Innovations in Ophthalmic Corticosteroid Delivery

MICHAEL J. ALLINGHAM, MD, PHD

Novel ophthalmic sustained-release corticosteroid delivery systems have become available in recent years and more are in various stages of development. Eyecare providers familiar with the properties, indications, and potential advantages of each are positioned to offer their patients with chronic inflammatory conditions (or who are undergoing surgery) state-of-the-art inflammation control and care.

Even as options expand for patients with chronic inflammatory conditions of the eye, there remains a need for novel long-acting, sustained-release antiinflammatory technologies—particularly those that deliver medicine to the posterior chamber—that are safe, effective, easy to administer, and whose duration of bioactivity align well with patients’ needs. Sustained-release antiinflammatory medications have the potential to reduce the frequency of disease flare-ups (that coincide with subtherapeutic medication levels at the end of short courses of therapy) and lead to better long-term outcomes.

In this article, we review trends in the development of sustained release technology, focusing on innovations in posterior chamber corticosteroid administration.

DRUG DELIVERY TRENDS

Optimal Pharmacodynamics
An ongoing challenge in developing corticosteroid therapies is identifying the optimum dose, potency, and duration to control inflammation, and delivering medication in a way that minimizes the potential side effects associated with cumulative anterior segment exposure.

Long-term control of inflammation has been possible for patients with uveitis since the advent of implantable sustained-release corticosteroid devices, beginning in 2005 with Retisert® (fluocinolone acetonide intravitreal implant) 0.59 mg (Bausch & Lomb, Bridgewater, NJ); however, the newfound convenience and efficacy associated with Retisert were accompanied by a substantial risk for serious side effects—mainly cataracts and glaucoma—related to long-term anterior segment exposure. Since then, sustained release devices have become available with varying pharmacokinetic profiles (eg, including lower overall dose, novel sustained release vehicles and administration methods, and shorter durations of effect) that allow more flexibility in dosing across a range of indications. Although short-acting (1 to 3 months) and long-acting (up to 36 months) agents are currently available or on the horizon, no drug to date offers robust intraocular levels for a medium-length duration of 6 to 12 months, which is the “sweet spot” for many patients with uveitis, in my opinion. A shorter duration version of a fluocinolone acetonide intravitreal implant is in the pipeline and might fill that unmet need.

Optimal Pharmacodynamics
A sustained-release corticosteroid device has the potential to achieve better inflammation control over the long-term for patients with uveitis. Assuming one is satisfied that patients are not experiencing intraocular pressure (IOP) elevations, use of a sustained delivery device could decrease the frequency of office visits, which may benefit patients.

See INSIDE for:
Controlling Inflammation After Corneal Cross-linking
William B. Trattler, MD
The control of ocular inflammation is a critical aspect of medical and surgical ophthalmic practice. Despite their side effects, antiinflammatory drugs are used to treat a very wide range of conditions throughout the eye, from ocular surface disease and allergic conjunctivitis to posterior segment conditions. Use of antiinflammatory agents is also critical in ocular surgery, contributing greatly to patient safety and positive outcomes.

The ocular antiinflammatory landscape is changing as research reveals more about the role of inflammation in a range of ocular conditions and as new antiinflammatory agents enter the market. Twenty years ago, for example, the idea of using a topical corticosteroid to treat dry eye and/or allergic conjunctivitis was viewed with alarm; today, it is accepted practice.

Although corticosteroids and nonsteroidal antiinflammatory drugs (NSAIDs) have been the mainstays of the ocular antiinflammatory armamentarium, a number of new agents with novel mechanisms of action (and new ocular drug delivery systems) have come to market or are being made ready for market.As indications expand and change, and as new drugs, formulations, and delivery systems become available, clinicians require up-to-date protocols for drug selection and use. Such protocols are also needed for routine (but nevertheless off-label) uses of corticosteroids and NSAIDs because important differences in efficacy, safety, and tolerability exist between these classes and among formulations within each of these classes.

