasone intraocular suspension) 9%?
   A. It contains triamcinolone
   B. It is formulated with mucus-penetrating particles
   C. It is preservative-free
   D. It is formulated for intracanalicular placement

2. Clinical trials Dextenza (dexamethasone insert) 0.4 mg for intracanalicular use have not demonstrated
   A. ACC clearing at post-operative day 14
   B. No ocular pain at post-operative day 8
   C. Low subjective scores from doctors for visibility
   D. High subjective scores from patients for convenience

3. The American Academy of Ophthalmology Preferred Practice Pattern guidelines state that:
   A. Omega-3 fatty acid products are unequivocally beneficial for DED treatment
   B. The ratio of dietary consumption of omega-3 and omega-6 fatty acids should be equal
   C. There is insufficient evidence to establish the effectiveness of EFA for DED
   D. Omega-6 fatty acids should be avoided for treating DED

4. Which of the following is NOT included among the warnings on the Dexycu label?
   A. Endothelial cell toxicity
   B. Cataract progression
   C. Infection exacerbation
   D. IOP elevation

5. The following can be stated about the DREAM study:
   A. The inclusion criteria were too restrictive to be relevant to real clinical practice
   B. The outcomes provide strong evidence for use of EFA for the treatment of DED
   C. The study design reflected real clinical practice more than the Epitropoulos study
   D. The placebo contained no EFA

6. Ophthalmologists should prescribe EFA supplementation for patients with DED because:
   A. The evidence for ocular benefits is unambiguous
   B. Significant improvement in tear osmolarity has been observed in all studies
   C. Many DED patients are ≥ 65 years old and may benefit from EFA supplementation
   D. Ophthalmologists should not prescribe EFA supplementation for DED

7. The composition of the tear film in patients with DED is characterized by:
   A. Increased levels of matrix metalloproteinase-9 (MMP-9)
   B. Decreased tear osmolarity
   C. Elevated proinflammatory cells
   D. Both A and C

8. Which of the following agents work by blocking phospholipase A?
   A. Bromfenac
   B. Prednisolone acetate
   C. Loteprednol etabonate
   D. B and C

9. New treatments under investigation for the treatment of DED are:
   A. Lacritin supplementation
   B. Lifitegrast and water-free antievaporative eye drops
   C. Low dose brimonidine
   D. A, B, and C

10. Which of the following is NOT currently a viable means for potentially lightening the post-operative drop burden for cataract patients?
    A. Intracameral NSAID injection at the end of surgery
    B. Using NSAID with once daily dosing
    C. Intracameral Vigamox injection at the end of surgery
    D. Use combination antibiotic/corticosteroid from compounding pharmacy

CONCLUSION

Of course, drug delivery technology is also other being applied to indications beyond cataract surgery. For example, a low dose loteprednol etabonate-MPP is in development for the treatment of dry eye disease;22 Dextenza is also in development for treatment of allergic conjunctivitis. By my estimation, we can look forward to better outcomes and happier patients as the march toward fewer drops and droppless delivery of medication continues.

Kenneth A. Beckman, MD, FACS, is Director of Corneal Services at Comprehensive EyeCare of Central Ohio and a clinical assistant professor of ophthalmology at The Ohio State University, Columbus, Ohio. Dr. Beckman is a consultant for Omersa and EyePoint Pharmaceuticals and is a stock shareholder for Ocular Science. Medical writer Noelle Lake, MD assisted in the preparation of this manuscript.

REFERENCES

The full reference list for this article is available online at: http://cme.ufl.edu/ed/self-study/toai/


1. OMDRIA [Prescribing Information] 2017. Omeros Corp, Seattle WA.


