Postsurgical Inflammation in MIGS

THOMAS W. SAMUELSON, MD  Minimally invasive glaucoma surgery (MIGS) provides a relatively safe option for patients with mild to moderate glaucoma, with multiple procedures that increase aqueous drainage via different routes. The potential for inflammation and the strategies for postsurgical management differ between MIGS approaches. As clinicians gain experience with recently developed surgical devices and procedures, they will be better able to tailor treatment to the needs of specific patients.

With the development of minimally invasive glaucoma surgeries (MIGS), there are now a wide variety of treatment options available. Trabeculectomy and aqueous tube shunt insertions remain the methods of choice in severe glaucoma cases, where large reductions in intraocular pressure (IOP) are required.1 For patients with early stage or mild to moderate glaucoma, MIGS offer less dramatic reductions in IOP than conventional surgery but with a reduced potential for inflammation and increased safety.2

CURRENT STATUS OF MIGS

Currently available MIGS are aimed at increasing aqueous outflow via Schlemm’s canal, the suprachoroidal space, or the subconjunctival space. MIGS that increase outflow via Schlemm’s canal were the first to gain FDA approval3 and are currently the most widely used.

iStent® (Glaukos Corporation, San Clemente, CA), which is FDA approved for use in conjunction with cataract surgery, is an implanted device that increases outflow via Schlemm’s canal, bypassing the trabecular meshwork (TM).3,4 Absolute IOP reductions of 1.3 mm Hg to 9.2 mm Hg have been reported after insertion of a single iStent combined with cataract removal,3 and progressively larger reductions in IOP have been reported when two or three devices are implanted in one eye.3 Trabectome® (NeoMedix, Tustin, CA) is an electrocauterizing device that ablates part of the TM in a 90° to 120° arc. IOP reductions of 4.3 mm Hg to 12.9 mm Hg have been reported with this MIGS.4 A recent study suggests that Trabectome may be most effective in patients with baseline IOP of less than 20 mm Hg.7 The Kahook Dual Blade® (New World Medical, Rancho Cucamonga, CA) and Gonioscopic-Assisted Transluminal Trabeculotomy (GATT, Glaucoma Associates of Texas, Dallas, TX) are both designed for more extensive removal of the TM than Trabectome and are potentially more effective at reducing IOP, but there is a greater incidence of hyphema with these procedures.3,7,8

Devices that increase drainage via the suprachoroidal space (CyPass®, Transcend Medical, Menlo Park, CA) or create a non-physiological subconjunctival route (XEN®, Allergan, Dublin, Ireland) were approved by the FDA in 20163,9 and consequently are not yet as widely used as approaches that target Schlemm’s canal. Data on the efficacy of these devices are limited, but reductions in IOP of 6.2 mm Hg and 9.1 mm Hg have been reported for XEN devices10,11 and up to 8.1 mm Hg for CyPass.3,12

See INSIDE for:
Advances in Antiinflammatory Treatment for Uveitis
by Quan Dong Nguyen, MD, MSC, FAAO
CHOOSING A MIGS PROCEDURE

The choice of procedure for a particular patient is based on multiple factors, including whether cataract surgery will also be performed, the severity of the patient’s glaucoma, the relative risk of progression, the target reduction in IOP, and likelihood that the patient will be compliant with postoperative medication.

Procedures targeting Schlemm’s canal may be less appropriate for patients who have preexisting chronic inflammation and who are likely to need long-term steroid therapy, because of the likelihood of a steroid-induced elevation in IOP after these procedures. The steroid response in these patients may be caused by inflammation of the TM, altered aqueous outflow, or the adverse effect of steroid on the distal outflow system. For these patients, a device that creates an additional subconjunctival drainage route, such as XEN, may be more appropriate.

Demographic data reveal how particular patient groups tend to respond to conventional glaucoma surgery. For example, African Americans are prone to fibrosis of the conjunctiva and sclera after trabeculectomy, and some studies have included demographic data for MIGS. It has been reported that GATT had a lower success rate in African Americans than Caucasians, whereas ethnicity had no significant effect on the outcome of XEN insertion. However, at present there are insufficient data available, and predictions about the responses of particular patient groups to MIGS cannot be made.