By putting the latest published evidence into the context of current clinical practice, topics in Ocular Antiinflammatories equips ophthalmologists to maintain competency and stay abreast of their actual and optimal inflammation management practices, across the range of clinical situations in which current and novel ocular antiinflammatories may be used.

REFERENCES

OFF-LABEL USE STATEMENT
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include patient discomfort from the injection, and, although incidence is low, migration of the implant from the vitreous to the anterior chamber, endophthalmitis, and risks associated with the need for larger needle size for placement (eg, hypotony, vitreous hemorrhage). However, the convenience of in-office injection can provide substantial benefit to the patient and ophthalmic professional.

**DRUG PLACEMENT TRENDS: THE SUPRACHOROIDAL SPACE**

There is an emerging trend toward identifying new routes of drug delivery beyond sub-tenon and intravitreal sites of injection. The suprachoroidal space, a potential space between the sclera and the choroid, is a new site and route of interest for delivering ophthalmic medications intended for the posterior segment. The interest stems from the hope that a sustained-release agent placed in the suprachoroidal space might achieve durable therapeutic levels in the posterior segment while reducing exposure to the front of the eye. A possible advantage, therefore, is a better safety profile (with regard to IOP and cataract development in the case of corticosteroids) compared to intravitreal injection or topical administration. In theory, endophthalmitis risk might also be decreased with suprachoroidal vs intravitreal injection since the needle tip does not enter the vitreous. However, more real world experience is needed before this potential benefit is confirmed.

Until recently, the suprachoroidal space has been poorly accessible by injection. The main obstacle has been that, as a potential space only, ordinary needles (eg, those designed for intravitreal injection) glide through it en route to the vitreous, giving no indication that the needle tip has pierced the sclera until it has also passed through to the choroid. In response to this challenge, researchers at Clearside Biomedical (Alpharetta, GA) engineered a very sharp, fine (30 gauge) proprietary micro-needle injector device, only 1000 microns in length, and a novel technique that facilitates injection into the suprachoroidal space.7 Suprachoroidal injection technique involves positioning the needle against the sclera 9 mm posterior to the limbus (a more posterior placement than ordinary intracameral injections), applying gentle pressure to the plunger (as if trying to dispense the contents), then advancing the needle forward with the plunger engaged. Whilst the needle is pressed against the sclera, no medicine can be released; however, once the needle tip cleats the sclera and enters the suprachoroidal space, resistance decreases, and the medication is injected.

**Corticosteroid Triamcinolone Acetonide (CLS-TA)**

The leading suprachoroidal pipeline product is corticosteroid triamcinolone acetonide (CLS-TA) (Clearside Biomedical, Alpharetta, GA), which has completed positive phase 3 trials for the treatment of macular edema associated with uveitis and a phase 2 study for DME.7 According to the company, the goals of developing CLS-TA included improved efficacy over current therapies, local administration, lower side effects, lower concentration of drug used, and less frequent administration of drug.11 Preclinical studies of suprachoroidal CLS-TA showed localization of triamcinolone acetonide (TA) principally to the sclera, choroid, and retina with limited exposure to the vitreous humor and no TA detected in the aqueous humor.12 Choroid and retinal drug accumulation with suprachoroidal placement is 1200% greater than the same drug delivered by intravitreal injection.13

**CLEARSIDE CLINICAL PROGRAM**

The phase 3 clinical trial PEACHTREE showed that suprachoroidal CLS-TA significantly improved vision and macular edema in noninfectious uveitis at all anatomical locations.14 One hundred sixty patients with uveitis (anterior, intermediate, posterior, or panuveitis) were enrolled in a double-blind, multicenter trial, randomized to receive either two injections of suprachoroidal CLS-TA (at baseline and week 12) or placebo, and followed for 6 months. Rescue corticosteroid was available for either arm as needed. A highly clinically meaningful primary endpoint was chosen—the proportion of subjects gaining ≥15 Early Treatment Diabetic Retinopathy Study (ETDRS) letters in best corrected visual acuity (BCVA) at week 24.

