Pipeline Update

MANY NEW ENTRIES, NO IMPACTFUL EXITS

A review of 51 candidates in clinical trials, including gene therapies and treatments for inherited retinal disease. Page 20

Online Video

Pearls for scleral buckling with tunnels – Page 16

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Interview with new NEI head Michael Chiang, MD – Page 7
The complement pathway in geographic atrophy – Page 30
The promise of targeting mitochondria in dry AMD – Page 34

RETINA-SPECIALIST.COM
There is a potential risk of arterial thromboembolic events (ATEs) following intravitreal use of VEGF inhibitors, including EYLEA. ATEs are defined as nonfatal stroke, nonfatal myocardial infarction, or vascular death (including deaths of unknown cause). The incidence of reported thromboembolic events in wet AMD studies during the first year was 1.8% (32 out of 1824) in the combined group of patients treated with EYLEA compared with 1.5% (9 out of 595) in patients treated with ranibizumab; through 96 weeks, the incidence was 3.3% (60 out of 1824) in the EYLEA group compared with 3.2% (19 out of 595) in the ranibizumab group. The incidence in the DME studies from baseline to week 52 was 3.3% (19 out of 578) in the combined group of patients treated with EYLEA compared with 2.8% (8 out of 287) in the control group; from baseline to week 100, the incidence was 6.4% (37 out of 578) in the combined group of patients treated with EYLEA compared with 4.2% (12 out of 287) in the control group. There were no reported thromboembolic events in the patients treated with EYLEA in the first six months of the RVO studies.

EYLEA is a registered trademark of Regeneron Pharmaceuticals, Inc.
EYLEA IMPROVED AND SUSTAINED VISION GAINS THROUGH 52 AND 100 WEEKS IN DME¹-³

<table>
<thead>
<tr>
<th></th>
<th>EYLEA 2 MG EVERY 4 WEEKS</th>
<th>EYLEA 2 MG EVERY 8 WEEKS</th>
<th>CONTROL</th>
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<tbody>
<tr>
<td><strong>VISTA</strong></td>
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<tr>
<td>MEAN CHANGE IN BCVA (52 WEEKS,¹ 100 WEEKS)</td>
<td>+12.5, +11.5 LETTERS</td>
<td>+10.7, +11.1 LETTERS</td>
<td>+0.2, +0.9 LETTERS</td>
</tr>
<tr>
<td>PROPORION GAINED ≥15 LETTERS (52 WEEKS,¹ 100 WEEKS)</td>
<td>41.6%, 38.3%</td>
<td>31.1%, 33.1%</td>
<td>7.8%, 13.0%</td>
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<td><strong>VIVID</strong></td>
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<tr>
<td>MEAN CHANGE IN BCVA (52 WEEKS,¹ 100 WEEKS)</td>
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<td>+10.7, +9.4 LETTERS</td>
<td>+1.2, +0.7 LETTERS</td>
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<tr>
<td>PROPORION GAINED ≥15 LETTERS (52 WEEKS,¹ 100 WEEKS)</td>
<td>32.4%, 38.2%</td>
<td>33.3%, 31.1%</td>
<td>9.1%, 12.1%</td>
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</tbody>
</table>

**VISTA and VIVID study designs:** Two randomized, multicenter, double-masked, controlled studies in which patients with DME (N=862; age range: 23-87 years, with a mean of 63 years) were randomized and received 1) EYLEA 2 mg administered every 8 weeks following 5 initial monthly doses; 2) EYLEA 2 mg administered every 4 weeks; or 3) macular laser photocoagulation (control) at baseline and then as needed. Protocol-specified visits occurred every 28 (±7) days. In both studies, the primary efficacy endpoint was the mean change from baseline in BCVA at week 52, as measured by ETDRS letter score. Efficacy of both EYLEA groups was statistically superior vs control at 52 and 100 weeks (P<0.01).

*Primary endpoint.
†Prespecified exploratory endpoint.
‡Secondary endpoint.
§Last observation carried forward; full analysis set.
¶Following 5 initial monthly doses.

The results of exploratory endpoints require cautious interpretation and could represent chance findings, as a multiplicity adjustment has not been applied.

anti-VEGF = anti–vascular endothelial growth factor; BCVA = best-corrected visual acuity; DME = Diabetic Macular Edema; ETDRS = Early Treatment Diabetic Retinopathy Study.

See more at HCP.EYLEA.US

ADVERSE REACTIONS

- Serious adverse reactions related to the injection procedure have occurred in <0.1% of intravitreal injections with EYLEA including endophthalmitis and retinal detachment.

- The most common adverse reactions (≥5%) reported in patients receiving EYLEA were conjunctival hemorrhage, eye pain, cataract, vitreous detachment, vitreous floaters, and intraocular pressure increased.

INDICATIONS

EYLEA® (afibercept) Injection 2 mg (0.05 mL) is indicated for the treatment of patients with Neovascular (Wet) Age-related Macular Degeneration (AMD), Macular Edema following Retinal Vein Occlusion (RVO), Diabetic Macular Edema (DME), and Diabetic Retinopathy (DR).

References:

Please see Brief Summary of Prescribing Information on the following page.

EYLEA® (afibercept) Injection For Intravitreal Injection

08/2020
EYL.20.07.0057
Table 1: Most Common Adverse Reactions (≥1%) in RVO Studies

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<th>Adverse Reaction</th>
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<tr>
<td>Conjunctival hemorrhage</td>
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<tr>
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Less common adverse reactions reported in ≥1% of the patients treated with EYLEA were hypersensitivity, retinal tear, and endophthalmitis.