The need to stay within FDA approval guidelines and the likelihood of reimbursement by the patient’s medical insurer are additional factors that must be considered. For example, iStent and CyPass are currently approved by the FDA only for use in patients with mild to moderate glaucoma in conjunction with cataract surgery. For patients who are not candidates for cataract surgery, XEN, which is approved as a standalone procedure for refractory glaucoma, as well as Trabectome, Kahook Dual Blade or GATT could be considered as alternatives.

TOPICS IN OCULAR ANTIINFLAMMATORIES, ISSUE 21

STATEMENT OF NEED

The control of ocular inflammation is a critical aspect of medical and surgical opthalmic 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 comfort 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 critical) 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 competencies and narrow gaps between their actual and optimal inflammatory management practices, across the range of clinical situations in which current and novel ocular antiinflammatories may be used.

REFERENCES


OFF-LABEL USE STATEMENT

This work may discuss off-label uses of medications.

GENERAL INFORMATION

This CME activity is sponsored by the University of Florida College of Medicine and supported by an unrestricted educational grant from Shire. The University of Florida College of Medicine designates this activity for a maximum of 1 AMA PRA Category 1 Credit™. There is no fee to participate in this activity. In order to receive CME credit, participants should read the report, and then take the posttest. A score of 80% is required to qualify for CME credit. Estimated time to complete the activity is 30 minutes. On completion and submission of the posttest, the test online at http://cme.ufl.edu/ed/self-study/toai/ System requirements for this activity are: For PC users: Windows® 2000, XP, 2003 Server, or Vista; Internet Explorer® 6.0 or newer, or Mozilla® Firefox® 2.0 or newer (JavaScript™ and Java™ enabled), For Mac® users: Mac OS® X 10.4 (Tiger®) or newer; Safari® 3.0 or newer, Mozilla® Firefox® 2.0 or newer (JavaScript™ and Java™ enabled). Internet connection required: Cable modem, DSL, or better.

DATE OF ORIGINAL RELEASE February 2018. Approved for a period of 12 months.

ACCREDITATION STATEMENT

This activity has been planned and implemented in accordance with the accreditation requirements and policies of the Accreditation Council for Continuing Medical Education (ACME) and the joint providership of the University of Florida College of Medicine and Candee Clinical/Science Communications, LLC. The University of Florida College of Medicine is accredited by the ACME to provide continuing medical education for physicians.

CREDIT DESIGNATION STATEMENT

The University of Florida College of Medicine designates this enduring material for a maximum of 1 AMA PRA Category 1 Credit™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

EDITORIAL BOARD / FACULTY ADVISORS

Marguerite B. McDonald, MD, FACS, practices at Ophthalmic Consultants of Long Island, and is a clinical professor of ophthalmology at the New York University School of Medicine. She is also an adjunct clinical professor of ophthalmology at Tulane University Health Sciences Center. She is a consultant to Allergan, Alcon, Abbott Medical Optics, Bausch + Lomb, FOCUS Laboratories, Shire, OcuSOFT, Altaire, Bio-Tissue, BlexhEx, Oculus USA, and Optical Express.

Vctor 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 has received grants and research support from Shire, and is a consultant for Allergan, Alcon, Bausch & Lomb, EyeGate Pharma, and Shire.

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, sells, or distributes healthcare goods or services consumed by or used on patients relevant to this manuscript.

Quan Dong Nguyen, MD, MSc, FAAO, is a uveitis and retina specialist and professor of ophthalmology at the Byers Eye Institute at Stanford University School of Medicine. He has received grants/research support from AbbVie, Allakos, Genentech, Gilead, Regeneron, and Santen. He is also a consultant for AbbVie, Genentech, Regeneron, and Santen.

Thomas W. Samuelsdon, MD, is a founding partner and attending surgeon of Minnesota Eye Consultants and an adjunct professor of ophthalmology at the University of Minnesota. Dr. Samuelsdon is a consultant for AcaMeds, Aerie Pharmaceuticals, Akorn Pharmaceuticals, Alcon Surgical, Abbott Medical Optics Inc.(AMO), AqueSys Inc, Allergan, Bausch + Lomb/Valeant, BELKIN Laser, EndoOptiks, Equinox, Glaukos, Ivantis, Inc., Ocular Surgery News, PolyActive, Santen, Shire, Transdisc Medical, Veracity Innovations, LLC, and Vindico Medical Education/SLACK Incorporated. He also has stock options for Equinox, Glaukos, and Ivantis, Inc.

