CME Monograph

TARGETING ANTERIOR UVEITIS: A FOCUS ON IONTOPHORESIS AND OTHER ADVANCED TECHNOLOGIES

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ACTIVITY DESCRIPTION

Anterior uveitis is the most common form of uveitis. It can be associated with significant morbidity, including permanent loss of vision, as a result of complications that can develop without appropriate treatment. Topical corticosteroid treatment to control inflammation is the mainstay for management of anterior uveitis, but there are limitations associated with its use. This educational activity reviews the challenges accompanying topical corticosteroid therapy and presents information on emerging therapeutics, with a focus on corticosteroid delivery by iontophoresis as a novel approach.

TARGET AUDIENCE

This educational activity is intended for ophthalmologists, including ophthalmology fellows.

LEARNING OBJECTIVES

Upon completion of this activity, participants will be better able to:

- Describe the mechanism of action of iontophoresis and other advanced drug-delivery technologies
- Review the safety and efficacy data on dexamethasone treatment via iontophoresis for the treatment of anterior uveitis
- Use dexamethasone treatment via iontophoresis in appropriate patient scenarios

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TARGETING ANTERIOR UVEITIS: A FOCUS ON IONTOPHORESIS AND OTHER ADVANCED TECHNOLOGIES

ANTERIOR UVEITIS: CURRENT MANAGEMENT AND EMERGING OPTIONS

Anterior uveitis, which involves inflammation of the iris and is often accompanied by ciliary body inflammation (iridocyclitis), accounts for up to 90% of uveitis cases in Western countries and has an estimated prevalence of 1 in 4500 people.[1-5] Affected patients can experience pain, photophobia, and decreased vision, and are at risk for permanent loss of vision from complications that can develop without appropriate treatment.

There are numerous identifiable etiologies for anterior uveitis. They can be broadly divided into infectious and noninfectious causes. A detailed history, physical examination, review of systems, and careful ocular examination are essential for identifying the underlying causes, which will direct a targeted treatment plan.

Elimination of all inflammation is the treatment goal for every case. Treatment for infectious uveitis requires pathogen-directed antimicrobial agents, with or without corticosteroids. Topical corticosteroid treatment is the standard for anti-inflammatory treatment of noninfectious anterior uveitis. Depending on the uveitis etiology, severity of the inflammation, and the presence of posterior segment involvement, topical corticosteroid treatment can be supplemented with periocular corticosteroid injections, intravitreal treatments, oral prednisone, topical and/or oral nonsteroidal anti-inflammatory drugs (NSAIDs), and/or systemic immunomodulatory treatment.[6] Patients can also be prescribed a cycloplegic agent to control pain and to minimize the development of synechiae.

There are a number of topical corticosteroid products from which to choose for treating anterior uveitis. Because of cost and insurance issues, generic prednisolone acetate suspension, 1%, can be used as first-line treatment. Results from randomized controlled clinical trials indicate that compared with prednisolone acetate, 1%, difluprednate emulsion, 0.05%, can provide greater efficacy, with the convenience of less frequent dosing. In 2 phase 3 studies, difluprednate emulsion, 0.05%, administered 4 times daily demonstrated superiority to prednisolone acetate suspension, 1%, used 8 times daily for clearing anterior chamber cells (ACCs).[7,8] The rate of study discontinuation due to lack of efficacy was also lower among patients treated with difluprednate than in patients treated with prednisolone.[9]

Although topical corticosteroid treatment is effective for anterior uveitis, several limitations are associated with its use. Barriers to penetration after topical delivery limit drug bioavailability at target tissues **(Figure 1)**.[10] To overcome this issue, a corticosteroid treatment regimen might require frequent dosing and a prolonged course of therapy.[11] Patient nonadherence to the demanding administration schedule and/or difficulties with drop administration can compromise treatment efficacy. In addition, intensive and ongoing therapy puts patients at risk for corticosteroid-related side effects of intraocular pressure (IOP) elevation and cataract development, along with preservative-related corneal toxicity.