The primary endpoint was met among 46.9% of CLS-TA-treated patients vs 15.6% of placebo-treated patients (P < 0.001).14 Improvement was significant throughout the study starting at week 4 (9.6 vs 1.3 change in ETDRS letters from baseline among treated and untreated arms, respectively). Mean change in central subfield thickness (CST) was also significantly decreased among treated patients compared with placebo-treated arms starting at week 4 through week 24 (152.6 vs -17.9 microns change from baseline among CLS-TA vs placebo-treated patients, respectively; P < 0.001). Resolution of anterior chamber cell and flare and vitreous haze were significantly reduced with CLS-TA treatment.14

There were no serious adverse events attributed to study drug. Adverse events occurring in >5% of subjects in the CLS-TA arm included elevated IOP (11.5% vs 15.6% with placebo), eye pain (12.5% vs 4.7%), and cataract (7.3% vs 6.9% with placebo).

TYBEE, a 6-month, phase 2, randomized, controlled trial in treatment-naive eyes with DME, compared suprachoroidal CLS-TA as an
adjunct to anti-vascular endothelial growth factor (VEGF) agent Eylea (intravitreal aflibercept) (Regeneron, Tarrytown, NY) dosed every 3 months, versus Eylea monotherapy dosed once monthly. Rescue Eylea was available at months 4 or 5.

The primary endpoint was the mean change in BCVA from baseline to week 24. Patients treated with combination therapy experienced a mean change in BCVA from baseline to week 24 of 12.3 letters vs a mean change in BCVA of 13.5 letters with monthly Eylea monotherapy (P > 0.05). These data indicate that CLS-TA treatment allowed for 50% fewer Eylea injections without significantly compromising visual outcomes.¹⁵

A secondary anatomical endpoint, mean change in CST from baseline to week 24 was significantly greater in the CLS-TA plus Eylea arm (-226 microns) compared with monthly Eylea monotherapy (176 microns; P = 0.035), indicating that the inclusion of suprachoroidal CLS-TA in the treatment regimen was associated with better drying of the macula.

These are promising results, and more work needs to be done to specify the role of corticosteroids in the treatment of DME and for whom combination therapy holds a real advantage. Of note, these studies report on findings of two suprachoroidal injections spaced 3 months apart. Assuming suprachoroidal CLS-TA becomes approved, the side effects and real-world tolerability of repeated injections in the suprachoroidal space would remain to be seen.

POSTOPERATIVE TRENDS: DEXAMETHASONE

Dexycu (dexamethasone intraocular suspension) 9% (EyePoint Pharma, Watertown, MA) is a newly available, preservative-free, long-acting corticosteroid formulation indicated for treatment of postoperative inflammation.¹³ Dexycu, which contains dexamethasone 51.7 mg in a proprietary, biodegradable liquid drug delivery vehicle called Verisome, is injected into the posterior chamber as a single 0.005 mL dose at the end of cataract surgery, and medication is released over about 21 days.³⁹

As efforts to simplify postoperative regimens are gaining traction, and patients, particularly those who opt for premium lenses, would likely welcome the convenience of “dropless surgery” afforded in part by a sustained-release antiinflammatory agent. Administration of Dexycu at the end of cataract surgery should reduce or eliminate the need for corticosteroid drops following surgery or, if combined with an intracameral antibiotic, a need for any postsurgical topical medication.

Patients at increased risk for postoperative cystoid macular edema—including those with comorbid conditions such as epiretinal membrane or uveitis, or surgical complications such as a ruptured capsule or high phaco energy requirement—are also particularly good candidates for Dexycu administration at the end of surgery, since in such cases, treatment at the site of inflammation is especially critical.

A summary of Dexycu clinical trial results was recently presented in Issue 26 of Topics in Ocular Antiinflammatories. Insert link to Candeo TOAI Issue 26

FUTURE DIRECTIONS AND UNMET NEEDS

In the implant category, I believe bioerodible technology will likely come to predominate for sustained-release drugs, especially for indications like wet age-related macular degeneration (AMD) that require long-term treatment. Agents such as Ozurdex that are formulated with a bioerodible vehicle leave no residual shell or vehicle once the dose is fully released. By contrast, nonbioerodible delivery technology as used in Yutiq, Iluvien, and Retisert leave a part of the vehicle in the eye.¹⁴ Consequences of a nonbioerodible delivery mechanism are unknown; in theory, they might impart a limit to repeated use.

