MASKING THE RISK of ENDOPHTHALMITIS after anti-VEGF injections
YUTIQ is designed to deliver a sustained release of fluocinolone for up to 36 months for patients with chronic non-infectious uveitis affecting the posterior segment of the eye.

- **Proven to reduce uveitis recurrence at 6 and 12 months**: At 6 months, 18% for YUTIQ and 79% for sham for Study 1 and 22% for YUTIQ and 54% for sham for Study 2. At 12 months, 28% for YUTIQ and 86% for sham for Study 1 and 33% for YUTIQ and 60% for sham for Study 2.
- **Extended median time to first recurrence of uveitis**: At 12 months, NE for YUTIQ/92 days for sham in Study 1; NE for YUTIQ/187 days for sham in Study 2.
- **Mean intraocular pressure (IOP) increase was comparable to sham**: Study was not sized to detect statistically significant differences in mean IOP.

* Study design: The efficacy of YUTIQ was assessed in 2 randomized, multicenter, sham-controlled, double-masked, Phase 3 studies in adult patients (N=282) with non-infectious uveitis affecting the posterior segment of the eye. The primary endpoint in both studies was the proportion of patients who experienced recurrence of uveitis in the study eye within 6 months of follow-up; recurrence was also assessed at 12 months. Recurrence was defined as either deterioration in visual acuity, vitreous haze attributable to non-infectious uveitis, or the need for rescue medications.

**INDICATIONS AND USAGE**

**YUTIQ** (fluocinolone acetonide intravitreal implant) 0.18 mg is indicated for the treatment of chronic non-infectious uveitis affecting the posterior segment of the eye.

**IMPORTANT SAFETY INFORMATION**

**CONTRAINDICATIONS**

- **Ocular or Periocular Infections**: YUTIQ is contraindicated in patients with active or suspected ocular or periocular infections including most viral disease of the cornea and conjunctiva including active epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, varicella, mycobacterial infections and fungal diseases.
- **Hypersensitivity**: YUTIQ is contraindicated in patients with known hypersensitivity to any components of this product.

**WARNINGS AND PRECAUTIONS**

- **Intravitreal Injection-related Effects**: Intravitreal injections, including those with YUTIQ, have been associated with endophthalmitis, eye inflammation, increased or decreased intraocular pressure, and choroidal or retinal detachments. Hypotony has been observed within 24 hours of injection and has resolved within 2 weeks. Patients should be monitored following the intravitreal injection.
- **Steroid-related Effects**: Use of corticosteroids including YUTIQ may produce posterior subcapsular cataracts, increased intraocular pressure and glaucoma. Use of corticosteroids may enhance the establishment of secondary ocular infections due to bacteria, fungi, or viruses. Corticosteroids are not recommended to be used in patients with a history of ocular herpes simplex because of the potential for reactivation of the viral infection.
- **Risk of Implant Migration**: Patients in whom the posterior capsule of the lens is absent or has a tear are at risk of implant migration into the anterior chamber.

**ADVERSE REACTIONS**

In controlled studies, the most common adverse reactions reported were cataract development and increases in intraocular pressure.

Please see brief summary of full Prescribing Information on adjacent page.

**References**: 1. YUTIQ® (fluocinolone acetonide intravitreal implant) 0.18 mg full US Prescribing Information. EyePoint Pharmaceuticals, Inc. May 2021. 2. Data on file.
YUTIQ® (fluocinolone acetonide intravitreal implant) 0.18 mg, for intravitreal injection
Initial U.S. Approval: 1983

BRIEF SUMMARY: Please see package insert for full prescribing information.

1. INDICATIONS AND USAGE. YUTIQ® (fluocinolone acetonide intravitreal implant) 0.18 mg is indicated for the treatment of chronic non-infectious uveitis affecting the posterior segment of the eye.

4. CONTRAINDICATIONS. 4.1. Ocular or Periocular Infections. YUTIQ® is contraindicated in patients with active or suspected ocular or periocular infections including most viral disease of the cornea and conjunctiva including active epithelial herpetic keratitis (dendritic keratitis), vaccinia, varicella, mycobacterial infections and fungal diseases. 4.2. Hypersensitivity. YUTIQ is contraindicated in patients with known hypersensitivity to any components of this product.

5. WARNINGS AND PRECAUTIONS. 5.1. Intravitreal Injection-related Effects. Intravitreal injections, including those with YUTIQ, have been associated with endophthalmitis, eye inflammation, increased or decreased intraocular pressure, and choroidal or retinal detachments. Hypotony has been observed within 24 hours of injection and has resolved within 2 weeks. Patients should be monitored following the intravitreal injection [see Patient Counseling Information (17) in the full prescribing information]. 5.2. Steroid-related Effects. Use of corticosteroids including YUTIQ may produce posterior subcapsular cataracts, increased intracocular pressure and glaucoma. Use of corticosteroids may enhance the establishment of secondary ocular infections due to bacteria, fungi, or viruses. Corticosteroids are not recommended to be used in patients with a history of ocular herpes simplex because of the potential for reactivation of the viral infection. 5.3. Risk of Implant Migration. Patients in whom the posterior capsule of the lens is absent or has a tear are at risk of implant migration into the anterior chamber.

6. ADVERSE REACTIONS. 6.1. Clinical Studies Experience. Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. Adverse reactions associated with ophthalmic steroids including YUTIQ include cataract formation and subsequent cataract surgery, elevated intraocular pressure, which may be associated with optic nerve damage, visual acuity and field defects, secondary ocular infections from pathogens including herpes simplex, and perforation of the globe where there is thinning of the cornea or sclera. Studies 1 and 2 were multicenter, randomized, sham injection-controlled, masked trials in which patients with non-infectious uveitis affecting the posterior segment of the eye were treated once with either YUTIQ or sham injection, and then received standard care for the duration of the study. Study 3 was a multicenter, randomized, masked trial in which patients with non-infectious uveitis affecting the posterior segment of the eye were all treated once with YUTIQ, administered by one of two different applicators, and then received standard care for the duration of the study. Table 1 summarizes data available from studies 1, 2 and 3 through 12 months for study eyes treated with YUTIQ (n=226) or sham injection (n=94). The most common ocular and non-ocular adverse reactions are shown in Table 1 and Table 2.