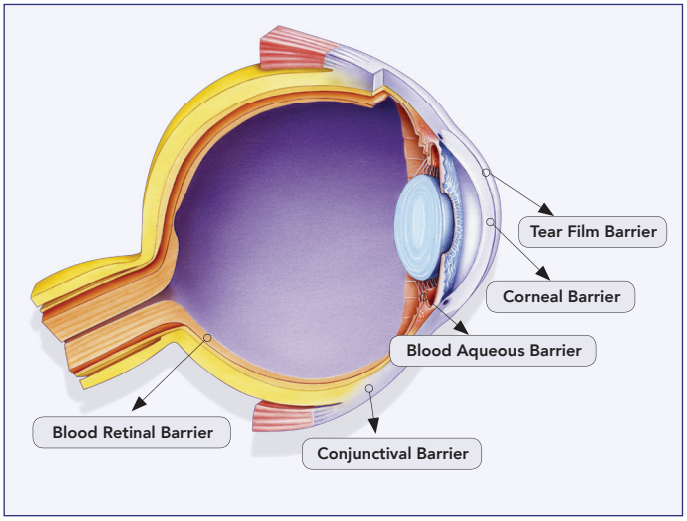

Figure 1. Ocular barriers to drug bioavailability[10]

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INVESTIGATIONAL TREATMENTS FOR ANTERIOR UVEITIS

The limitations associated with topical corticosteroid therapy have prompted interest in the development of alternative treatments that can offer better drug delivery and/or greater safety. Drug delivery using nanoparticle technology and other nanocarriers is one area under investigation.[12,13] Nanoparticles carrying corticosteroids can be engineered to achieve increased penetration through ocular surface barriers and prolonged contact with the ocular surface and target tissues.[12-14] To date, however, this approach has not been evaluated as a treatment for anterior uveitis in any clinical trials.

Treatments for anterior uveitis that have advanced to clinical testing include reproxalap (formerly ADX-102 and NS2), a novel aldehyde "trap" that rapidly binds free aldehydes, which are potent intracellular proinflammatory compounds.[15,16] The drug-aldehyde dimer is transported intracellularly, where it is quickly metabolized. In a phase 2 clinical trial, reproxalap showed promising activity as a treatment for noninfectious anterior uveitis, and was not associated with IOP elevation.[15,16] Phase 3 studies investigating reproxalap for the treatment of uveitis and allergic conjunctivitis are ongoing,[17,18] and a phase 2 study is investigating reproxalap in patients with dry eye disease.[19]

CLS-TA is a triamcinolone acetonide formulation delivered into the suprachoroidal space using a proprietary microinjector system.[20] It is being developed as a treatment for macular edema associated with noninfectious uveitis, including anterior uveitis, as well as for retinal vein occlusion and diabetic macular edema. Topline results from a phase 3 study evaluating CLS-TA for the treatment of noninfectious uveitis showed the percentage of patients with a ≥ 15 ETDRS (Early Treatment Diabetic Retinopathy Study) letter gain from baseline to week 24 was significantly higher in the CLS-TA arm than in the control arm receiving a sham injection (46.9% vs 15.6%; $P < .001$). Elevated IOP occurred in 11.5% of patients receiving CLS-TA. There were no serious treatment-related adverse events.

Noninvasive transscleral delivery of dexamethasone represents another novel approach for treating anterior uveitis. Two independent companies (Aciont Inc and EyeGate) using different

technologies are developing this approach. The first is a system for passive delivery of dexamethasone sodium phosphate (DSP) using a scleral lens-type applicator (Visulex-P). This system was evaluated in a phase 1/2 study that randomized 44 patients with noninfectious anterior uveitis into 3 groups to receive (1) prednisolone acetate, 1%, up to 6 drops daily; (2) DSP, 8%, weekly; or (3) DSP, 15%, weekly.[21] Rates of resolution of ACCs were similar in the 3 treatment arms at follow-up visits on study days 8, 15, and 29. The investigational treatments were well tolerated and associated with slight IOP elevation only at the first follow-up visit on day 8.