DISCLAIMER

Participants have an implied responsibility to use the newly acquired information to improve patient outcomes and as a basis for professional development. The information presented in this activity is not meant to serve as a guideline for patient care, procedures, medications, and other courses of diagnosis and treatment discussed or suggested in this activity. It should not be used for the diagnosis or treatment of their patients’ conditions and possible contraindications or dangers in use, applicable manufacturer’s product information, and comparison with recommendations of other authorities.

COMMERCIAL SUPPORTERS

This activity is supported by an unrestricted educational grant from Shire.
MANAGING INFLAMMATION AFTER MIGS

The degree of tissue disruption and the potential to cause inflammation varies between MIGS. Consequently, the preferred postoperative management strategies differ between procedures. An attractive feature of iStent is the minimal inflammation induced by the procedure. Inflammation induced by combined iStent insertion and cataract surgery has been reported to be similar to that induced by cataract surgery alone. Consequently, management of inflammation following cataract surgery plus iStent insertion follows the same course as for cataract surgery alone. The recommended strategy, based on clinical experience, is nonsteroid antiinflammatories for approximately one month, with topical steroids for the first two weeks. The short exposure to steroid antiinflammatories limits the likelihood of a steroid response and elevated IOP.15

Procedures that involve excision of tissue, such as Trabectome, Kahook Dual Blade or GATT, are more disruptive, can result in hyphema, and are therefore likely to generate a prolonged inflammatory response.16 Hyphema is similarly known to occur after CyPass insertion.7 Inflammation of the conjunctiva and Tenon’s capsule has been observed in the clinic after transscleral procedures such as XEN or InnFocus MicroShunt® (Santen Pharmaceutical Co, Japan, not yet FDA approved) insertion. For these procedures, a longer period of steroid therapy is also recommended, similar to trabeculectomy.

Antibiotics and antiinflammatory agents can also be injected at the time of surgery.17 However, steroid injections or other sustained release steroid preparations may be problematic for patients undergoing canal surgery or suprachoroidal surgery because of the likelihood of a steroid response and the difficulty in withdrawing the steroid if IOP becomes elevated. This is far less of a concern with transscleral surgeries such as Xen or the InnFocus device.

MANAGING IOP AFTER MIGS

A reduced need for topical glaucoma medication after surgery has been reported for all FDA-approved MIGS.3,18 Based on clinical experience, it may be possible to withdraw all glaucoma medications after insertion of CyPass, XEN and InnFocus® devices, at least initially. Although the number of topical glaucoma medications administered can be reduced after Schlemm’s canal surgeries, such as iStent®, the possibility of a steroid response and elevated IOP makes it inadvisable to discontinue all medications, at least until steroid therapy is completed.

Continued monitoring for signs and symptoms of glaucoma is vital after surgery. The goal of MIGS is to control IOP with a reduced reliance on medication and a smaller risk of surgical complications than conventional surgery.16 It is possible that the reduction in IOP after MIGS will not be sufficient and that the patient will require additional surgery.3 Vigilant follow-up monitoring will enable additional procedures to be performed without delay. While there are significant advantages to MIGS surgeries in terms of safety, it is vital that MIGS surgeons are willing to move on to more aggressive therapies should the MIGS procedure fail to adequately lower IOP.

CONCLUSIONS

As more clinical experience is gained with MIGS, the different perioperative courses for each procedure are becoming better understood. Whereas the perioperative period after iStent insertion is expected to follow a similar course to cataract surgery, it is becoming apparent that the postsurgical course is different for other MIGS devices. For example, although choroidal effusion is not reported as an adverse outcome after CyPass insertion,12 clinical experience shows that it is possible in some patients. This can cause a refractive change, resulting in a temporary myopic shift. With XEN, there is a possibility of hypotony, which is usually transient and generally resolves without further surgical intervention.11 Each type of MIGS has its own advantages and disadvantages. As more clinical experience is gained with the various procedures, the ability of the clinician to select the most appropriate approach for a patient and to meet their specific needs will continue to increase.