Table 1: Ocular Adverse Reactions Reported in ≥ 1% of Subject Eyes and Non-Ocular Adverse Reactions Reported in ≥ 2% of Patients

<table>
<thead>
<tr>
<th>ADVERSE REACTIONS</th>
<th>YUTIQ (N=226 Eyes) n (%)</th>
<th>Sham Injection (N=94 Eyes) n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cataract†</td>
<td>63/113 (56%)</td>
<td>13/56 (23%)</td>
</tr>
<tr>
<td>Visual Acuity Reduced</td>
<td>33 (15%)</td>
<td>11 (12%)</td>
</tr>
<tr>
<td>Macular Edema</td>
<td>25 (11%)</td>
<td>33 (35%)</td>
</tr>
<tr>
<td>Uveitis</td>
<td>22 (10%)</td>
<td>33 (35%)</td>
</tr>
<tr>
<td>Conjunctival Hemorrhage</td>
<td>17 (8%)</td>
<td>5 (5%)</td>
</tr>
<tr>
<td>Eye Pain</td>
<td>17 (8%)</td>
<td>12 (13%)</td>
</tr>
<tr>
<td>Hypotony Of Eye</td>
<td>16 (7%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Anterior Chamber Inflammation</td>
<td>12 (5%)</td>
<td>6 (6%)</td>
</tr>
<tr>
<td>Dry Eye</td>
<td>10 (4%)</td>
<td>3 (3%)</td>
</tr>
<tr>
<td>Vitreous Opacities</td>
<td>9 (4%)</td>
<td>8 (9%)</td>
</tr>
<tr>
<td>Conjunctivitis</td>
<td>9 (4%)</td>
<td>5 (5%)</td>
</tr>
<tr>
<td>Posterior Capsule Opacification</td>
<td>8 (4%)</td>
<td>3 (3%)</td>
</tr>
<tr>
<td>Ocular Hyperemia</td>
<td>8 (4%)</td>
<td>7 (7%)</td>
</tr>
<tr>
<td>Vitreous Haze</td>
<td>7 (3%)</td>
<td>4 (4%)</td>
</tr>
<tr>
<td>Foreign Body Sensation In Eyes</td>
<td>7 (3%)</td>
<td>2 (2%)</td>
</tr>
<tr>
<td>Vitrits</td>
<td>6 (3%)</td>
<td>8 (9%)</td>
</tr>
<tr>
<td>Vitreous Floaters</td>
<td>6 (3%)</td>
<td>5 (5%)</td>
</tr>
<tr>
<td>Eye Pruritus</td>
<td>6 (3%)</td>
<td>5 (5%)</td>
</tr>
<tr>
<td>Conjunctival Hyperemia</td>
<td>5 (2%)</td>
<td>2 (2%)</td>
</tr>
<tr>
<td>Ocular Discomfort</td>
<td>5 (2%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Macular Fibrosis</td>
<td>5 (2%)</td>
<td>2 (2%)</td>
</tr>
<tr>
<td>Glaucoma</td>
<td>4 (2%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Photopsia</td>
<td>4 (2%)</td>
<td>2 (2%)</td>
</tr>
</tbody>
</table>

Table 2: Summary of Elevated IOP Related Adverse Reactions

<table>
<thead>
<tr>
<th>ADVERSE REACTIONS</th>
<th>YUTIQ (N=226 Eyes) n (%)</th>
<th>Sham Injection (N=94 Eyes) n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IOP elevation ≥ 10 mmHg from Baseline</td>
<td>50 (22%)</td>
<td>11 (12%)</td>
</tr>
<tr>
<td>IOP elevation &gt; 30 mmHg</td>
<td>28 (12%)</td>
<td>3 (3%)</td>
</tr>
<tr>
<td>Any IOP-lowering medication</td>
<td>98 (43%)</td>
<td>39 (41%)</td>
</tr>
<tr>
<td>Any surgical intervention for elevated IOP</td>
<td>5 (2%)</td>
<td>2 (2%)</td>
</tr>
</tbody>
</table>

Figure 1: Mean IOP During the Studies

8. USE IN SPECIFIC POPULATIONS. 8.1 Pregnancy. Risk Summary. Adequate and well-controlled studies with YUTIQ have not been conducted in pregnant women to inform drug associated risk. Animal reproduction studies have not been conducted with YUTIQ. It is not known whether YUTIQ can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Corticosteroids have been shown to be teratogenic in laboratory animals when administered systemically at relatively low dosage levels. YUTIQ should be given to a pregnant woman only if the potential benefit justifies the potential risk to the fetus. All pregnancies have a risk of birth defect, loss, or other adverse outcomes. In the United States general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively. 8.2 Lactation. Risk Summary. Systemically administered corticosteroids are present in human milk and can suppress growth, interfere with endogenous corticosteroid production. Clinical or nonclinical lactation studies have not been conducted with YUTIQ. It is not known whether intravitreal treatment with YUTIQ could result in sufficient systemic absorption to produce detectable quantities of fluocinolone acetonide in human milk, or affect breastfed infants or milk production. The developmental and health benefits of breastfeeding should be considered, along with the mother’s clinical need for YUTIQ and any potential adverse effects on the breastfed child from YUTIQ. 8.4 Pediatric Use. Safety and effectiveness of YUTIQ in pediatric patients have not been established. 8.5 Geriatric Use. No overall differences in safety or effectiveness have been observed between elderly and younger patients.

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As temperatures drop, retinal innovation heats up

Retina specialists—whether they are researching novel therapies, recovering missing data or scrutinizing mask use during procedures—continue to investigate treatment of chronic disease in the compassionate, meticulous style of the specialty.

On page 7, Ashay D. Bhatwadekar, PhD, MPharm, discusses changes in the retina due to aging and the unique challenges older patients present when treating diabetic retinopathy.

Delving into diagnostics on page 10, Jose Agustin Martinez, MD, highlights imaging options for teleretinal screening for diabetic retinopathy and how artificial intelligence fits into the picture. Automated retinal image analysis may improve patient adherence to treatment plans, he adds.

On page 14, Peter Y. Chang, MD, describes how autoimmune diseases can manifest as noninfectious uveitis. Because autoimmune diseases alter the pathophysiology of uveitis, it is essential to think through local vs systemic therapy options, he notes.

Universal masking during anti-VEGF injections decreases the chances of endophthalmitis, Sunir Garg, MD, reports in our cover story (page 16). When masking became the norm in March 2020 due to the COVID-19 pandemic, Garg conducted a study on its effects on endophthalmitis incidence and found the number of cases dropped when everyone in the room bore a mask.

A recent literature review on X-linked retinitis pigmentosa, co-authored by Nan Li, MD, PhD, MHS (page 20), shines a light on the lack of data regarding the humanistic and economic burden of inherited retinal disease.