The other dexamethasone transscleral delivery system being developed for the treatment of noninfectious uveitis has been evaluated most recently in a completed phase 3 study.[22] This system improves intraocular drug delivery of a 40-mg/mL dexamethasone phosphate solution formulated for iontophoresis (EGP-437).

OCULAR IONTOPHORESIS

Intraocular penetration of a topically administered medication through the intact barriers of the cornea and sclera depends on passive diffusion, which is a slow process driven by a concentration gradient.[10] Intraocular accumulation of most systemically administered medications also relies on passive diffusion of the compound through blood vessel walls, although some substances, such as ascorbic acid, enter the eye from the systemic circulation through an active transport mechanism in the ciliary processes.

Iontophoresis, which means "ions that are being carried," uses a weak electric current to promote drug penetration to its target (electrorepulsion). This delivery technique is based on the electrical principle that ions with like charges repel each other. With iontophoretic delivery, application of an electric current to an aqueous drug solution using a cathodic or anodic electrode hydrolyzes the water molecules into hydroxide or hydronium ions, respectively.[23] An opposite-charged electrode is placed at a distal site to complete the electrical current, and the ions generated by hydrolysis drive the like-charged drug molecule into tissues **(Figure 2).**[23,24]

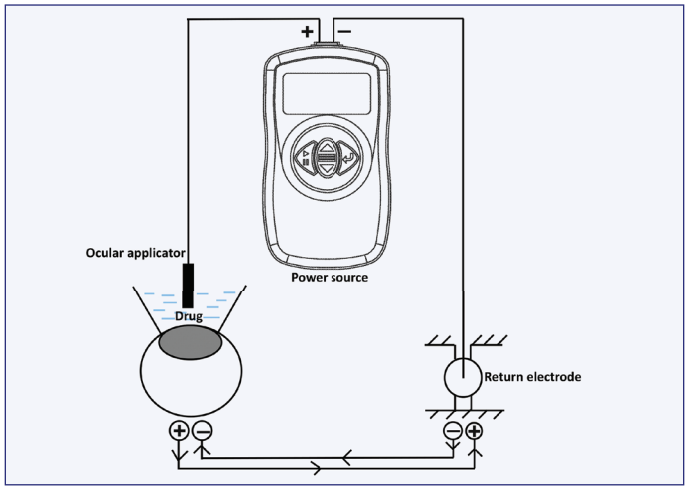

Figure 2. Ocular anodal iontophoresis delivery of a positively charged drug

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Drug penetration with iontophoretic delivery is affected by properties of the barrier tissue (eg, lipophilicity/hydrophilicity, charges, and thickness); the ion being delivered (ie, charge density in the pH of the delivery setting, concentration, molecular size, and molar potency); and the applied electric current (level and duration).[25,26]

Iontophoresis has a long history of use in dentistry, dermatology, and rheumatology for improving drug delivery.[25] Iontophoresis was first evaluated for ocular delivery more than a century ago.[23] It was not developed commercially until the 1980s, when it was introduced to treat hyperhydrosis.[27] At approximately the same time, iontophoresis began to be used for the delivery of anti-inflammatory drugs into joint spaces to avoid trauma caused by intra-articular injections[25] and has been studied for delivery of a variety of medications to treat several ocular diseases **(Table 1)**.[28,29] Most recently, it has been used in studies related to treating dry eye disease,[30] keratoconus,[31] anterior uveitis,[11] and age-related macular degeneration.[32]

Table 1. Compounds and Conditions Investigated in Studies of Ocular Iontophoresis[28,29]