Thomas W. Samuelson, MD, is a founding partner and attending surgeon of Minnesota Eye Consultants and an adjunct professor of ophthalmology at the University of Minnesota. Dr. Samuelson is a consultant for AcuMEMS, Aerie Pharmaceuticals, Akorn Pharmaceuticals, Alcon Surgical, Abbott Medical Optics Inc.(AMO), AqueSys Inc., Allergan, Bausch + Lomb/Valeant, BELLKIN Laser, Endo Optiks, Equinox, Glaukos, Ivanits, Inc., Ocular Surgery News, PolyActiva, Santen, Shire, Transcend Medical, Veracity Innovations, LLC, and Vindico Medical Education/SLACK Incorporated. He also has stock options for Equinox, Glaukos, and Ivanits, Inc. Medical writer David Loebel, PhD, of Markey Medical Consulting Pty Ltd, assisted in the preparation of this manuscript.

REFERENCES

4. Samuelson TW, Katz LJ, Wells JM, Duh YJ, Giamparcaro JE; US iStent

To obtain CME credit for this activity, go to http://cme.ufl.edu/ed/self-study/toai/


NGUYEN REFERENCES continued from page 7


25. Acathar prescribing information. 2015, Mallinckrodt ARD Inc. Hazelwood, MO


To obtain CME credit for this activity, go to http://cme.ufl.edu/ed/self-study/toai/

ADVANCES IN ANTIINFLAMMATORY TREATMENT FOR UVEITIS

QUAN DONG NGUYEN, MD, MSC, FAAO
Options for the treatment of uveitis are expanding in new and interesting directions.

In the US, noninfectious uveitis affects an estimated 121 per 100,000 (about 300,000 total) adults per year and is a leading cause of vision loss.1,2 About 15 persons per 100,000 (or 38,000) are newly diagnosed each year, most commonly in the third and fourth decades of life.2 Uveitis prevalence and underlying cause (or type) vary by geographic locale. For example, overall uveitis prevalence is higher in India and more commonly associated with an infectious cause such as tuberculosis.

Uveitis may be the result of infectious or noninfectious causes; additionally, ocular malignancy may give the appearance of uveitis, so-called “masquerading” uveitis. It is critical that comprehensive ophthalmologists be able to recognize signs and symptoms of uveitis, eg, ocular redness, pain, photophobia, and blurred vision, and then diagnose the type and anatomic distribution of uveitis if present.3

Anterior uveitis—which accounts for a majority of uveitis cases—is characterized by inflammation that is confined to the anterior uvea or iris and is often managed by the comprehensive ophthalmologist. Initial management is aimed at controlling inflammation quickly and completely and preventing recurrences, all with the lightest possible side effect burden to the patient. Such goals can usually be achieved with short-term topical corticosteroids, albeit not without significant risks for cataract and ocular hypertension or glaucoma development.4

Patients with evidence of intermediate uveitis, posterior uveitis, panuveitis, and choreoretinitis have more severe disease and higher risk for complications such as macular edema and optic nerve inflammation. Such patients are typically referred to a uveitis specialist for management due to the complexity of their disease and the risks associated with many available treatments, discussions around which are necessarily lengthy and often not compatible with the comprehensive practitioner’s workflow.

This article presents a review of basic tenets of treating uveitis, current treatment options, and several drugs and devices that are new, reemerging, or in development.

TREATMENT APPROACH

Uveitis antiinflammatory treatment regimens are designed to align with the circumstances, needs, and wishes of the individual patient. Treatment may include local, systemic, or combined local and systemic therapies, depending in part on whether disease is local or systemic and ocular involvement unilateral or bilateral. The end goal is to achieve the best benefit-to-risk ratio, suppressing inflammation and preserving vision while hopefully limiting side effects and preserving quality of life.

Current uveitis treatments include corticosteroids, nonsteroidal antiinflammatory drugs (NSAIDs), and a large category of corticosteroid-sparing agents including, from least to most potent: 1) antimetabolites (eg methotrexate and mycophenolate), 2) T cell inhibitors or calcineurin inhibitors (eg, cyclosporine A), 3) alkylating agents (eg, cyclophosphamide and chlorambucil), and 4) antitumor necrosis factor (TNF)-α biologics (eg, infliximab, adalimumab).