As mentioned, there remain a number of unmet needs for sustained-release corticosteroid agents, including agents with 6 month to 1 year duration of effect. Development of locally acting, steroid-sparing antiinflammatory and immunomodulatory agents would also be a great advance.

As research progresses, the potential to use the suprachoroidal space for sustained-release medication delivery of diverse molecules—angiogenic molecules, anti-VEGF, antiangiogenic molecules, and even NSAIDs—might benefit patients with DME, vein occlusion, AMD, among other conditions. Clearside Biomedical lists (a) a proprietary compound for treatment of retinal vascular disease and (b) gene therapy for orphan diseases as suprachoroidal therapies entering preclinical study.⁷

Michael J. Allingham, MD, PhD is a medical retina specialist and assistant professor of ophthalmology at Duke Eye Center. He is actively engaged in both clinical and basic research with a goal of identifying novel therapeutic targets for macular diseases, particularly those that manifest macular edema. Dr. Allingham states that he is a consultant for Clearside Biomedical. Medical writer Noelle Lake, MD assisted in the preparation of this manuscript.

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Controlling Inflammation After Corneal Cross-linking

WILLIAM B. TRATTLER, MD

While corneal collagen cross-linking (CXL) using the epithelial-off method (Dresden protocol) is currently FDA-approved for the treatment of progressive keratoconus and post-laser in situ keratomileusis (LASIK) ectasia, the procedure is not without complications. Post-surgical inflammation causing corneal haze and infectious keratitis leading to corneal scarring can occur if early management strategies are not implemented. By increasing awareness of the possible complications and administering appropriate pre- and postoperative care, such events may be mitigated and optimal outcomes achieved for patients.

Corneal collagen cross-linking (CXL) is a procedure used most commonly for the treatment of progressive keratoconus and post-laser in situ keratomileusis (LASIK) ectasia in adults. Affecting approximately 0.9% to 3.3% of individuals, with a higher prevalence in individuals of South East Asian and Indian ethnicity, keratoconus is a corneal ectatic disease characterized by progressive focal thinning and irregular astigmatism. The condition may lead to reduced visual acuity and, if severe, the need for a corneal transplant. Post-LASIK ectasia is characterized by compromised integrity of the corneal strength following LASIK surgery. It can present from months to many years to even more than a decade following LASIK. For both conditions, most treatments focus on strengthening corneal structure and integrity.

TECHNIQUES OF CORNEAL COLLAGEN CROSS-LINKING

The procedure of riboflavin/ultraviolet A (UVA)-induced CXL was first reported in a clinical study in 2003. The procedure involves the production of reactive oxygen species from the interaction of the photosensitizing agent riboflavin with UV-A light, which results in the formation of chemical bonds within the corneal stroma and subsequent mechanical stiffening of the cornea. Microstructural changes include increased collagen fiber diameter, keratocyte apoptosis, resistance to thermal shrinkage, changes in corneal swelling properties, and increased resistance to collagenous degradation.

There are two CXL methods: the epithelial-off method (Dresden protocol) in which an 8 mm to 9 mm zone of corneal epithelium is debrided followed by the instillation of riboflavin eyedrops/UV-A application; and the investigational epithial-on method, in which the epithelium remains intact with the addition of riboflavin eyedrops. The latter technique avoids postoperative complications associated with epithelial healing of debrided corneal tissue. The epithelial-on method is the only FDA-approved option. The epithelial-on method is still under investigation in separate multicenter clinical trials conducted by both Avedro and CXLO. Worldwide, other studies of the epithial-on technique are being undertaken using modified riboflavin formulations to enhance penetration through the intact, hydrophobic corneal epithelium, and by using iontophoresis.