Lejla Vajzovic, MD, reviews two novel treatments in surgical retina: the port delivery system (PDS) and RGX-314 (page 22). Both are showing promise as durable therapy options for patients with retinal degeneration.

Finally, on page 24, Ashvini Reddy, MD, describes current sustained drug delivery options for chronic ophthalmic conditions as well as challenges in new therapy development.

Thank you for reading this edition of Modern Retina™.

Mike Hennessy Sr, Chairman and founder of Modern Retina™’s parent company, MJH Life Sciences™
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24 FOCAL POINTS: Sustained drug delivery in ophthalmology, By Ashvini Reddy, MD
Bad medicine
Mixing politics, medical science can be problematic

When you mix medicine with politics, you get politics.

The above quote points to the dangers that result when political movements adopt certain medical and scientific observations or theories in order to justify certain political initiatives. Challenging the truth of those theories incurs the wrath of those who have staked their political futures on those same theories. In this way the central tenet of science – that we advance by constantly testing our theories so as to support them or reject them in favor of new theories – is discarded.

Medicine - a science (as well as a compassionate art) – does not seem to be immune from this phenomenon. I have spoken to epidemiologists who tell me that masks probably don’t provide much protection while other experts maintain the masks do tamp down viral transmission. Some political leaders have imposed strict mask mandates while other political leaders have specifically banned any such mandates in their areas of control.

Arguments pro and con are occurring loudly in the streets as part of political demonstrations and also in courtrooms around the country. Frequently, each side claims to be “following the science.”

It is nice to see the value of masks (or the lack thereof) in the setting of intravitreal injections tested in a dispassionate manner in an article in this issue of Modern Retina by Sunir Garg, MD. There certainly is a reasonable basis to suspect that masks might reduce circulating organisms that could land on the conjunctiva and be tracked into the eye with the needle.

Proving or disproving the value of a specific intervention is quite challenging when the rate at which the observed outcome (endophthalmitis) is so uncommon. Sample sizes may need to be so large that it may be difficult or impractical to answer the question in a timely manner.

Frequently, each side claims to be ‘following the science.’

It is tempting in such situations to simply fall back upon some arbitrary practice that seems logical to regulatory agencies or might reduce the risk of lawsuits. For example, despite the absence of credible evidence that postoperative antibiotics drops reduce the risk of endophthalmitis after cataract surgery, they are prescribed for millions of patients each year in the U.S.

Here’s to science and the open-minded ophthalmologists who want to put their prevailing practices to the test!
As cases of diabetes increase worldwide, the disease is accompanied by a precipitous increase in its most common complication, diabetic retinopathy (DR). At the same time, the aging population is growing, which is significant considering that the risk of developing DR increases the longer individuals live with diabetes and that the consequences of DR are unique in older patients.

In a recently published article, Ashay D. Bhatwadekar, PhD, and colleagues reviewed these issues to increase awareness and identify the best strategies for patient care.

"Understanding age-related retinal changes that increase vulnerability to DR in older individuals and age-related therapeutic challenges is essential for optimizing treatment of DR within the senior population," said Bhatwadekar, an associate professor of ophthalmology at the Eugene and Marilyn Glick Eye Institute, Indiana University School of Medicine, in Indianapolis.

"Proper treatment of DR in [senior patients] could reduce the overall burden of diabetes."

**AGE-RELATED RETINAL CHANGES**

The authors pointed out that the retinal structure is altered with age in several ways. Macular blood flow decreases by 20% on average and the retina becomes thinner, with the change in thickness especially affecting the inner nuclear layer. In addition, the response of the microglia to injury slows, Müller cells become more susceptible to oxidative stress and the extent of lipofuscin accumulation in retinal pigment epithelial cells increases.

"The changes in blood flow that occur with aging may worsen ocular perfusion abnormalities in diabetes, and
proliferation of microglia in the outer retina can contribute to proinflammatory responses,” Bhatwadekar said.

There are also age-related metabolic changes affecting the retina that are relevant for the development of DR. Disease-specific pathophysiologic mechanisms, such as accumulation of advanced glycation end products and the polyol pathway that contribute to oxidative stress, take advantage of the aging retina’s vulnerability that is associated with a defunct antioxidant defense system.

In addition, the effects of the VEGF pathway, which promotes angiogenesis, vascular permeability, and inflammation, could be augmented in the eyes of elderly individuals by the presence of a decreased retinal blood flow, Bhatwadekar explained.

Other DR pathogenic pathways that may be exacerbated by aging-related alterations relate to protein kinase C activation and hexosamine.

CLINICAL ISSUES
Clinical studies of DR in aging individuals highlight the heightened concerns in senior patients. Not only does the prevalence of DR increase with age, but available evidence points to associations with depression and cognitive decline.

The article reviews current treatments for DR and diabetic macular edema, including a discussion of their mechanisms and role in clinical care. In addition, summary information is presented about emerging treatments that are being investigated in both preclinical and clinical trials. These include aldose reductase inhibitors that work by inhibiting the polyol pathway, a treatment that increases expression of sirtuin 1, protein kinase C inhibition and gene therapy to introduce VEGF genes. In addition, there is interest in sodium-glucose cotransporter 2 inhibition and angiopeptin-2 inhibition.

TREATMENT CHALLENGES
Highlighting the therapy-related challenges occurring in the senior population, the article discusses problems with medication adherence and age-related changes in drug pharmacokinetics and pharmacodynamics.

Anatomic and physiologic changes that occur with aging and the effects of medications that are commonly used by elderly individuals can lead to decreased absorption of orally administered drugs with the potential for reduced efficacy. Thus, the need may arise to consider modifications in the dosing regimen or delivery method.

As noted in the article, an increase in proteases within the vitreous that has been noted with aging suggests there may be age-related pharmacokinetic differences in drugs administered by intravitreal injection.

Changes in drug distribution within the eye also may occur, and the potential for age-related differences in systemic distribution, drug metabolism and elimination also needs to be considered when investigating medications administered via an extraocular route.

Older individuals are more prone to medication nonadherence, which should be considered in their use of oral medications and in maintaining follow-up when receiving in-office treatments for diabetic eye disease.

“In the future, it is necessary to consider all of the above factors when treating senior patients with DR,” Bhatwadekar said. “Special programs directed toward tailoring and monitoring therapy may provide a better therapeutic outcome for elderly patients.”

REFERENCE

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Bhatwadekar is an ad hoc pharmacist at PCA Pharmacy. He reports no other relevant conflicts of interest.

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PANORAMA study outlines variables to watch in NPDR
W. Lloyd Clark, MD, reveals the study’s findings on the effects of nonperfusion and leakage areas on DME and complications in nonproliferative diabetic retinopathy.