Table 2: Most Common Adverse Reactions (≥1%) in DME Studies

<table>
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<tr>
<th>Adverse Reaction</th>
<th>EYLEA (N=578)</th>
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Less common adverse reactions reported in ≥1% of the patients treated with EYLEA were hypersensitivity, retinal tear, and endophthalmitis.

Table 3: Most Common Adverse Reactions (≥1%) in CRVO Studies

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<th>Adverse Reaction</th>
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Less common adverse reactions reported in ≥1% of the patients treated with EYLEA were injection site reactions and retinal detachment with or without macular edema.

Table 4: Most Common Adverse Reactions (≥1%) in suckling infants

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Less common adverse reactions reported in ≥1% of the patients treated with EYLEA were injection site reactions and retinal detachment with or without macular edema.
COVID essentially drove my family quackers. Let me explain.

Looking through the holiday cards we received this season, it was clear the main theme was the pandemic bringing families closer and renewing appreciations for the little things in life. In my home, while some of that has been true, all five of us yearn for a more balanced 2021.

From a family perspective, our kids need the social interaction and consistent extracurricular activities we took for granted before COVID. For me, as travel plummeted, in-person conferences were promptly replaced by Zoom meetings. The new norm appears to be holding these calls during hours preferably reserved for family and/or personal time—evenings and weekends. Part of me looks forward to some work-related travel with more balanced separation between work and family time. Plus, without time in transit, I now realize that it used to provide a protected space for focused work on manuscripts and protocols.

From a patient perspective, balance away from an environment of isolation and anxiety is needed. While we as physicians have become accustomed to a masked-culture in close quarters during clinic, many of our patients still spend most of their time alone and in fear, commonly not openly discussing it, separated from family and friends.

From a patient perspective, balance away from an environment of isolation and anxiety is needed. While we as physicians have become accustomed to a masked-culture in close quarters during clinic, many of our patients still spend most of their time alone and in fear, commonly not openly discussing it, separated from family and friends.

The only practical means of achieving balance across this spectrum appears to be widespread vaccination. I got my second dose of the Pfizer vaccine in early January. I encourage you to get your shots as soon as possible. With five vaccine programs projected to have commercial products by midyear and remarkably safe and effective data to date from both the Pfizer and Moderna versions, widespread medically induced immunity this year seems achievable.

Bringing it back to retina, multiple pharmaceutical companies have accepted the hypothesis that an out-of-balance complement cascade is a key driver of progression, with over a dozen therapeutics in human clinical trials. On page 30 Drs. Oleg Alekseev, Eleonora M. Lad and Nathan Steinle explore this pathway in detail. 2021 promises to be a momentous year for GA, with a possible announcement of data from the highly anticipated ongoing Apellis Phase III program.

A second theme of the holiday cards was adopting a new pet. Most were dogs. On a whim last spring, we brought home two Duclair ducks. While not as cuddly or playful as your typical Goldendoodle or King Charles cavalier, the ducks have been quite entertaining and recently started producing delicious eggs. While Zooming, social distancing with masks, dogs and ducks are all fine, I greatly look forward to more balance in 2021, although I may continue to quack occasionally.

By Charles C. Wykoff, MD, PhD
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Now director of National Eye Institute, Dr. Michael Chiang comes full circle

A self-described physician originally trained as an engineer, Michael F. Chiang, MD, has taken over as the third permanent director of the National Eye Institute after 10 years as associate director of the Casey Eye Institute at Oregon Health and Science University. Now that he oversees the largest eye research organization in the world—its 2020 fiscal year budget is $835 million—Dr. Chiang is in a unique position to set the course for science in ophthalmology.

It seems like a natural progression for someone who’s witnessed the translation of research from the bench to the clinic. He’s one of the early investigators of telemedicine, biometrics and artificial intelligence—phrases that resonate much more today than they did when his work started 20 years ago.

Work on telemedicine for ROP

“I was basically a clinician-scientist who was building and evaluating telemedicine systems for retinopathy of prematurity diagnosis, and over the years we evolved that to things like artificial intelligence and big data and electronic health records, and I’ve gotten to see how that research is really starting to make a difference in the lives of people,” Dr. Chiang tells Retina Specialist in an exclusive interview.

That research translated to the clinic in the form of a training system for neonatal intensive care unit nurses to take retinal photos to screen infants for ROP. “Gradually more and more people have begun to be early adopters of telemedicine for ROP, and then gradually now we’ve developed policy statements showing that it’s within the acceptable standard of care to do that if you’re really careful, and then insurance companies have begun to reimburse for that,” he says. “So it’s really been amazing to me to see that cycle of how clinical needs drive research, drives early adoption, and drives policy and clinical care.”

(Continued on page 8)
Now director of NEI, Dr. Michael Chiang comes full circle
(Continued from page 7)

Dr. Chiang started at NEI last November, but, in a way, going to the NEI’s headquarters in Bethesda, Md., brings him full circle. A little over 20 years ago while he was a resident at Johns Hopkins University in Baltimore, he had an opportunity to meet with then-NEI director Carl Kupfer, MD, the first to hold that post before he retired in 2000. “He invited me to his office in Bethesda and I spent the afternoon there, and he gave me some advice that really affected the course of my career,” Dr. Chiang recalls.

A formative impact

A resident meeting with a giant of eye research must have had an impact. “I’ve gotten to know program directors at the NEI over the years that have really had, in many ways, a formative impact on the direction of my research through things like giving me advice and introducing me to collaborators,” Dr. Chiang says.