The KXL system was Food and Drug Administration (FDA) approved in 2016 (Avedro Inc, Waltham, MA) for the treatment of progressive keratoconus and post-LASIK ectasia in adults. It can be used off-label with laser vision correction procedures, intrastromal ring implantation, thermokeratoplasty procedures and, more recently, to treat infectious keratitis. The topical ophthalmic photosensitizer solutions used in CXL are 1) riboflavin 5-phosphate in 20% dextran ophthalmic solution 0.146% (Photorexa®, Avedro Inc, Waltham, MA), which is FDA-approved for use in all CXL procedures, and 2) riboflavin 5-phosphate ophthalmic solution 0.146% (Photorexa®, Avedro Inc, Waltham, MA), which is FDA-approved for use when the corneal stroma is thinner than 400 mm after completion of the Photorexa® induction period. The KXL system irradiates target tissue with UVA radiation for 30 minutes at 3 mW/cm² via operator alignment of lasers and self-calibration of UVA irradiation intensity.

POTENTIAL COMPLICATIONS OF CORNEAL COLLAGEN CROSS-LINKING

The epithelial-off CXL technique is often associated with significant postoperative pain, and visual recovery can be gradual. Perhaps of more significance are the potential consequences of inflammation, including corneal haze, corneal scarring, infectious keratitis, sterile infiltrates, delayed epithelial healing, corneal perforation, photophobia, failure of treatment, excessive corneal flattening with a hyperopic shift, and endothelial failure. These complications, while possible, are not typically observed following the epithelial-on method. Further, long-term studies show that progression of keratoconus after CXL may occur in 3 to 8% of cases.

Figure 1: Representative slit lamp biomicroscopy image of clinical haze after CXL (original magnification x16).

Slit-lamp observations suggest that more than 90% of cases post-CXL will show corneal haze, with a greater tendency in patients who have more advanced keratoconus (Figure 1). One randomized, controlled trial investigated the natural history of stromal haze in patients with keratoconus or ectasia using Scheimpflug densitometry as an objective measure of haze versus subjective physician-determined slit lamp-assessed haze. The study confirmed that, relative to baseline haze (14.9 ± 1.9), there was a significant increase in postoperative haze at 1 month (23.4 ± 4.4) that plateaued at 3 months (22.4 ± 4.8; P < 0.001) and then decreased at 6 months (19.4 ± 4.8) and 12 months (17.0 ± 3.8) using Scheimpflug densitometry (P < 0.01), which was not different to the results based on slit-lamp observation. Further, there was significant remnant haze at 12 months in the keratoconus group compared to the ectasia group. Prior to treatment, as measured by quantitative real-time polymerase chain reaction (PCR) on RNA isolated from tissue debridement, the epithelium and stroma from the cone apex of patients with keratoconus show characteristically elevated levels of the inflammatory factors TNF-α, IL-6, and matrix metalloproteinase 9 (MMP-9) but reduced lysyl oxidase (LOX), which crosslinks collagen and elastin into insoluble fibres, and collagen IVA1. Thus, pre- and postoperative consideration of inflammation is important.

The occurrence of infectious keratitis after epithelial-off CXL is rare. Nonetheless, this severe complication can lead to melting of the cornea or scarring with irreversible visual acuity loss, requiring keratoplasty. Symptoms of redness, decreased vision, and pain can develop, and corneal infiltrates can appear shortly after the procedure prior to the epithelial defect healing. Differential diagnosis includes peripheral sterile infiltrates due to enhanced cell-mediated immunity to staphylococcal antigens at a high concentration in the area of tear pooling.

Another complication that may arise following epithelial-off CXL for post-LASIK ectasia is diffuse lamellar keratitis (DLK), a condition in which inflammatory cells accumulate in the flap interface. While rare, the relatively recent (2016) FDA-approval of the KLX system (Avedro Inc, Waltham, MA) for the treatment of post-LASIK ectasia may see an increased incidence of DLK. Since the condition can present with corneal edema and corneal inflammation, findings similar to other conditions, it is important to ensure that DLK is not overlooked and untreated in the early post-CXL period.