Fluocinolone acetonide implants in DME
Victor Gonzalez, MD, discusses decreased need for anti-VEGF injections following 0.19-mg fluocinolone acetonide implants in diabetic macular edema patients.
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Tackling teleretinal screening for diabetic retinopathy

TSDR programs prove a cost-effective option in preventing blindness

By Jose Agustin Martinez, MD; Special to Modern Retina™

Diabetic retinopathy (DR) is the leading cause of permanent blindness in working-age adults, and the number of patients with diabetes worldwide is expected to reach 693 million by 2045. Consequently, it is necessary to find a more effective means of screening patients for DR.

A viable testing option is teleretinal screening for diabetic retinopathy (TSDR), a technology that has been used successfully in a variety of cultures and demographic settings, has been well reported in recent years, and whose cost effectiveness has also been confirmed.

Typically, referable diabetic retinopathy (RDR) is defined as diabetic retinopathy worse than mild nonproliferative diabetic retinopathy and/or macular edema, based on the international classification of DR.

In longstanding (10-20 years) TSDR programs, the incidence of sight-threatening diabetic retinopathy decreases over time, suggesting the program’s effectiveness and the possible need to refine the indications for screening in those programs.

**ARTIFICIAL INTELLIGENCE**

Recent publications have discussed the use of artificial intelligence (AI) as well as different cameras, including tabletop and handheld devices, to facilitate TSDR programs.

Multiple deep learning image assessment software have been developed. To date, 2 AI-based autonomous cameras have been approved by the FDA (IDx-DR, Digital Diagnostics; Eyenuk), and several other automated AI-based algorithms with varying degrees of sensitivity and specificity are available worldwide.

Sensitivity is a measure of how well a test can identify true positives and specificity, a measure of how well it can identify true negatives. In both diagnostic and screening tests, there is usually a tradeoff between sensitivity and specificity, such that higher sensitivities will mean lower specificities and vice versa.

Sensitivity (true positive rate) is determined by dividing the number of true positives by the total number of positives. Specificity (true negative rate) is the number of true negatives divided by the total number of negatives. In TSDR programs, a high specificity rate is more important than a high sensitivity rate to ensure that patients with the disease are seen by a specialist.

Although a high sensitivity rate could ideally keep individuals without disease out of the specialist’s office, it is better to see “false positives” (due to lower sensitivity) than “false negatives” (due to low specificity). TSDR programs with high specificity will do a better job of not missing patients with disease, thus meeting its main objective of identifying patients in need of a DR specialist.

**THREE IMAGING OPTIONS**

Three different fundus images have been used in TSDR programs. The gold standard is the Early Treatment Diabetic Retinopathy Study (ETDRS) 7 standard field (7SF) image. However, the burden of multiple image capture makes 7SF photographs unrealistic for a TSDR program. The most common image capture technique is less than 7SF, which usually involves an image of the posterior...
pole that includes the disc, macula, and vascular arcades. Alternatively, ultra-widefield images, which capture over 200 degrees of retina, have also been used in some DR screening programs. These techniques were found to be essentially similar in effectiveness, although the less than 7SF may have a higher number of ungradable images.

Autonomous AI software is gradually being integrated into TSDR programs, but the current standard is point-of-care image capture with a fundus camera in a primary care setting, followed by a review of the image by an eye care provider via a web-based platform. One advantage of this method over the FDA-approved autonomous interpretation algorithms is that it allows screening not only for diabetic eye disease but also for such other pathologies as cataracts (hazy view), glaucoma (increased optic disc cupping), macular holes, epiretinal membranes, and macular degenerations, making it possible for patients with sight-threatening disease to be triaged and, depending on diagnosis, contacted for a timely examination.

Reading centers vary depending upon the health care system; some readers are located in the same community as the camera, and others are centralized in a distant center. A study confirmed some utility in centralizing the reading center. But there are benefits to keeping the reading center in the same community as the cameras, including increased accountability among patients, primary care physicians, reading centers and ophthalmologists. A systems-based approach allows all stakeholders to give input when determining processes that improve adherence rates. One study suggests that local collaboration may increase adherence rates. Local relationships and referral patterns enable better communication among stakeholders, and community pride may promote cooperation in reducing risk of vision loss in these patients.

At present, AI algorithms are FDA-approved only for the detection of diabetic eye disease (DED) and/or RDR. Consequently, other pathologies will be missed by screening programs that employ only the AI component. This limitation may become more important as teleretinal imaging expands to screen for other disease states.

**MISSING FOLLOW-UPS**

A criticism of TSDR programs is lack of adherence to the recommended follow-up exams among patients with RDR, even though adherence rates range widely, from 9.5% to 81.9% depending on the study. Adherence rates for these follow-up exams are determined by dividing the ratio of the number of patients seen by a specialist by the number of patients diagnosed with RDR. In one study, automated retinal image analysis (performed in a primary care setting and allowing for immediate interpretive feedback to the patient) improved adherence by more than 36 percentage points, from 18.7% to 55.4%.

Consequently, AI cameras may not only provide instantaneous diagnostic information to patients, but also increase adherence rates among patients with RDR. Conversely, barriers to full utilization exist in some programs that make implementation difficult. The incidence of RDR increases with failure to attend screening appointments: 5-9 consecutive misses increase RDR likelihood from 4% to 15%, and 10 or more consecutive misses increase RDR likelihood to 20%.

Reports confirm TSDR is able to detect macular edema, with one report confirming the presence of lipid, which increases the chances of macular edema. However, sensitivity and specificity in diagnosing macular edema varies widely among reports.

Initially, these TSDR programs were focused on underserved communities, be they uninsured, rural, or urban public health systems. More recently, insured population groups have been studied, likewise with promising results. TSDR is effective for all population subgroups. As one would expect, regions and/or communities with lower access to health care have higher DR rates and, consequently, potentially would benefit more from the deployment of TSDR.

TSDR is likely to become the standard strategy for screening diabetic patients for DR in most clinical settings around the world. Ophthalmologists engaged in the fight to prevent blindness from DR will be well-served by understanding the different aspects of TSDR and their communities by being involved in its deployment.

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Martinez reports no financial disclosures related to this content.
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References
Autoimmune disease and the eye: Current thinking and approaches to treatment

By Peter Y. Chang, MD; Special to Modern Retina™

Autoimmune uveitis comprises a diverse group of diseases that can differ widely in clinical presentation and duration. Although a number of systemic autoimmune diseases can manifest as non-infectious uveitis (NIU)—for example, psoriasis, ankylosing spondylitis, multiple sclerosis, sarcoidosis, and ulcerative colitis—many cases of NIU are idiopathic. Indeed, in the US, most uveitis is of non-infectious or autoimmune origin, with a majority of those cases being idiopathic.