Compounds	Ocular Conditions
Antibiotics	Cataract
Antiviral drugs	Corneal leukemia
Antifungal drugs	Corneal ulcers
Antimetabolites	Episcleritis
Ocular hypotensive agents	Glaucoma
Corticosteroids	Keratitis
Fluorescein	Optic atrophy
Genes (oligonucleotides)	Recalcitrant posterior synechiae
Nonsteroidal anti-inflammatory drugs	

Ocular iontophoresis can be done using a transcorneal or a transscleral approach and with different types of applicator systems. Transcorneal iontophoresis is effective for delivering agents into the anterior segment,[33] but in phakic eyes, only transscleral iontophoresis can deliver therapeutic concentrations to the anterior and posterior segments.[23,28] Proof-of-concept studies show that with modulation of the parameters affecting iontophoretic compound penetration, a wide array of therapeutics, including small molecules, biologics, and nanoparticles, can be preferentially delivered into the anterior or posterior tissues of the eye to reach therapeutically meaningful concentrations using transscleral iontophoresis.[34,35]

Dexamethasone Delivery Via Iontophoresis

A variety of active pharmaceutical ingredients are being developed for ocular iontophoresis, but only EGP-437 has advanced to a confirmatory phase 3 clinical trial.[36] Preclinical studies conducted in rabbits showed that with iontophoresis, concentrations of corticosteroids (methylprednisolone and dexamethasone) in anterior and posterior segment tissues and fluids exceeded those achieved after intravenous or topical administration.[34,35,37] The results of these studies also showed a dose-response relationship between the intraocular levels of the corticosteroids and the applied current, duration of iontophoresis, and drug concentration. Ocular iontophoresis

resulted in negligible systemic corticosteroid levels and was not associated with any clinical or histological evidence of toxicity.

Iontophoretic delivery of EGP-437 is performed with a proprietary system that comprises an annular ocular applicator, an external battery, and an anodic electrode that is placed on the forehead **(Figure 3)**.[29] The ocular applicator features a foam annulus that serves as a reservoir for the dexamethasone phosphate solution. This annulus makes contact with the perilimbal conjunctiva. The ocular applicator houses the cathodic electrode that transfers current from the battery to the drug reservoir, resulting in the creation of negatively charged hydroxyl ions.

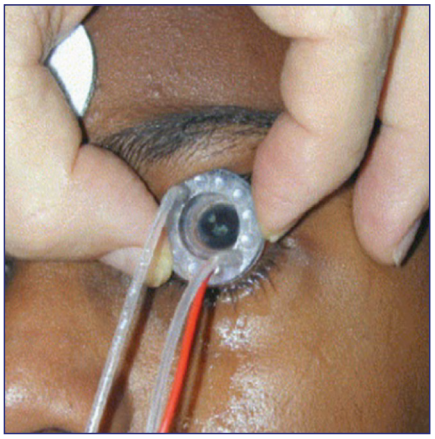

Figure 3. Ocular applicator of a transscleral iontophoresis system

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A phase 1/2 study of EGP-437 treatment for noninfectious anterior uveitis evaluated 4 electric current dose levels: 1.6, 4.8, 10.0, and 14.0 mA-min.[11] It enrolled 40 patients with an ACC score ≥ 1.5 who received a single iontophoretic treatment (4-minute application) and were followed to day 28.

An ACC score of 0, analyzed as the primary efficacy end point, was achieved by 47.5% and 60.0% of patients on days 14 and 28, respectively.[11] At both visits, the highest response rates were achieved in the 2 lower-dose groups **(Table 2)**, presumably because the higher current levels drove the dexamethasone deeper into the eye, rendering it less effective for treating inflammation in the anterior segment.

Table 2. Percentage of Patients Achieving an Anterior Chamber Cell Score of 0[11]

Dose Group*, mA-min	Percentage of Patients	
	Day 14	Day 28
1.6	80	80
4.8	60	60
10.0	20	50
14.0	30	50
Total	47.5	60

* n = 10 in each dose group. Kaplan-Meier analysis was performed to determine the anterior chamber cell score for each dose group.