Research into retinal disorders may figure prominently in the direction of NEI, not only because of Dr. Chiang’s own work in ROP. He credits his predecessor at NEI, Paul A. Sieving, MD, PhD, now a professor at the University of California Davis School of Medicine, for his work in inherited retinal degenerations.

“Within the past few years it’s really been amazing to see how advances in gene therapy and technologies like CRISPR can deliver treatments for patients in the operating room,” Dr. Chiang says.

“It’s been inspiring for me to see how there are patients that I’m seeing today who would’ve gone blind a generation ago if it weren’t for those advances in science and technology,” Dr. Chiang adds. “There’s never been a more exciting time to be doing something like this because of all of those advances in areas such as genetics, immunology, neuroscience, medical imaging and technology.”

Lessons from Casey Eye

Dr. Chiang is a pediatric ophthalmologist who, because he’s done so much work in ROP, admits to having been mistaken for a retina specialist earlier in his career. He also credits two renowned retina specialists he worked with at Casey Eye—David J. Wilson, MD, director at Casey Eye, who’s done extensive work in ocular oncology, and Andreas K. Lauer, MD, chair of ophthalmology and a leading researcher in age-related macular degeneration—for helping him to prepare for the NEI job. “I got to see how as an administrator I could build teams of people who were able to accomplish things on a larger scale by working together,” says Dr. Chiang.

That perspective has helped him form both short- and long-term goals for the NEI. In the short term, he sees supporting the National Institutes of Health staff and research community through the COVID-19 pandemic. “In the longer term,” he says, “my goal is basically to develop plans where we can make those scientific advances that are ultimately going to lead to eliminating preventable causes of blindness and improving quality of life for people around this country,” he says.

Dr. Chiang also says he’ll continue to see patients, albeit “on a smaller scale.”

“As a researcher, and as somebody who now leads an institute and is going to be closely involved with things like policymaking, I think it’s important to have that contact with patients,” Dr. Chiang explains. “It always reminds me of why we do what we do.”

—Richard Mark Kirkner

A call, and a template, to revise AAO hydroxychloroquine guideline

Three versions of the American Academy of Ophthalmology guidelines for dosing of hydroxychloroquine and screening of hydroxychloroquine retinopathy have been released since 2002, but their uptake by rheumatologists—the specialists who typically prescribe the drug—has been woefully inadequate, authors of a recent literature review argue.

To remedy the situation and to write guidelines that the prescribing physicians will actually use, the authors, reporting in the American Journal of Ophthalmology, call for putting rheumatologists on the writing committee.

The most recent guideline, released in 2016, calls for discontinuing HCQ at the earliest sign of retinal toxicity, but David J. Browning, MD, of Charlotte Eye, Ear, Nose and Throat Associates and lead author of the AJO “Perspective,” tells Retina Specialist that adherence to those guidelines by rheumatologists is “pretty bad.” At least one study reported that about half of patients start out on doses that exceed the 5 mg/kg of real body weight the 2016 guideline recommends.
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A call to revise AAO hydroxychloroquine guideline (Continued from page 8)

“When you look it into it, it’s possible that it may have to do with the fact that they are guidelines by ophthalmologists that are promulgated to rheumatologists,” Dr. Browning says. “There weren’t any rheumatologists on the guideline committee; their voices weren’t heard.”

Widely prescribed

HCQ is widely prescribed for autoimmune disorders. The Lupus Foundation of America reports that 1.5 million Americans have the disease. A similar number have RA, according to estimates from the Olmsted County, Minnesota, study.¹

Pre-COVID-19, around 30,000 new prescriptions for HCQ or chloroquine were written monthly, according to Morbidity and Mortality Weekly Report,² although since March 2020 new prescriptions written by specialists who don’t typically prescribe HCQ and chloroquine shot up 80-fold because of the pandemic.

Regardless of COVID-19, about 400,000 prescriptions for HCQ are dispensed monthly, according to MMWR.³

Expecting rheumatologists to discontinue HCQ at the first sign of retinal toxicity may be a stretch, Dr. Browning notes. “It’s somewhat shortsighted to say all we care about is preventing eye toxicity when the rheumatologist has to balance the control of the underlying autoimmune disease with the need to prevent eye toxicity,” he says.

The AJO report also notes that since the last guideline update, screening tools for retinal toxicity have improved markedly. “The most sensitive is multifocal electroretinography, which is not as widespread as the other modalities but is getting more widespread as costs come down,” Dr. Browning. “Second would be our increasingly sensitive spectral-domain and swept-source optical coherence tomography.”

Other tools are fundus autofluorescence, micropereimetry and even standard 10-2 automated perimetry, which is more subjective. “Most of time physicians use several tests; they don’t just use one,” he says.

More nuanced approach

Those tests probably enable a more nuanced approach to managing HCQ retinopathy. “Maybe we don’t need to say stop the drug at the very earliest evidence of toxicity,” he says. “It may be acceptable to reduce dosing and carefully monitor, and only if there’s progression to a more advanced stage—but not advanced retinopathy—compared to very early detected toxicity, that we consider stopping the drug.”

The call is to put the question out for analysis, and to give rheumatologists a seat at the writing committee table. Notably, one of Dr. Browning’s co-authors, Naoto Yokokawa, MD, is a rheumatologist in Tokyo.