PATHOPHYSIOLOGY

The autoimmune mechanisms at work in the pathogenesis of uveitis are not completely understood; but it is known that the retina contains several potent autoantigens that are expressed in the thymus and secondary lymphoid tissue, where immunological tolerance is maintained. Regulatory T cells, which help maintain self-tolerance and control immune responses, are also present in the retina. In the context of an autoimmune disease, local dynamics of immune cell trafficking within the eye may be altered, and the resulting remodeling may put the eye at risk of nonspecific immune activation, precipitating clinical signs of inflammation.

UNCOVERING AUTOIMMUNE-MEDIATED UVEITIS

Uveitis is categorized anatomically as anterior, intermEDIATE, posterior, or panuveitis, with symptoms that generally correspond to the location of inflammation. When the inflammation predominantly affects the anterior segment, patients may experience pain, sensitivity to light, and redness; posterior-segment inflammation can result in floaters, flashes, blurry vision, and blind spots. Although patients with posterior uveitis may not experience pain, it is generally the most dangerous in terms of vision, as choroidal inflammation and its resultant scarring can affect the retina, optic nerve, and macula very quickly.

In my experience, it is common for patients with NIU to present to the clinic without a previous diagnosis of systemic autoimmune disease; typically, they have experienced some worrisome vision loss or irritation that prompts their visit. They may, however, have other extraocular symptoms that they have been neglecting, such as joint pain (inflammatory joint pain is typified by exacerbation following a period of inactivity, such as waking in the morning), nail pitting, or hair loss. Every patient new to our practice is asked to complete a 9-page questionnaire to help uncover ocular and systemic symptoms that he or she may not otherwise think to report.

In terms of ocular findings, diagnosis of anterior uveitis is relatively straightforward at the slit lamp; in cases of posterior-segment involvement, imaging tools such as optical coherence tomography (OCT), fluorescein and indocyanine green angiography, and fundus autofluorescence are essential adjuncts. For certain uveitic enti-
ties, visual field testing and electro-retinogram can be helpful. In general, the diagnostic workup for a patient with NIU often requires time, consideration, and collaboration with other specialists. In addition to review of systems and ocular exam, we do bloodwork to rule out infection and help identify signs of systemic autoimmune activity (eg, HLA haplotyping, antinuclear antibodies, serum angiotensin-converting enzyme, lysozyme, to name a few). Even when a systemic workup is negative for infection or clearly defined autoimmune disease, patients can be comforted that we still have effective ways of managing uveitis that is presumed autoimmune, noninfectious in nature.

**CURRENT TREATMENT APPROACHES**

Our knowledge of ocular immunology has grown immensely over the past decade or two, revealing a complex web of interconnected pathways, signaling molecules, and surface markers involved in acute and chronic inflammation. In treating NIU and other autoimmune-mediated diseases, it is rarely as simple as blocking a single molecule and turning a single switch on or off. In recent years, targeted biologic treatments for autoimmune disease have been approved, including some specifically for NIU.

Humira (adalimumab, AbbVie) is the first FDA-approved biologic therapy for noninfectious uveitis affecting the posterior segment. Most of the other systemic immunosuppressive therapies used to treat uveitis are off-label, including methotrexate, mycophenolate, azathioprine, and cyclosporine. Although these therapies have been used for many years, they do not have FDA approval for this indication and lack the support of randomized controlled trials.5

Through clinical experience, we know that these are excellent steroid-sparing medications. Although these therapies are well accepted today, in the past, many considered them as overly aggressive. Now, uveitis has become a “mainstream” subspecialty, and fellows at many respected academic and private institutions are well trained in the use of systemic therapies. In addition, physicians tend to refer patients to uveitis specialists much earlier than in the past, which lowers patients’ exposure to systemic steroids and their associated side effects.

In and out of specialists’ practices, however, steroids are still the mainstay of treatment because rapid control of inflammation is essential to preserving vision.

**LOCAL VS SYSTEMIC THERAPY**

For patients with NIU and a well-defined systemic autoimmune disease, systemic treatment is usually the best choice to control disease throughout the body. The question of systemic vs local treatment becomes more controversial if, after doing a head-to-toe work-up, the patient only manifests NIU and no other complaints. In such cases, it may make sense to treat systemically if the uveitis is bilateral, but perhaps locally if unilateral (but that ultimately depends on the specific diagnosis).

Local treatments for NIU are largely corticosteroids, though intraocular injection of agents such as sirolimus and methotrexate have been studied.6 7 Key considerations for local therapy include age and lens status, as well as individual or family history of glaucoma or steroid-induced ocular hypertension. A very young phakic patient, or one with numerous risk factors for glaucoma, may not be a good candidate for local corticosteroid therapy. On the other hand, patients who are pregnant or trying to conceive, or those who are immunocompromised, may be poor candidates for systemic therapy. Recently, even those with only a theoretical risk of compromised immunity (eg, due to age or recent recovery from cancer) are often reluctant to undergo systemic immunosuppression because they fear the SARS-CoV-2 infection.

Current approved options for local therapy include topical steroids, shorter-acting intra- and periocular steroids, such as triamcinolone acetonide, and sustained-release intravitreal implants, including Ozurdex (dexamethasone intravitreal implant 0.7 mg, AbbVie) and YUTIQ (fluocinolone acetonide intravitreal implant 0.18 mg, EyePoint Pharmaceuticals). Ozurdex is typically effective for about 3 to 4 months when used to treat uveitis, while YUTIQ releases a consistent low dose of fluocinolone for 36 months. The surgically implanted Retisert (fluocinolone acetonide intravitreal implant 0.59 mg, Bausch + Lomb), which also lasts about 36 months, is generally reserved for more severe presentations in which a higher dose of steroid is warranted.

I usually bring patients on systemic immunosuppressive therapy back for follow-up every 2 to 3 months to examine the eyes for signs of recurrent inflammation and perform blood testing to ensure the efficacy and safety of the therapy. For patients who receive local, sustained-release steroid treatment such as YUTIQ and Retisert, I also follow them every 3 months to monitor intraocular pressure.

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The risk of presumed infectious endophthalmitis does not increase following administration of anti-vascular endothelial growth factor (VEGF) injections, and universal masking (everyone, including doctor, patient, and technician) may actually decrease the risk of culture-positive endophthalmitis, according to Sunir Garg, MD, from MidAtlantic Retina, the Retina Service of Wills Eye Hospital, Philadelphia.