It is common practice to take a stepladder approach to selecting antiinflammatory treatments, starting with lower potency/low side effect options and then advancing to more potent options as needed.4 Taking treatment for HLA-B27 associated anterior uveitis as an example, patients who fail to adequately respond to topical corticosteroids—that is, who have active inflammation despite once per day or every other day corticosteroid dosing—may require additional therapies, such as an NSAID (eg, naproxen sodium) or an antimetabolite agent (eg, methotrexate).4

But there is no fixed formula, and some conditions call for stronger therapy from the outset. Inflammation associated with Vogt-Koyanagi-Harada or birdshot chorioretinopathy, for example, responds well to the T cell inhibitor cyclosporine in combination with low-dose corticosteroids, with or without an antimetabolite.5 Sarcoid posterior uveitis is typically treated with low-dose corticosteroids and methotrexate; multifocal choroiditis with mycophenolate, which is slightly stronger than methotrexate, and possibly one or more additional agents.6 Treatment of granulomatosis with polyangiitis (GPA) or other severe vasculitis typically starts even further up the ladder with an alkylating agent or a biologic.7

To obtain CME credit for this activity, go to http://cme.ufl.edu/ed/self-study/toai/
BILOGICS
Variable efficacy and common side effects associated with current steroid-sparing therapies have driven the development of alternative approaches. Biologic therapies are typically reserved for second or third line use (ie, treatment-recalcitrant cases) or in cases of severe disease, such as uveitis associated with Adamantiales-Behcet’s diseases. Currently available biologic therapies target immune marker TNF-α and selected interleukins; biologics targeting other molecules are in development.

Infliximab (Remicade; Janssen Biotec, Inc. Horsham, PA) is approved for a range of systemic autoimmune conditions—from rheumatoid arthritis (RA) to ankylosing spondylitis—and is sometimes used off-label in the treatment of uveitis. Based on the positive results from multinational phase 3 clinical trials VISUAL 1 and VISUAL 2, adalimumab (Humira; Abbie Inc, North Chicago, IL) was recently approved for subcutaneous treatment of noninfectious intermediate and posterior uveitis and panuveitis, making it the first approved biologic with a uveitis indication.8,10

Interleukin 6 (IL-6) is an inflammatory cytokine thought to play a role in a range of autoimmune diseases including uveitis.11 Biologics that block IL-6 are currently being investigated for the treatment of uveitis. Tocilizumab (Actemra; Genentech Inc., South San Francisco CA), an IL-6 inhibitor indicated for the treatment of RA, has shown promising results in early clinical trials aimed at controlling inflammation in patients with non-ante rior uveitis. Six-month results of the multicenter, open-label STOP-Uveitis trial (N = 37) revealed that monthly infusions of intravenous (IV) tocilizumab reduced vitreous haze and macular edema and improved visual acuity in patients with noninfectious intermediate or posterior uveitis or panuveitis.12 Treatments were well tolerated.

Sarilumab (Sanoﬁ, Bridgewater, NJ), an IL-6 inhibiting therapy currently approved for treatment of RA, is also being investigated for the treatment of noninfectious uveitis. The SATURN study was a phase 2 multicenter trial that compared sub cutaneous sarilumab dosed once every other week versus placebo (against a background of corticosteroid with or without methotrexate) in the treatment of intermediate, posterior, or panuveitis; ﬁnal results are to be reported.15

CORTICOSTEROID DELIVERY AND TOPICAL ALTERNATIVES
Sustained Delivery
Sustained delivery of corticosteroids for local noninfectious uveitis treatment has been possible since the 2005 approval of Retisert® (flucinolone acetonide implant, Bausch + Lomb, Rochester, NY). Retisert, which lasts about 30 months, is an extremely effective means for controlling inﬂammation in treated eyes; however, patients are virtually guaranteed to have worsening of their cataract and are at high risk for developing ocular hypertension and glaucoma.14 Over the past decade, researchers have been trying to develop improved intraocular corticosteroid delivery systems with lower risks to patients.