To support that effort, Dr. Browning says that prospective research is needed. “All these guidelines come from retrospective studies that have a bias,” he says. ☺

—Richard Mark Kirkner

REFERENCES

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Rebecca Russ Soares, MD, MPH, and Jason Hsu, MD

A 65-year-old woman with a complaint of progressive blurred vision in both eyes for six months was referred to the clinic. She complained that driving at night and walking in the dark had become difficult. Her ocular history was unremarkable.

On further questioning, she reported a medical history significant for Crohn’s disease. She had undergone multiple small-bowel resections, which ultimately led to short-bowel syndrome and loss of a substantial amount of weight three months before her visit. She was not taking any medications. Her family and social history were otherwise unremarkable.

Workup and imaging findings

On presentation, visual acuity was 20/40 in both eyes. Intraocular pressures were normal. The anterior segment was unremarkable bilaterally. Fundus examination revealed multiple yellow-white punctate dots with a granular appearance throughout the posterior pole and mid-periphery in both eyes (Figure 1). The macula exhibited a stippled appearance.

The optic nerves and vasculature were normal in both eyes. Fundus autofluorescence (Figure 2) revealed bilateral stippled hyperautofluorescence. Optical coherence tomography (Figure 3) revealed a jagged ellipsoid zone irregularity with focal hyperreflective excrecences localizing to the spots seen on the fundus examination.

FTA-ABS/RPR was negative. Testing for zinc was within normal limits. Vitamin A was found to be low at 8.5 (normal >22.9).

The diagnosis is …

We diagnosed vitamin A deficiency retinopathy and referred the patient to her gastroenterologist and primary-care physician, in addition to a nutritionist. She was started on 10,000 IU of oral vitamin A supplementation daily with plans for possible intramuscular injection if her short-gut syndrome precluded vitamin absorption.

Follow-up

Two months after the initial daily supplementation with oral vitamin A, the patient reported an improvement in night vision. Her visual acuity remained stable at 20/40 in both eyes, and the anterior segment remained normal without signs of xerosis. Fundus examination and OCT remained stable.

A disease of malnutrition

Vitamin A is a fat-soluble vitamin found in dairy, meat, fish and leafy green vegetables. It’s an essential nutrient for immune function, epithelial cell maintenance and, in the retina, for the production of rhodopsin in rods. Vitamin A deficiency often first affects the visual system by causing night blindness. Later, loss of conjunctival goblet cell function leads to conjunctival and corneal xerosis, manifested by the classic “Bitot spot.”

Vitamin A deficiency has historically been a disease related to malnutrition, especially in children and breastfeeding women in developing countries. Paradoxically, vitamin A deficiency, once considered rare in developed countries, is increasing in prevalence. As bariatric surgery has become a common solution to morbid obesity, the spectrum of malabsorption
syndromes complicating bariatric surgery has led to an increase in the incidence of vitamin A deficiency and night blindness.\textsuperscript{3–5} Other syndromes and surgical interventions that interfere with vitamin A absorption in the duodenum have also been associated with night blindness.\textsuperscript{6,7}

**Role of multi-modal imaging**

Night blindness from vitamin A deficiency doesn’t always present with fundoscopic findings. In some cases the only objective manifestation is peripheral constriction on visual-field testing and diminished scotopic responses on electroretinography.\textsuperscript{8}

Vitamin A deficiency retinopathy, on the other hand, describes patients with fundoscopic disease. Classically, vitamin A retinopathy presents as yellow-white spots that may or may not resolve with treatment.\textsuperscript{9,10} Some have theorized that these yellow-white dots represent the disruption of the retinoid cycle with subsequent accumulation of photoreceptors underneath the retina but overlying the RPE.\textsuperscript{11} Such accumulation is thought to “block” autofluorescence, yielding the hypoautofluorescence of these spots reported.\textsuperscript{11} OCT findings further reveal the hyperreflective deposits under the ellipsoid zone band, again possibly shed photoreceptors.\textsuperscript{11}

**Treatment options**

In patients having bariatric surgery or other types of significant small bowel resection, prophylactic supplementation with 5,000 to 10,000 IU of vitamin A daily is recommended to prevent deficiency.\textsuperscript{12}

For adults with night blindness, the World Health Organization similarly recommends a daily oral dose of up to 10,000 IU of vitamin A for at least four weeks. Patients with concomitant severe xerophthalmia should receive 200,000 IU of oral vitamin A daily for two days and then once two weeks later. Those unable to absorb vitamin A should receive intramuscular vitamin A.\textsuperscript{13}

Few case reports characterize the response of the flecked fundus lesions to vitamin A replenishment. Some have found no improvement in the lesions years after supplementation,\textsuperscript{9} while others find a marked improvement.\textsuperscript{10} Interestingly, OCT may also show reduced central sub-foveal thickness that resolves with treatment.\textsuperscript{9}

**REFERENCES**

Management of noninfectious uveitis is an already daunting task for most of us. Doing so in the setting of pregnancy can cause even more apprehension as we have to consider avoiding harm not only to the mother but also to the fetus.

The course of noninfectious uveitis during pregnancy hasn’t been well established. However, general trends have been described. Numerous therapeutic options exist for controlling ocular inflammation in these patients. I’ll discuss what we know about the course of uveitis during pregnancy as well as management options and treatment approaches.

Autoimmune uveitis course
Pregnancy is known to have an ameliorating effect on a variety of autoimmune diseases. However, prospective, randomized control studies of pregnancy in uveitis have been lacking. Because uveitis is a rare condition, studies in pregnancy are limited by the number of eligible patients.