This is important considering the devastating consequences of endophthalmitis and the exponential increase in the administration of anti-VEGF injections during the past decade.

However, because conflicting information exists about whether masking helps or hurts endophthalmitis risk, Garg conducted a study with 12 large retina practices around the country to determine whether universal masking while administering intravitreal injections during the pandemic increased the risk in the incidence of endophthalmitis. He cited three recent studies: one indicating that thermal cameras showed face masks directed streams of air toward the eyes, another reporting that masks altered the type and amount of bacterial flora around the eye and that taping the upper portion of masks might limit bacterial dispersion, and a third showing that mask use by physicians did not alter endophthalmitis risk and, interestingly, that there were no cases of oral flora in the masked physician group.

To settle the debate, Garg conducted a retrospective comparative cohort study that included all intravitreal injections (bevacizumab [Avastin, Genentech], ranibizumab [Lucentis, Genentech], and aflibercept [Eylea, Continued on PAGE 18]
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INCIDENCE OF ENDOPHTHALMITIS

More than 500,000 intravitreal anti-VEGF injections were administered during the study period (294,514 and 211,454, respectively). There were 85 cases of presumed endophthalmitis (0.0289%; 1 in 3,464 injections) in the no-face-mask group and 45 (0.0213%; 1 in 4,699 injections) in the face-mask group, a difference that did not reach significance ($P = .097$).

A closer look showed significantly ($P = .041$) more cases of culture-positive endophthalmitis in the no-mask group, ie, 27 (0.0092%; 1 in 10,908 injections), compared with 9 (0.0040%; 1 in 23,494 injections) in the mask group.

Garg also found 3 flora-associated cases of endophthalmitis in the no-mask group and 1 in the mask group, a result that did not reach significance.

FACE-MASK TAPING

A deeper look at 18,602 of the 211,454 (9%) injections administered when taping was required to secure the top portion of the mask showed 4 cases of endophthalmitis (0.021%; 1 in 4,650 injections) and no cases of oral flora-associated endophthalmitis, a finding similar to that in the no-taping cohort.

Comparable outcomes in visual outcomes were seen between the 2 groups following endophthalmitis treatment.

"Universal masking does not seem to increase the risk of developing endophthalmitis, and it may cause a reduction in culture positive endophthalmitis," Garg concluded. "However, even with universal masking, endophthalmitis still occurs in a small percent of cases."

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Garg has no financial disclosures related to this content.
THE PRE-LESION—WHERE COMPLEMENT OVERACTIVATION IS CAUSING THE NEXT WAVE OF DESTRUCTION IN GEOGRAPHIC ATROPHY¹,²

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Unraveling burdens of X-linked retinitis pigmentosa

Recent literature review reveals dearth of data, highlights need for more research

By Cheryl Guttman Krader, BSPharm; Reviewed by Nan Li, MD, PhD, MHS

X-linked retinitis pigmentosa (XLRP) is a rare inherited retinal disease for which there is not only a major unmet treatment need but also a need for greater understanding and awareness of its personal and societal burdens, according to authors of a recent article.

Published online in June 2021, the 8-page article presents the findings from a literature search and review conducted to identify and describe the clinical, humanistic and economic burdens of XLRP or RP in the United States, Japan, France, Germany, Italy, Spain and the United Kingdom. Although the search found a paucity of relevant literature, it is reasonable to conclude from the available evidence that XLRP clearly carries a significant humanistic and economic burden, according to Nan Li, MD, PhD, MHS.

Li is the director of access at Janssen Retina DAS in Raritan, New Jersey, and a coauthor of the paper.

“XLRP causes progressive vision loss, with many affected patients becoming legally blind by age 40,” Li said. “Currently there are no approved treatments for XLRP, and unfortunately, we continue to see very limited data on this condition.”

Li also noted that additional research on inherited retinal diseases (IRD) is crucial to underscore the need for therapies and to highlight their potential to dramatically improve lives of patients and caregivers.

“Our identification of the information gaps is an important first step in assessing how best to support people with these conditions,” she said. “Therapies are currently being developed, and that is crucial.”

However, if researchers, regulators, payors and advocacy groups do not understand the needs of patients with diseases like XLRP, they may not truly realize the potential groundbreaking nature of future treatments and the myriad ways they can improve the lives of patients and their families, Li said.

**KEY FINDINGS**

Li said her group’s analysis of the published literature essentially shows the lack of knowledge about the many challenges patients face with early-onset and progres-
sive vision loss due to XLRP.

“We could not identify any studies assessing the humanistic or economic burden of the XLRP form of RP specifically,” Li said. “Given the scarcity of studies focusing on patients with XLRP, we looked to the evidence from studies of the wider RP population to infer conclusions about the burden of XLRP, and we did find articles relating to RP in general.”

From the latter publications, it was learned that with progression of RP, affected individuals experienced a range of psychosocial, functional, physical and economic burdens. For example, the published reports showed that patients developed feelings of loss, isolation and fear. They also suffered other negative effects on quality of life resulting from the loss of enjoyment from vision-related hobbies and pastimes. Inability to work because of their impaired vision bore psychosocial consequences for people with RP because of loss of social support as well as economic consequences arising from lost productivity.

“Extrapolating from the findings from the RP-related research and considering first that the onset of disease is earlier for XLRP than RP, and second that XLRP is associated with more rapid progression of vision loss, it is reasonable to expect XLRP may create a greater burden for patients and their caregivers than does RP,” Li said.

MOVING FORWARD
The identification of the gap in research to characterize the burdens of XLRP is an important first step in assessing how best to support people affected by the condition.

“Our hope is to more fully understand the myriad ways the therapies currently in development for XLRP can potentially improve the lives of patients and families,” Li said. “There is so much more to uncover and know about XLRP and other IRDs and the people living with them.”

Li and colleagues are working with patient advocacy groups to generate more evidence about the cost of these illnesses. In addition, they are looking closely at patient and caregiver well-being, including the emotional burden of disease.

“Last year we partnered with Retina International on a study to estimate the societal disease burden and economic impact of IRDs in the United States and Canada,” Li said. “The study found that individuals living with an IRD incur significant economic costs and reductions in their quality of life.”

Li also explained that families, friends, government, employers and society end up taking on significant economic costs as well.

“As we look ahead, our Janssen team anticipates initiating more research on these topics, working hand-in-hand with our stakeholders and partners,” Li said.