Two phase 3 studies investigating EGP-437 for the treatment of noninfectious anterior uveitis have been recently completed, and results have yet to be published. The initial phase 3 study included 193 patients with an ACC score ≥ 1 who were randomized to receive EGP-437 delivered for 3 minutes on days 0 and 7 or a 14-day tapering regimen of prednisolone acetate, 1% (8 times daily for 1 week, then 6 times daily for 1 week).[22] The primary efficacy end point was the percentage of patients with an ACC score of 0 at day 14.

Enrollment in the confirmatory phase 3 study was completed in April 2018.[36] In this study, patients were randomized to receive EGP-437 or a tapering regimen of topical prednisolone acetate, 1%. The primary outcome measure was the proportion of patients with an ACC count of 0 at day 14.

Safety

According to the phase 1/2 study, dexamethasone iontophoresis is safe and well tolerated.[11] At the low current densities used, it was not associated with any serious adverse events or electrical burns, and there have been no reports of systemic corticosteroid-mediated effects. The most commonly reported adverse events have been mostly mild in severity. The adverse events in the phase 1/2 study included conjunctival hyperemia (16%), punctate keratitis (11%), conjunctival edema (10%), eyelid edema (6%), and eye pain (6%). The punctate keratitis might have developed secondary to ocular surface exposure while the eye was kept open for the procedure. Instilling a drop of an artificial tear to keep the cornea hydrated during the treatment might be an effective solution to prevent punctate keratitis.

Whereas topical treatment with dexamethasone or prednisolone can cause clinically significant IOP elevation, IOP remained relatively stable and in the normal range in most patients treated with EGP-437 for anterior uveitis.[11,38] Patients with glaucoma; those with IOP ≥ 25 mm Hg, a requirement for ocular antihypertensive medications; or with a history of a steroid response were excluded from clinical trials investigating EGP-437.[11,36] Because of its promising safety profile, however, it can be reasonable to consider EGP-437 in such patients, albeit with careful IOP monitoring. Should EGP-437 become commercially available, decisions on patient selection would need to be individualized and take into account contraindications, cautions, and warnings in the prescribing information.

Role in Clinical Practice

From a practical perspective, experience obtained in premarketing clinical trials indicates that EGP-437 iontophoresis could be readily integrated into clinical practice. The procedure is easy to learn and perform. It can be administered by a technician, an optometrist, or a physician assistant. The setup is simple and straightforward. The ocular applicator is placed after anesthetizing the eye with topical anesthetic, without the need of a speculum. The short, well-tolerated treatment has met with good patient acceptance.

Anterior uveitis can be associated with severe inflammation and can be a chronic or relapsing condition. Clinical experience and additional studies are needed to determine the efficacy and safety of EGP-437 iontophoresis combined with topical corticosteroids either to accelerate and improve uveitis resolution or to use repeatedly as part of an ongoing or intermittent treatment regimen.

UVEITIS CASE STUDY: ACUTE ENDOGENOUS NONINFECTIOUS ANTERIOR UVEITIS

From the Files of John Sheppard, MD, MMSc, FACS

Case History

A 25-year-old white man presents with a 2-day history of severe pain, redness, photophobia, and blurred vision in his right eye. He has ankylosing spondylitis and is positive for human leukocyte antigen B27 (HLA-B27). The patient has a history of 2 previous ipsilateral uveitic flares, hepatitis, and acute gastroenteritis. Visual acuity is 20/80 OD and 20/20 OS. Intraocular pressure is 12 mm Hg OD and 18 mm Hg OS. **Figure 4** shows photographs from the slit-lamp examination.