Nonetheless, a number of case reports and retrospective studies have described the course of uveitis in pregnancy. Based on these reports, uveitis appears to worsen in the first trimester, but tends to be less active later on. Subsequently, an increase in ocular inflammation occurs in the postpartum period.

A case series that included pregnant patients with Vogt-Koyanagi-Harada-associated uveitis, Behçet’s disease-associated uveitis and idiopathic uveitis reported an increased probability of having a uveitis flare in the first four months of pregnancy but a decreased probability later on. More than 50 percent of this cohort experienced a uveitic flare within six months of delivery.

An Australian study reported similar results. It included pregnant patients with uveitis associated with idiopathic disease, Behçet’s disease, sarcoidosis, Fuchs heterochromic uveitis, multifocal chorioretinitis, HLA-B27 disease and juvenile idiopathic arthritis. The study found a lower rate of flares in the second trimester vs. the first, but found no statistically significant difference in the rate of flares between the second and third trimesters. In the postpartum period, uveitis activity tended to relapse.

A retrospective cohort study compared pregnant and nonpregnant patients with uveitis, matching them for demographics and anatomical location of uveitis. Most of these patients had idiopathic uveitis, but other diseases were uveitis associated with relapsing polychondritis, Behçet’s disease, juvenile idiopathic arthritis, ankylosing spondylitis and inflammatory bowel disease. The flare rate was significantly lower in pregnant women than in nonpregnant periods or in nonpregnant controls. Among pregnant patients, uveitis flares were most common in the first trimester.

Based on the available studies, the consensus is that uveitis worsens during the first trimester of pregnancy, but then improves during the second and third trimesters. Increased rates of flare should be expected in the postpartum period.

Treatment approaches and options
The choice of immunosuppressive agents to control noninfectious uveitis in pregnancy is limited by their potential for teratogenicity and adverse fetal outcome. The Table lists medications commonly used for autoimmune uveitis and the Food and Drug Administration pregnancy risk category for each.

Corticosteroids are the first line of treatment to acutely control ocular inflammation. The most common topical formulations used in uveitis are prednisolone and difluprednate (Durezol, Novartis). The...
periocular selection is triamcinolone, which is injected into the sub-Tenon’s space. Intravitreal choices include preservative-free triamcinolone, dexamethasone implant (Ozurdex, AbbVie) and long-acting fluocinolone acetonide implant (Yutiq, EyePoint Pharmaceuticals). Retisert (Bausch + Lomb), a surgically placed sustained-release fluocinolone implant, is another local option.

Short-acting local delivery options are the ideal initial approach to noninfectious uveitis during pregnancy because their systemic absorption is minimal, thus reducing the risk of potential harm to the mother and fetus.

Alternatives to local delivery

If local delivery results in inadequate control of ocular inflammation, then systemic corticosteroids are the next option. The FDA places most systemic corticosteroids in category C (adverse fetal effects reported in animal reproduction studies but well-controlled human studies are lacking). However, prednisone and prednisolone, the most commonly used systemic steroids in uveitis, are included in category B (animal reproduction studies have failed to demonstrate a risk to the fetus, and there are no adequate and well-controlled studies in pregnant women).

When using systemic steroids in the first trimester, discuss the potential risk of cleft lip and palate in infants. Systemic steroids can generally be used during pregnancy if medically warranted. However, they should be used in low doses and limit their use in the first trimester.

Immunomodulatory agents can be used for long-term control of noninfectious ocular inflammatory diseases. However, some of these medications are known teratogens and others lack sufficient safety data. Of the anti-metabolites, methotrexate and mycophenolate mofetil have been shown to be teratogenic and should be avoided.

Azathioprine is an FDA category D medication (investigational studies have documented risk to the human fetus, but potential benefits may warrant treatment in pregnant women despite these risks). Azathioprine hasn’t been definitively shown to increase miscarriages or structural defects, but it should be used only in low doses for sight-threatening uveitis.

The use of biologic response modifiers has grown rapidly in the treatment of uveitis. The most common are the tumor necrosis factor (TNF) inhibitors adalimumab (Humira, AbbVie) and infliximab (Remicade, Janssen Biotech), both of which are in FDA category B. No conclusive evidence has demonstrated either of them has antagonistic effects to the embryo or increase the risk of fetal death.

Studies have shown the passage of TNF-inhibitors across the placenta appears to be the highest in the third trimester.

(Continued on page 18)

Indications for medications to treat noninfectious uveitis during pregnancy

<table>
<thead>
<tr>
<th>Medication</th>
<th>FDA Category*</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systemic steroids</td>
<td>B (prednisone, prednisolone) and C</td>
<td>May be used in low doses if necessary. Limit in first trimester to decrease risk of cleft palate.</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>X</td>
<td>Known teratogen; don’t use.</td>
</tr>
<tr>
<td>Mycophenolate mofetil</td>
<td>D</td>
<td>Known teratogen; don’t use.</td>
</tr>
<tr>
<td>Azathioprine</td>
<td>D</td>
<td>May be used in low doses if necessary. No definitive evidence of structural defects to the fetus or adverse events.</td>
</tr>
<tr>
<td>Infliximab</td>
<td>B</td>
<td>May be used, but consider stopping in the third trimester to decrease risk of fetal immune system alteration.</td>
</tr>
<tr>
<td>Adalimumab</td>
<td>B</td>
<td>May be used, but consider stopping in the third trimester to decrease risk of fetal immune system alteration.</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>C</td>
<td>May be used in low doses if necessary. No definitive evidence of structural defects to the fetus or adverse events.</td>
</tr>
<tr>
<td>Tacrolimus</td>
<td>C</td>
<td>May be used in low doses if necessary. No definitive evidence of structural defects to fetus or adverse events.</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>D</td>
<td>Known teratogen; don’t use.</td>
</tr>
<tr>
<td>Chlorambucil</td>
<td>D</td>
<td>Known teratogen; don’t use.</td>
</tr>
</tbody>
</table>