MANAGEMENT OF POSTOPERATIVE INFLAMMATION

The primary goal of the treating physician post-CXL should be to optimize epithelial healing as quickly as possible, specifically within 3 to 5 days, although healing may take longer in patients with irregular, steep corneas and those who have apical scars. A typical postoperative approach is to administer topical steroid eyedrops four times a day for the first week post-CXL and, once the epithelium has healed, continue the drops for 1 to 4 weeks to suppress inflammation or longer if signs of haze or inflammation persist. Topical steroids may also be required if haze develops much later in the postoperative period. Since pain is common with the epithelial-off CXL procedure, a nonsteroidal anti-inflammatory drug (NSAID) eyedrop may be administered in conjunction with the steroidal eyedrops in the first few days post-procedure.

Generally, any steroidal eyedrop is effective for controlling inflammation, including generic prednisolone acetate, loteprednol (Lotemax Gel®, Bausch+Lomb, Bridgewater, NJ) and difluprednate (Durezol®, Alcon, Fort Worth, TX). Where there may exist a concern regarding elevated intraocular pressure (IOP) for a patient, a lighter steroid such as loteprednol may be advantageous. For more effective management of haze, the more potent prednisolone or difluprednate may be preferred. Recent advances in loteprednol formulations – Inveldys (Kala) and Lotemax SM (B&L) – may allow the use of a potent topical steroid with a lower risk of IOP elevation in patients requiring extended therapy for corneal haze.

An important consideration when managing post-CXL inflammation with steroids in keratoconus patients is the thin and flexible nature of the cone-like cornea, which may present difficulty when assessing IOP. These patients often measure low IOP measurements regardless of the actual pressure in the eye and, as such, it may be difficult to assess accurately the steroid response. Minimizing the frequency and strength of steroids when possible will attenuate severe IOP spikes in these patients.

MANAGEMENT OF POSTOPERATIVE INFECTION

For the treatment of infectious keratitis arising post-CXL surgery, identification of the pathogenic agent is important so that the infection may be treated effectively. Studies have shown that infection is predominantly due to gram-positive bacteria (Staphylococcus epidermidis, Staphylococcus aureus, Streptococcus salivarius, and Streptococcus oralis) and less frequently to gram-negative bacteria.
(Escherichia coli and the virulent Pseudomonas aeruginosa). Since UVA irradiation kills both bacteria and fungi, it is more likely that contact with a pathogenic agent occurs during the early postoperative period rather than during surgery by factors such as the epithelial defect, topical anesthetics, use of a soft bandage contact lens, and topical anti-inflammatory medications. Bacterial keratitis may be treated with topical monotherapy (e.g., fluoroquinolones) in cases where small, superficial infiltrates are observed, while larger and/or non-responsive infiltrates should be treated more aggressively (e.g., fortified tobramycin 13.6 mg/mL/topical vancomycin 25 mg/mL). Fungal keratitis and *Acanthamoeba* keratitis should be considered in patients in high risk geographic areas and who are non-responsive to antibacterial medications. For patients with a history of herpetic corneal disease, systemic antiviral prophylaxis prior to epithelial-off CXL should be considered.

**OTHER PERIOPERATIVE CONSIDERATIONS: DRY EYE AND BLEPHARITIS**

The most important consideration when performing epithelial-off CXL is to optimize epithelial healing post-procedure to ensure full recovery of the cornea. To this end, it is critical to identify and address any pre-existing eye conditions or risk factors prior to surgery that may impact that healing process and influence the local inflammatory response to surgery. One such condition is dry eye, as it has the potential to impact negatively epithelial healing. While CXL outcomes in patients with pre-existing dry eye are shown to be positive, the use of punctal plugs to raise the tear film or an amniotic graft such as Prokera® (Bio-Tissue Inc., Miami, FL) to enhance corneal nerve density/sensitivity and reduce dry eye symptoms are effective in facilitating epithelial healing. 