Ozurdex® (dexamethasone intravitreal implant) (Allergan, Irvine, CA), a biodegradable implant that releases drug for up to 6 months (after peaking at 2 months), is approved for treatment of posterior uveitis.15 In a single study, Ozurdex placement was statistically superior to sham treatment in controlling inﬂammation, improving visual acuity, and reducing macular edema.16 Over 26 weeks of observation, there was a non-statistically signiﬁcant trend toward higher rates of cataract worsening and IOP elevation in treated eyes.16 While effective in the short term, antiinflammatory treatment is often needed beyond 3 to 4 months; and the effect of repeated Ozurdex implants is not clear, which limits its utility for chronic uveitis.15

A flucinolone acetonide sustained-release device for the treatment of noninfectious posterior uveitis is in development by pSivida Corp (Watertown, MA).17 The device, called Durasept®, is implanted via intravitreal injection and delivers low-dose drug over 3 years. According to the website, phase 3 trials have been completed and NDA ﬁling is planned for December of 2017 or January of 2018.17 It will be important to see the data on this product when it is made available.

Iontophoresis
Iontophoresis—the use of a controlled electrical current to drive charged molecules across a membrane—is being studied as a means for enhancing intraocular delivery of dexamethasone with the hope of equivalent or better inﬂammation control with lower total medication exposure compared with depot methods or drops.18 A placebo-controlled phase 3 study of ocular iontophoresis with dexamethasone phosphate ophthalinic solution EGP-437 using the EyeGate® II Drug Delivery System (EGDS) (EyeGate Pharmaceuticals, MA, USA) in patients with anterior uveitis demonstrated comparable efﬁcacy to prednisolone acetate 1% topical ophthalinic solution and signiﬁcantly fewer incidents of intraocular pressure (IOP) increase.19,20 A second phase 3 trial to conﬁrm the role of iontophoresis as a practical tool in the management of uveitis is ongoing.21

Aldehyde Trap
Aldehydes are proinflammatory mediators thought to be involved in the propagation of ocular inﬂammation associated with ocular allergy and uveitis; extracting or trapping aldehydes represents a steroid-independent pathway for reducing ocular inﬂammation. According to the company’s press release, a phase 2 trial of ﬁrst-in-class aldehyde trap molecule 0.5% ADX-102 (in development by Aldeyra Therapeutics, Lexington, MA) administered four times daily for treatment of noninfectious anterior uveitis, resulted in efﬁcacy comparable to topical corticosteroid treatment, with 53% vs. 38% of patients, respectively, achieving grade 0 anterior chamber cell count by 4 weeks.22 Patients treated with ADX-102 were also less likely to require rescue therapy compared with those treated with corticosteroids. Importantly, no patient treated with ADX-102 had IOP elevations. Further studies evaluating aldehyde traps for the treatment of anterior uveitis and ocular allergy are underway.

NOVEL INVESTIGATIONAL STRATEGIES
ACTH Gel
A puriﬁed porcine analogue of the naturally occurring
human hormone adrenocorticotropic hormone (ACTH) has been available since the 1950s as short-term therapy for a broad range of inflammatory and autoimmune disease including RA, multiple sclerosis, systemic sarcoidosis, and uveitis.\textsuperscript{23} Also called repository corticotropin injection (RCI) and marketed as H.P. Acthar Gel (Mallinckrodt Pharmaceuticals Inc., Hampton, NJ), ACTH gel is thought to stimulate endogenous release of cortisol and bind to melanocortin receptors, resulting in a range of antiinflammatory effects including but not limited to reducing TNF-α, IL-2, and T-cell proliferation.\textsuperscript{24} ACTH gel—which can be injected subcutaneously (SC) or intramuscularly—has been associated with reduced need for other more toxic agents including biologics, corticosteroids, and disease-modifying antirheumatic drugs (DMARDs).\textsuperscript{25,26}