*Definitions of FDA categories: B—Animal-reproduction studies haven’t demonstrated a risk to the fetus, but adequate, well-controlled studies in pregnant women are lacking. C—Animal-reproduction studies have shown adverse effects on the fetus, but well-controlled human studies are lacking. D—Documented risk to the human fetus based on investigational studies, but may confer potential benefits that warrant treatment in pregnant women despite the risks to the fetus. X—Animal or human studies have demonstrated teratogenic effects; risk to the fetus clearly outweighs any potential benefit to the mother; contraindicated in pregnancy.
Scleral buckling, either as a primary procedure or in combination with vitrectomy, is an important skill for any vitreoretinal surgeon. The six pearls here will help you place the buckle more efficiently and safely.

**Choosing your band**

A 41 band (3.5 mm width), which I prefer, or thinner bands (e.g., 240 band, 2.5 mm width) can be easily placed with scleral tunnels. Tunneling is the most efficient technique in my hands. Broader bands (e.g., 42 band, 4 mm width) offer wider indentation but are better suited for sutured fixation. When using a 240 band in a combined scleral buckle with vitrectomy, consider placing it farther back from the rectus muscles than you would the 41 because the smaller width provides less posterior coverage.

**Tunneling your buckle**

Create scleral tunnels by making two parallel, radial, partial thickness incisions with a 64 blade and dissecting the bridging sclera with a Castroviejo scleral dissector. Aim to make the tunnels about 0.5 mm wider than the band width. Trimming the band ends to a point with a bevel helps pass the band without an assistant. To make the tunnel wider, extend posteriorly (and not anteriorly) because the band will slide toward the anterior-most edge of the tunnel. If you’re new to buckling, aim to cause 1 mm of indentation, which can be done by tightening the circumference of a flush buckle by $6.28 \text{ mm} (C=2\pi r)$.1

**Perforation**

During the initial sclera incisions, the appearance of uveal tissue, vitreous or subretinal fluid indicates scleral perforation. Ease tension on the muscle sutures to avoid further extrusion. Fortunately, the scleral perforation will be supported on the buckle, but close the perforation using a... (Continued on page 18)
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Helping keep patients connected with clinical and research advancements.
Scleral buckling with tunnels
(Continued from page 16)

7-0 vicryl suture. You can still tunnel that quadrant, but restart away from the perforation.

Check the sclera
In eyes with thinner sclera, I’ll suture the band in lieu of scleral tunnels (5-0 nylon on a spatulated needle). In patients with severe ectasia, you may not be able to tunnel or suture a buckle safely. If only one quadrant is involved, then you can skip this quadrant altogether. For more than one quadrant, then I would defer placement of an encircling band.

Elements
A tire can be used to selectively increase indentation. When adding a tire for a 240 band, I use a 287, for a 41 band, use a 287WG (wide groove). You can tunnel the other quadrants of the buckle, but suture in the quadrant(s) of the tire, placing the suture at least 1 to 2 mm anterior and posterior to the tire. The farther the sutures are from the tire, the greater the indentation. To support more posterior pathology, use meridional elements such as the 103, 106 or 112 implant (3, 6 and 12 mm in circumferential width, respectively). Meridional elements slide under the buckle and don’t need to be sutured.

Corticosteroids
In younger patients or if there’s extensive cryotherapy, I use sub-Tenon’s triamcinolone (Kenalog) and a short course of postoperative low-dose oral corticosteroids.

Uveitis in pregnancy
(Continued from page 15)

leading to the recommendation that these agents should be stopped at the beginning of the third trimester to prevent potential immunosuppression in the infant.

Cortilizmab pegol (Ginzzu, UCB) is a TNF-inhibitor that has minimal to no placentation transfer from mother to fetus, and has been shown to be an effective option to control intraocular inflammation.

The calcineurin inhibitors cyclosporine and tacrolimus have been used less frequently in uveitis since more efficacious medications such as TNF-inhibitors have emerged. The evidence is inconclusive that calcineurin inhibitors may increase the risk of prematurity and have unfavorable fetal side effects. They should only be used in pregnancy if medically warranted.

Alkylating agents such as cyclophosphamide and chlorambucil are known teratogens and should be avoided during pregnancy.

Bottom line
During pregnancy, ocular inflammation tends to increase in the first trimester and decrease in the second and third trimesters. An increase in uveitis flares should be expected postpartum. Local steroid delivery should be the first approach to controlling inflammation. Systemic steroids and immunosuppressive therapy may be used in cases refractory to local steroid administration. When choosing therapy, work closely with the obstetrician and patient to evaluate the risks and benefits for the mother and child.

REFERENCES
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The COVID-19 pandemic has slowed clinical trials, but a number of investigative agents in retina continued to move toward commercialization in the past year, setting up 2021 to be a year with many significant readouts.

The past year has seen significant advances in exudative retinal disease treatments using gene therapy and targeting the complement pathway, but no significant approvals.