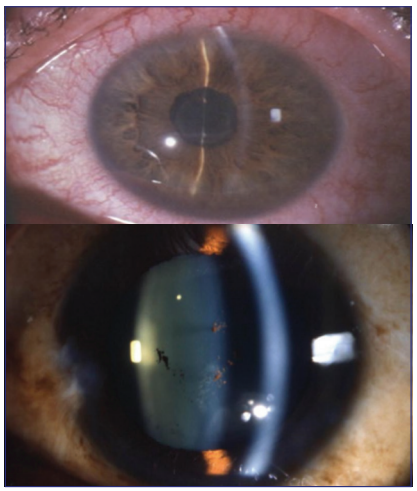

Figure 4. Slit-lamp examination images of the case patient

Images courtesy of John Sheppard, MD, MMSc, FACS

Discussion

Dr Sheppard: The inflammation in eyes with HLA-B27+ anterior uveitis can be severe and difficult to control. The uveitis is often associated with systemic inflammatory disease that mandates patient referral to a rheumatologist.[39] Treatment for the uveitis can require intensive corticosteroid therapy, with administration that is topical, oral, or by periocular injection.

I think iontophoretic delivery of dexamethasone would be useful for managing this type of anterior uveitis. Where would you position it in your treatment algorithm for anterior uveitis? Although EGP-437 was used as standalone corticosteroid treatment in clinical trials, I can imagine using it as induction therapy and for a steroid-sparing benefit. I would probably do the iontophoretic treatment and start patients on topical difluprednate, to be used twice daily, for example, instead of 4 times daily, which is my current standard.

Dr Korenfeld: I also think that iontophoretic corticosteroid delivery could be used as induction therapy. I would use it as a substitute for a corticosteroid injection, and I would also follow it with topical corticosteroid treatment.

Dr Silverstein: I agree with Dr Korenfeld. Using iontophoresis as induction therapy will be first-line treatment at the time of diagnosis in patients with noninfectious uveitis. Repeated applications during early follow-up examinations might be necessary and should be discussed with the patient beforehand. The patient will be prescribed difluprednate, 1%, atropine, and an NSAID to be used topically. If a fibrinoid reaction is present, oral prednisone will also be included in the regimen; if an oral steroid is contraindicated, an oral NSAID will be prescribed. Iontophoretic corticosteroid delivery is first-line therapy because hitting the inflammatory response hard initially is critical to avoid synechiae formation, secondary glaucoma, cataract formation, and cystoid macular edema (CME).

Dr Sheppard: Although HLA-B27–associated ocular inflammation typically presents as anterior uveitis, complications involving the posterior segment often occur, including the development of CME.[39] What are your thoughts about using iontophoresis for corticosteroid delivery to treat these presentations?

Dr Korenfeld: It could be reasonable, considering that with proper selection of the treatment parameters, iontophoresis can deliver high levels of dexamethasone into posterior segment tissues and fluids.[34,35]

Dr Fein: Data from a pilot phase 1b/2a study investigating EGP-437 for the treatment of macular edema provided clinical evidence supporting its efficacy for controlling inflammation in the posterior segment.[40] The study enrolled 25 patients with macular edema associated with retinal vein occlusion, diabetic retinopathy, or postsurgical CME.[40,41] Iontophoresis with EGP-437 was performed on days 0, 4, and 9 at 10.0 mA-min (3.5 mA). The primary outcome was reduction in mean subfield thickness on days 4, 9, 14, and 21. As a control, patients with no improvement at day 14 were given the dexamethasone intravitreal implant and reevaluated at day 21 or 28.[40]

Although this study was terminated because of slow enrollment, data were reported from 19 patients, and the interim results indicate that noninvasive treatment with iontophoresis can deliver dexamethasone to the posterior segment.[40] Responses were better in pseudophakic eyes than in phakic eyes. There were no serious treatment-related adverse events. There were also no IOP elevations, perhaps because the higher electric current level delivers the dexamethasone into the posterior segment and avoids the anterior segment. It should also be noted that the edema returned when the drug cleared from the tissues.