Although approved for the treatment of ocular inflammation for decades, there is a paucity of data around the efficacy, safety, and optimal dosing of ACTH gel injection for the treatment of uveitis. A recent case report demonstrates the use of ACTH gel in a patient with uveitis and retinal vasculitis.\textsuperscript{26} Recently, a number of clinician scientists have developed renewed interests in ACTH gel for the treatment of uveitis. A randomized, multicenter phase 2 study on the safety and bioactivity of two dosing regimens of ACTH gel SC in patients with non-infectious uveitis, the ACTHAR Study, as well as a multicenter phase 2 study of ACTH gel SC in patients with scleritis, the ATLAS Study, have been launched in the United States.\textsuperscript{27}

Sirolimus

Sirolimus (also known as rapamycin) is a small molecule derived from the soil microbe Streptomyces hygroscopicus that binds and inhibits the mammalian target of rapamycin (mTOR).\textsuperscript{28} Sirolimus, which has long been of interest for its antineoplastic potential, is currently the active ingredient in a drug-eluting cardiac stent for the prevention of coronary vessel stenosis and an immunomodulating agent in patients who have undergone renal transplant.\textsuperscript{28,29}

Locally delivered sirolimus, subconjunctival and intravitreal, was first evaluated in patients with non-infectious uveitis in the SAVE Study,\textsuperscript{30} followed by the SAVE-2 Study which evaluated two different doses of intravitreal sirolimus.\textsuperscript{31} Subsequently, an NDA was filed with the FDA in February 2017 for Opsiria (sirolimus 440 μg intravitreal injection; Santen Pharmaceuticals, Osaka, Japan) based on the results from phase 3 clinical trials Sirolimus Study Assessing Double-Masked Uveitis Treatment (SAKURA-1 and -2).\textsuperscript{32,33} If approved, sirolimus stands to become the first locally delivered injected immunomodulatory agent for the treatment of intermediate, posterior, and panuveitis. A phase 3b open-label, long-term extension trial SPRING is ongoing.\textsuperscript{33}

CONCLUSION

Suspecting and detecting uveitis starts in the comprehensive eye care clinic, where most cases may be managed. Therapeutic options are expanding from novel corticosteroid delivery systems and small molecule disease-modifying anti-rheumatic drugs (DMARDs) to biologics and other immunomodulators.

Quan Dong Nguyen, MD, MSc, FAAO, is a uveitis and retina specialist and professor of ophthalmology at the Byers Eye Institute at Stanford University School of Medicine. He has received grant/research support from AbbVie, Allakos, Genentech, Gilead, Regeneron, and Santen. He is also a consultant for AbbVie, Genentech, Regeneron, and Santen. Medical writer Noelle Lake, MD, assisted in the preparation of this manuscript.

REFERENCES


NGUYEN REFERENCES continue on page 4
1. Hyphema has been reported with which MIGS?
   A. Trabectome
   B. GATT
   C. CyPass
   D. A, B, and C

2. When performed in combination with cataract surgery, which MIGS procedure generates minimal extra inflammation?
   A. Trabectome
   B. iStent insertion
   C. Kahook
   D. GATT

3. Which of the following best characterizes the mechanism of action of potential corticosteroid alternate ADX-102, in development by Aldeyra?
   A. Calcineurin inhibitor
   B. Aldehyde trap
   C. Superoxide scavenger
   D. JAK agonist

4. Elevated IOP due to steroid response may be more likely with which MIGS?
   A. Cypass
   B. XEN
   C. iStent
   D. None of the above

5. Which MIGS creates a non-physiological drainage route via the subconjunctival space?
   A. iStent
   B. CyPass
   C. XEN
   D. InnFocus

6. Which of the following is NOT a corticosteroid-sparing agent?
   A. Mycophenolate
   B. Cyclosporine
   C. Infliximab
   D. All of the above are corticosteroid-sparing agents

7. Biologic agents currently available for the treatment of uveitis target which molecule?
   A. IL-2
   B. IL-6
   C. TNF-α
   D. None of the above

8. Sirolimus (rapamycin) has which of the following actions?
   A. Antimicrobial
   B. Immunosuppressive
   C. Antiinflammatory
   D. All of the above

9. Which MIGS increases drainage via Schlemm’s canal?
   A. iStent
   B. CyPass
   C. XEN
   D. InnFocus

10. The most common form of uveitis is:
    A. Anterior
    B. Intermediate
    C. Posterior
    D. Panuveitis