Blepharitis and vernal conjunctivitis are other conditions that require attention prior to performing epithelial-off CXL. Chronic ocular exposure to bacteria, such as that observed with blepharitis, has the potential to exacerbate host defence mechanisms and activate inflammatory processes, which may lead to sterile infiltrate production and bacterial keratitis following CXL, although more studies are required. To prevent post-procedural complications, the use of prophylactic antibiotics is advisable. In contrast, the use of NSAIDs has been shown to increase the risk of patients developing sterile infiltrates four-fold following epithelial-off CXL.

**CONCLUSION**

Epithelial-off CXL has had a significant positive impact on the prognosis of keratoconus, post-LASIK ectasia, and other conditions in which corneal integrity is compromised. In the absence of implementing pre-operative strategies to mitigate risk factors predicting poor outcomes or giving attention to infection and inflammation in the immediate postoperative phase of epithelial healing, epithelial-off CXL can lead to serious complications. Continued research into customized CXL techniques and riboflavin formulations (more so for the less invasive procedure of epithelial-on CXL) can enhance the safety and long-term benefits of this important therapeutic option and expand its application to new indications such as infectious keratitis and corneal ectasia.

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1. Which management strategies for post-CXL inflammation are recommended?
   A. Topical steroidal eyedrops administered for only 5 days after Epi-Off CXL
   B. High potency steroidal eyedrops administered every hour for keratoconus patients
   C. Topical steroidal eyedrops and NSAIDs if indicated for pain
   D. Topical NSAID applied QID for 2-3 weeks following Epi-Off CXL

2. Which of the following is true regarding suprachoroidal CLS-TA dosed once every 3 months in clinical trials?
   A. Improved visual acuity at 24 weeks in uveitis patients
   B. Reduced central subfield thickness at week 24 in uveitis and, as adjunct to Eylea, in DME patients
   C. Both A and B
   D. None of the above

3. Which of the following statements is accurate regarding the newly approved product Dexycu (dexamethasone intraocular suspension) 9%?
   A. It contains triamcinolone
   B. It is preservative-free
   C. It is indicated for chronic inflammation associated with DME
   D. It is formulated for periocular injection

4. Technique for injecting medication into the suprachoroidal space
   A. Requires patients be placed under general anesthesia
   B. Requires a proprietary micro-needle/injector system
   C. Involves aspirating suprachoroidal fluid once the needle pierces the sclera
   D. Increases patient risk for hypotony because a large gauge needle is used

5. Which duration of effect is currently NOT available from a sustained release corticosteroid available in the US?
   A. 3 weeks
   B. 1 to 3 months
   C. 6 to 12 months
   D. 2 to 3 years

6. Which statements are correct regarding post-CXL infectious keratitis:
   A. Infection is predominantly due to gram-negative bacteria
   B. Small superficial infiltrates outside of the visual axis should be treated aggressively with fortified tobramycin/vancomycin
   C. Pathogen identification is not critical to achieving optimal infection control when there is a large central corneal ulcer
   D. Infection is predominantly due to gram-positive bacteria

7. Which peri-operative management strategies are relevant for epithelial-off CXL:
   A. Use of an amniotic graft such as PROKERA to help close a persistent epithelial defect
   B. Use of prophylactic antibiotics for treatment of blepharitis prior to CXL
   C. Use of punctal plugs to raise the tear film for dry eye
   D. All of the above

8. Corneal haze and infectious keratitis may result from which procedure:
   A. Epithelial-off CXL for post-LASIK ectasia
   B. Epithelial-on CXL
   C. Dresden protocol CXL for keratoconus
   D. All of the above

9. Which of the following corticosteroid implants is NOT placed via an in-office procedure?
   A. Iluvien
   B. Yutiq
   C. Ozurdex
   D. All of the above can be placed via an in-office procedure

10. Corneal collagen cross-linking is FDA-approved for which clinical presentations:
    A. Post-LASIK ectasia and stable keratoconus
    B. Pellucid Marginal Degeneration and progressive keratoconus
    C. Infectious keratitis and stable keratoconus
    D. Post-LASIK ectasia and progressive keratoconus