Two emerging potential blockbusters encountered setbacks in 2020. Brolucizumab (Beovu, Novartis), approved in late 2019, was the subject of an American Society of Retina Specialists’ update alerting members to reports of retinal vasculitis linked to the drug. Abicipar pegol, the designed ankyrin repeat protein (DARPin) therapy that AbbVie inherited with its acquisition of Allergan, failed to gain regulatory approval when the Food and Drug Administration issued a complete response letter that noted the post-administration rate of intraocular inflammation resulted in an unfavorable benefit-risk ratio. Both brolucizumab and abicipar remain in our list, the former because Novartis is seeking an additional indication for diabetic macular edema, the latter because trials are ongoing and AbbVie continues to pursue development.

Three lists this year

Each year the list gets bigger, and this year’s breaks out into three different listings: biologics, steroids and light-activated treatments for exudative disease; gene therapies for exudative disease; and treatments for inherited retinal disease.

By Richard Mark Kirkner, Editor

How the list was compiled

This listing was compiled from company press releases and regulatory filings, published reports in the literature, searches on ClinicalTrials.gov, and presentations at the American Academy of Ophthalmology Retina Subspecialty Day, Angiogenesis, Exudation and Degeneration, American Society of Retina Specialists, Retina Society, EURETINA and the Ophthalmology Innovation Summit Retina Innovation Showcase. This year’s listing includes investigational stem cell and gene therapies for exudative disease as well as investigative treatments for inherited retinal disorders.
A Phase II/III trial (n=300, NCT03845582) of this oral modified form of vitamin A for geography atrophy secondary to dry AMD is recruiting with a completion date set for July. Alkeus is also pursuing concurrent trials in Stargardt disease.

NEW: ANX007 (Annexon Biosciences)

Intravitreal ANX007 is designed to bind to complement factor 1q and inhibit activation of all downstream components of the classical complement cascade, including C3 and C5 without disrupting their normal function in other complement pathways. Based on results of the Phase Ib trial in glaucoma, Annexon has filed to start a Phase II trial in geographic atrophy (n=240, NCT04656561).

APX3330 (Ocuphire)

A Phase II trial started enrollment in January to evaluate the safety of APX3330 in 100 people with moderately severe to severe NPDR.
Biologics, steroids and light-activated treatments for exudative disease in human trials

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<th>Description/active agent</th>
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<td>Abicipar pegol (AbbVie/Molecular Partners)</td>
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<td>Afibercept high-dose (Regeneron Pharmaceuticals)</td>
<td>Anti-VEGF-A and anti-placental growth factor (PLGF)</td>
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<tr>
<td>AKST4290 (formerly ALKA290) (Alkasex Inc.)</td>
<td>Oral small-molecule CCR3 inhibitor</td>
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<td>NEW: ALX-001 (Alkeus Pharmaceuticals)</td>
<td>Oral formulation of modified vitamin A</td>
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<td>NEW: ANX007 (Annexon Biosciences)</td>
<td>Intravitreal antigen-binding fragment (Fab) to complement factor q1</td>
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<td>NEW: APX3330 (Ocuphire Pharma)</td>
<td>Twice-daily oral treatment targets Ref-1 protein</td>
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<td>AR-1105 (Aerie Pharmaceuticals)</td>
<td>Biodegradable dexamethasone implant</td>
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<td>NEW: AXT107 (Asclepix Therapeutics)</td>
<td>Intravitreal self-forming gel depot peptide</td>
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<td>Brolucizumab (Novartis)</td>
<td>Humanized monoclonal antibody fragment</td>
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<td>NEW: CLS-AX (Clearside Biomedical)</td>
<td>Small-molecule tyrosine kinase inhibitor (Tki) suspension for suprachoroidal injection</td>
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<td>Conbercept (Chengdu Kanghong Biotechnology)</td>
<td>Recombinant fusion protein targeting vascular endothelial growth factor A and -B and PLGF</td>
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<td>EYP-1901 (EyePoint Pharmaceuticals)</td>
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<td>NEW: GEM103 (Gemini Therapeutics)</td>
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<td>ICON-1 (Iconic Therapeutics)</td>
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<td>NEW: IONIS-FB-LRx (Ionis Pharmaceuticals)</td>
<td>Anti-sense oligonucleotide inhibiting CFB</td>
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<td>KSI-301 (Kodiak Sciences)</td>
<td>Anti-VEGF biopolymer conjugate</td>
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<td>NEW: LBS-008 (Bellele Bio)</td>
<td>Oral small-molecule retinol binding protein (RBP4) specific antagonist</td>
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<td>Humanized lgG1 monoclonal antibody inhibiting C3</td>
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<td>NEW: R07250284 (Genentech/Roche)</td>
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<td>Risutegabin (Allegro Ophthalmics)</td>
<td>Luminate broad-spectrum anti-inTEGRIN peptide</td>
</tr>
<tr>
<td>THR-149 (Oxiron)</td>
<td>Plasma kallikrein inhibitor</td>
</tr>
<tr>
<td>THR-687 (Oxiron)</td>
<td>Pan-arginylglycylaspartic acid (RGD) integrin antagonist</td>
</tr>
<tr>
<td>Valeda Light Delivery System (LumiThera)</td>
<td>Light-delivery system using photobiomodulation</td>
</tr>
<tr>
<td>Xflam (Ocunexus)</td>
<td>Oral small-molecule connexin43 hemichannel blocker</td>
</tr>
<tr>
<td>NEW: Xipere (CLS-TA, Clearside Biomedical)</td>
<td>Tramcinolone acetonide 40 mg/mL suspension for suprachoroidal injection</td>
</tr>
<tr>
<td>Zimura (iPervis bio)</td>
<td>Avacincaptad pegol CFC5 inhibitor</td>
</tr>
</tbody>
</table>

and mild PDR (NCT04692668). APX3330 is a twice-daily oral tablet; dosing is five 120-mg tablets daily.