TAKE-HOME POINTS

Topical corticosteroid treatment is the cornerstone of therapy for anterior uveitis, but it has limitations relating to intraocular penetration, patient compliance, and side effects.

Transscleral iontophoretic corticosteroid delivery shows promise as an alternative method for addressing some of the challenges of topical treatment:

- Preclinical studies showed that high corticosteroid concentrations are attained in anterior and posterior segment tissues and fluids
- A phase 1b/2a clinical trial showed that EGP-437, a dexamethasone phosphate formulation for ocular iontophoresis, cleared ACCs after just 1 or 2 treatments, and had minimal to no adverse effect on IOP

More data on transscleral iontophoresis for the treatment of anterior uveitis are needed. The same holds true for the other modalities under investigation, which include a novel aldehyde trap compound, nanoparticles, suprachoroidal triamcinolone acetonide, and a diffusion-based dexamethasone delivery system.

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1. Transscleral iontophoresis increases intraocular delivery of a compound by:
   A. Altering epithelial tight junctions
   B. Changing the compound's charge
   C. Electrorepulsion
   D. Increasing active transport

2. Which of the following is NOT a reason for interest in ocular iontophoresis as an alternative to topical administration for corticosteroid treatment?
   A. Avoids preservative-related ocular surface toxicity
   B. Improves bioavailability
   C. Has a lower cost
   D. Overcomes compliance issues

3. What is the anti-inflammatory mechanism of action of reproxalap?
   A. Binds free aldehydes
   B. Binds to intercellular adhesion molecule-1
   C. Prevents release of proinflammatory cytokines by immune cells
   D. It has the same mechanism of action as corticosteroids but has a unique route of delivery

4. Top-line results from a phase 3 study evaluating CLS-TA (triamcinolone acetonide delivered into the suprachoroidal space) for the treatment of noninfectious uveitis showed the investigational agent:
   A. Caused no IOP elevations
   B. Failed to meet its primary end point
   C. Was associated with a significantly higher percentage of patients gaining ≥ 15 ETDRS letters at week 24 compared with the control group
   D. Was associated with a significantly higher percentage of patients achieving an ACC score of 0 by day 7 compared with the control group

5. The efficacy of iontophoretic drug delivery is affected by properties of the:
   A. Electric current density
   B. Barrier tissue
   C. Ion being delivered
   D. All the above

6. In a phase 1/2 study evaluating EGP-437 for the treatment of noninfectious anterior uveitis, the treatment response rate was higher in groups treated with:
   A. Higher electric current dose levels
   B. Higher concentration of dexamethasone phosphate
   C. Lower electric current dose levels
   D. Topical difluprednate

7. In a phase 1/2 study of noninfectious uveitis, 47.5% and 60.0% of patients receiving EGP-437 at days 14 and 28, respectively, had which of the following responses?
   A. Increased IOP
   B. Decreased IOP
   C. ACC score of 0
   D. No change in ACC score

8. Which was the most commonly reported adverse event in the phase 1/2 study evaluating EGP-437 for the treatment of noninfectious anterior uveitis?
   A. Conjunctival hyperemia
   B. Eye pain
   C. Eye burning
   D. Eyelid bruising

9. Which uveitic anatomic location might be appropriately treated with iontophoretic delivery of EGP-437?
   A. Choroid
   B. Iris
   C. Optic nerve
   D. Pars planta

10. In a phase 1/2 study, the rate of resolution of ACCs at serial follow-up visits in eyes treated with a system for passive delivery of dexamethasone using a topical scleral lens-type applicator (Visulex-P) was:
   A. Dose related, depending on the concentration of dexamethasone used
   B. Dose related, depending on the electric current used
   C. Higher than that of the control group treated with topical prednisolone acetate
   D. Similar to that of the control group treated with topical prednisolone acetate