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Li has no financial disclosures related to this content.
Anti-VEGF therapies have been highly beneficial for patients with exudative age-related macular degeneration (AMD), but these patients often require frequent treatment to maintain visual acuity, asserting the need for sustained-release therapies.

Lejla Vajzovic, MD, an associate professor of ophthalmology at Duke University Eye Center in Durham, North Carolina, discussed 2 novel surgical options that facilitate increased durability.

PORT DELIVERY SYSTEM

The port delivery system (PDS) (Susvimo; Genentech), a recently FDA-approved drug delivery system, is a permanent refillable intraocular implant that rests at the pars plana. The device contains a customized formulation of ranibizumab (Lucentis; Genentech) that can be refilled in the office.

The phase 3 Archway study of patients with wet AMD showed a favorable benefit-risk profile for the ranibizumab PDS implant. The change in best-corrected visual acuity at weeks 36 and 40 was comparable to the outcome of monthly ranibizumab injection. The approach maintained visual acuity with a reduced treatment burden.

Vajzovic emphasized the importance of strict adherence to the surgical steps during implantation.

“Control of hemostasis is critical at all steps to ensure optimal visualization and minimize the risk of postoperative vitreous hemorrhage,” she said.

Precise handling of the conjunctiva and Tenon capsule and anchoring both to the limbus during closure are crucial to optical outcomes, Vajzovic pointed out.

Vajzovic provided 4 key points about insertion of the ranibizumab PDS implant:

- The sclera is incised layer by layer to expose the pars plana, followed by pars plana laser ablation incision to reduce the chances of intraocular bleeding. The incision size is kept at 3.5 mm for the secure fit of the implant and pars plana hemostasis.
- The conjunctiva and Tenon capsule are manipulated and anchored to the limbal sclera with a slight overapproximation, which keeps the implant covered.
- Control of hemostasis is critical to minimize vitreous hemorrhages.
- During the refill/exchange procedure, the surgeon stands on the contralateral side of the study eye, using a perpendicular approach and precise targeting.

The ranibizumab PDS implant received FDA approval in October following positive phase 3 results.

RGX-314

RGX-314 is a novel adeno-associated virus vector that delivers an anti-VEGF drug that has shown favorable results in phase 1/2a neovascular AMD studies. The study tested 5 doses administered to patients who previously required frequent injections. The subretinal dosing to date has been completed in 42 subjects in dose-escalating cohorts. The patients were followed up to 2 years.

This procedure involves a vitrectomy followed by subretinal injection of the device with subsequent bleb formation. The patients generally required only a subconjunctival steroid injection.

The interim conclusions drawn from the results were that RGX-314 was well tolerated by all patients and that the treatment provided a long-term, durable treatment effect seen with the 3 highest doses. The patients in the 2 highest-dose cohorts have been followed for more than 1.5 years with stable to improved vision and reductions in the treatment burden. Those in cohort 3 who were followed for more than 3 years had the same results.

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This article is adapted from Vajzovic’s presentation at the Women in Ophthalmology 2021 Summer Symposium. Vajzovic is a consultant to RegenXBio Inc and Roche/Genentech.

Two novel options: PDS and RGX-314
Approaches facilitate increased durability for patients with retinal degeneration

By Lynda Charters
Is there another driver of disease hiding just beyond the VEGF pathway? Take a closer look at the crucial role angiopoietins play in vascular instability.¹

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Ang-2=angiopoietin-2; Ang-Tie=angiopoietin/Tie; DME=diabetic macular edema; nAMD=neovascular age-related macular degeneration; VEGF=vascular endothelial growth factor.

Sustained drug delivery in ophthalmology
Current options, challenges in developing novel therapies

By Ashvini Reddy, MD; Special to Modern Retina™

ALTHOUGH MANY CHRONIC MEDICAL conditions affecting the eyes can be managed with oral medication, most chronic ocular conditions, such as diabetic retinopathy, macular degeneration, ocular inflammation and glaucoma, require medication to be delivered locally, usually as eye drops or injections. Despite their apparent ease of administration, incorrect and inconsistent use of eye drops is surprisingly prevalent. More than 90% of postcataract patients self-administer their eye drops incorrectly, and about 30% of postglaucoma surgery patients are nonadherent to topical treatment.1,2

Fortunately, an increasing number of ophthalmic medications enable sustained drug delivery via intraocular or intracanalicular depots. For appropriate patients, there is significant benefit in terms of adherence, which may translate into improved efficacy and persistence with therapy. For example, in glaucoma, sustained delivery of bimatoprost via the recently-approved Durysta implant (bimatoprost implant 10 mcg, Allergan) substantially reduces the administration burden for patients while exposing target tissues to therapeutic levels of drug over several months.

Similarly, taking the example of chronic noninfectious ocular inflammation, sustained delivery of corticosteroids to the retina can offer a major advantage over conventional eye drops and frequent intra/periocular injections.

CORTICOSTEROID IMPLANTS
Sustained-release steroids are available as biodegradable and nonbiodegradable implants with different active compounds and durations of effect (Table 1). For short-term control of postoperative inflammation, Dextenza (dexamethasone ophthalmic insert 0.4 mg, Ocular Therapeutix) is an intracanalicular insert that releases steroid onto the ocular surface, and Dexycu (dexamethasone intraocular suspension 9%, EyePoint) is a controlled-release suspension that is injected into the posterior chamber. Both are bioerodible and designed to release dexamethasone for the first month following surgery.3

Another bioerodible formulation of dexamethasone, Ozurdex (dexamethasone 0.7 mg, Allergan), is an intravitreal implant that lasts 3 to 6 months. For some patients with uveitis and uveitic macular edema that have been unresponsive to previous treatments, Ozurdex offers greater drug release in the first 2 months, then tapers over the following few months. Patients also tend to like that it’s bioerodible.

For other patients, a more consistent, longer-term release of drug is desirable, such as that offered by Yutiq (fluocinolone acetonide intravitreal implant 0.18 mg, EyePoint) and Iluvien (fluocinolone acetonide intravitreal implant 0.19 mg, Alimera), which are indicated in the US for noninfectious uveitis affecting the posterior segment and for diabetic macular edema, respectively. Both are nonbiodegradable polymer conjugates injected intravitreally, which provide a continuous microdose of fluocinolone over about 3 years.

The Durasert sustained-release technology, the foundation of both Yutiq and Iluvien, is also at work in Retisert (fluocinolone acetonide intravitreal implant 0.59 mg, Bausch + Lomb), which provides a higher dose of fluocinolone and must be implanted surgically, rather than as an in-office injection.

SAFETY CONSIDERATIONS
A history of intraocular pressure elevation following topical steroid drops should be considered carefully when weighing the option of a sustained-release steroid implant. I tend...
to use shorter-acting sustained-release options (Dextenza, Dexycu) for short-term postoperative inflammation or for a patient whom I suspect may have a stronger response to steroids, which is generally a very safe way to go. If a longer extent of treatment is desired, I will generally start with a sustained-release steroid that has a shorter duration of effect first, such as Ozurdex, to make sure the patient is steroid tolerant before switching to a longer-acting implant, such as Yutiq.

Another issue to consider with intraocular implants is the potential for migration within the eye; when it occurs, it can be a problem. If the implant migrates forward from the vitreous, it can result in damage to anterior segment structures, with the potential to impact vision. Thus, intravitreal implants should be used with caution in patients who have a compromised posterior capsule or are aphakic.

### PORT DELIVERY

**Reducing the burden**

Patients who receive regular—often monthly—anti-VEGF injections shoulder a significant burden in terms of time, expense, and invasiveness of treatment. A study from 2016 found that each injection appointment (including travel time) took an average of 4.5 hours, and 53% of working patients needed to take off at least 1 day per appointment. In my practice, I’ve found these injections to be especially challenging for working-age patients who are also trying to balance jobs, family obligations, and other health problems.

One approach to reduce this burden is the port delivery system (PDS), which entails a surgically-placed, permanent, and refillable drug-releasing port. The ranibizumab PDS (Susvimo, Genetech) requires refills approximately every 15 months and has been FDA approved for wet age-related macular degeneration (AMD), and is in development for treatment of diabetic retinopathy and diabetic macular edema.

### DEVELOPING A SUCCESSFUL SUSTAINED-RELEASE OPHTHALMIC DRUG: Challenge Accepted

Challenges with developing sustained-release drugs for the eye often amount to issues with safety—the reason many products ultimately fall off the path to approval. The general principle of local, sustained delivery to ocular tissues is sound; but often, in the case of intravitreal therapies, adverse events, such as inflammation, intraocular pressure increase, and corneal issues due to implant migration are where these drugs fail. Moreover, in many cases, efficacy of investigational sustained-release drugs is adequate, but noninferiority or superiority to existing formulations is difficult to demonstrate.

However, the trials also showed abicipar had more clinically significant medication-related ocular adverse events when compared with ranibizumab. Ultimately, the FDA deemed the benefit-risk ratio with abicipar unfavorable.

### CLINICAL TRIAL PROCESS: Rigorous and Necessary

A few late-stage clinical trials are currently exploring other novel techniques to prolong duration of efficacy of intravitreal injections. KSI-301 is an anti-VEGF monoclonal antibody conjugated with a large biopolymer.

In the phase 1 study, 55% of patients achieved a 6-month retreatment interval; top-line results from phase 3 trials for neovascular AMD, diabetic macular edema, and retinal vein occlusion are expected to begin reading out in late 2021. GB-102 uses bioabsorbable microparticles to encapsulate sunitinib malate, a tyrosine kinase inhibitor that targets both VEGF-A and platelet-derived growth factor. This formulation may extend the intravitreal retreatment interval to 6 months, and a phase 2 trial in patients with neovascular AMD is underway.

However, one needs to keep in mind that despite promising early-phase results, several sustained-release agents have not fared as well in late-stage trials. When it comes to developing new ophthalmic drugs and devices, we must keep in mind that local, sustained delivery works, particularly in the posterior segment. With the agents available to us, our threshold for efficacy and safety of new alternatives is higher than it may have been 15 years ago. The recent example of abicipar is illustrative: 2-year results from a pair of phase 3 studies (CEDAR, NCT02462928, and SEQUOIA, NCT03336333) indicated that abicipar, a DARPin anti-VEGF agent, was noninferior for achieving stable vision in people with wet AMD with fewer injections when compared with ranibizumab.

“**Our highly selective and rigorous FDA-approval process should make physicians and patients feel confident in the medications that are available on the market and being used to treat them.”**
not everything can be tolerated inside the eye.

As much as I want my patients to have access to more treatment options—particularly those that work over months and even years—we know in advance that a lot of these drugs won’t make it to market, and I believe this fact confirms we are running clinical trials very well. Our highly selective and rigorous FDA-approval process should make physicians and patients feel confident in the medications that are available on the market and being used to treat them.

I am glad there are partnerships that bring physicians, research groups, and pharma together, working hard to bring new and better treatment options to patients, investigating drugs and their adverse events thoroughly before the public has access to them. Patients with chronic medical conditions deserve to have treatment options that are both effective and convenient to use long-term.

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### TABLE 1. Sustained-Release Anti-Inflammatory Agents

<table>
<thead>
<tr>
<th>Drug</th>
<th>Molecule</th>
<th>Formulation</th>
<th>Duration</th>
<th>Administration</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yutiq</td>
<td>Fluocinolone acetonide 0.18 mg</td>
<td>Nonbioerodible polymer implant</td>
<td>36 months</td>
<td>Intravitreal injection</td>
<td>Noninfectious posterior uveitis</td>
</tr>
<tr>
<td>Retisert</td>
<td>Fluocinolone acetonide 0.59 mg</td>
<td>Nonbioerodible polymer implant</td>
<td>30 months</td>
<td>Surgical placement into posterior segment</td>
<td>Noninfectious posterior uveitis</td>
</tr>
<tr>
<td>Ozurdex</td>
<td>Dexamethasone 0.7 mg</td>
<td>Resorbable polymer implant</td>
<td>Up to 6 months</td>
<td>Intravitreal injection</td>
<td>Noninfectious posterior uveitis (also macular edema following BRVO or CRVO, and DME)</td>
</tr>
<tr>
<td>Dexcyu</td>
<td>Dexamethasone 9%</td>
<td>Intraocular suspension</td>
<td>1 month</td>
<td>Intracamerlal injection (posterior chamber)</td>
<td>Postoperative inflammation</td>
</tr>
<tr>
<td>Dextenza</td>
<td>Dexamethasone 0.4 mg</td>
<td>Reversible hydrogel implant</td>
<td>1 month</td>
<td>Intracamerlal injection (posterior chamber)</td>
<td>Postoperative inflammation and pain</td>
</tr>
<tr>
<td>Iluvien</td>
<td>Fluocinolone acetonide 0.19 mg</td>
<td>Nonbioerodible polymer implant</td>
<td>36 months</td>
<td>Intravitreal injection</td>
<td>DME</td>
</tr>
</tbody>
</table>

BRVO: branch retinal vein occlusion; CRVO: central retinal vein occlusion; DME: diabetic macular edema.
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