**AR-1105 (Aerie Pharmaceuticals)**

This biodegradable intravitreal dexamethasone implant was the subject of positive topline results from a completed Phase II trial in patients with macular edema associated with retinal vein occlusion (n=49, NCT03739593). Aerie reports the results showed positive and sustained treatment effects with two different formulations of AR-1105, with the second formulation demonstrating a duration of up to six months.

In its third-quarter 2020 report, Aerie says it’s evaluating the clinical and regulatory pathway for the agent. Complete results are still pending.

**NEW: AXT107 (Asclepix Therapeutics)**

Patient enrollment started in January in the Phase I/IIa CONGO trial to evaluate the safety and bioactivity of AXT107 in patients with DME (n=18, NCT04697758). AXT107 inhibits vascular endothelial growth factor A and VEGF-C, and activates Tie2 as well. The FDA late last year cleared the Investigational New Drug application (IND) for AXT107 for DME, nAMD and macular edema following RVO.

**Brolucizumab (Novartis)**

Novartis reports topline results of the Phase III KITE study in DME demonstrated non-inferiority vs. af-
<table>
<thead>
<tr>
<th>Indication</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neovascular age-related macular degeneration</td>
<td>Trial readouts continue after negative complete response letter.</td>
</tr>
<tr>
<td>nAMD</td>
<td>Phase II/III (n=640) commenced enrollment; Phase III (n=960) due for completion this year.</td>
</tr>
<tr>
<td>nAMD</td>
<td>Phase IIb trial (n=100) initiated; completion due in April.</td>
</tr>
<tr>
<td>Geographic atrophy secondary to dry AMD (also Stargardt)</td>
<td>Phase II/III trial (n=300) ongoing; completion due at year end.</td>
</tr>
<tr>
<td>GA secondary to dry AMD (also glaucoma)</td>
<td>Phase II trial (n=240) to start in March.</td>
</tr>
<tr>
<td>Nonproliferative diabetic retinopathy, proliferative DR</td>
<td>Phase II trial in DR/DME (n=100) scheduled to begin in first quarter.</td>
</tr>
<tr>
<td>Macular edema associated with retinal vein occlusion</td>
<td>Phase II trial completed, results pending.</td>
</tr>
<tr>
<td>Diabetic macular edema</td>
<td>First patient dosed in Phase IIb trial January 2021.</td>
</tr>
<tr>
<td>DME</td>
<td>Topline Phase III results reported; results anticipated in Phase III KESTREL trial.</td>
</tr>
<tr>
<td>nAMD</td>
<td>Enrollment started in Phase IIb trial; completion due in 2022.</td>
</tr>
<tr>
<td>nAMD</td>
<td>Enrollment completed in two Phase III trials; results due in 2022.</td>
</tr>
<tr>
<td>nAMD</td>
<td>First patient enrolled in Phase I trial in January 2021.</td>
</tr>
<tr>
<td>GA secondary to dry AMD</td>
<td>Phase II ReCLAIM-2 trial ongoing; completion expected 2022.</td>
</tr>
<tr>
<td>nAMD, DME, RVO</td>
<td>Phase II STARWAY trial results reported; Phase III trials ongoing for both indications.</td>
</tr>
<tr>
<td>GA secondary to dry AMD</td>
<td>Phase II GALLEGO trial (n=360) and Phase II open-label trial (n=260) currently recruiting.</td>
</tr>
<tr>
<td>nAMD, DME, RVO</td>
<td>Phase IIb ALTISIMO (n=56, nAMD), Phase IIb/III (n=32, nAMD); and Phase IIa (n=21, DME, RVO) results pending.</td>
</tr>
<tr>
<td>GA secondary to dry AMD</td>
<td>Phase II CATALINA trial started July 2020.</td>
</tr>
<tr>
<td>AMD, DME and branch RVO</td>
<td>Phase III safety studies due for completion this year.</td>
</tr>
<tr>
<td>GA secondary to dry AMD</td>
<td>Interim Phase IIa data (n=24) reported.</td>
</tr>
<tr>
<td>nAMD, DME, RVO</td>
<td>Phase IIb/III (n=153) results reported; Phase III trials to begin this year.</td>
</tr>
<tr>
<td>nAMD</td>
<td>Interim Phase I data (n=26) report favorable safety profile.</td>
</tr>
<tr>
<td>nAMD, DME, RVO</td>
<td>Results of Phase II trials (n=51) concluded in 2019 pending.</td>
</tr>
<tr>
<td>GA secondary to dry AMD</td>
<td>Post-hoc Phase II results reported; topline Phase III results expected later in year.</td>
</tr>
<tr>
<td>nAMD, DME, DR</td>
<td>Phase III Archway trial (n=419) expected to complete in spring; extension study ongoing.</td>
</tr>
<tr>
<td>nAMD</td>
<td>Phase I trial (n=56) started recruitment October 2020. Results due 2026</td>
</tr>
<tr>
<td>DME</td>
<td>Pilot study data pending.</td>
</tr>
<tr>
<td>DME, dry AMD</td>
<td>Preliminary Phase II results reported; Phase IIb/III study planned for 2021.</td>
</tr>
<tr>
<td>DME</td>
<td>Phase II KALAHARI trial started September; completion scheduled 2023.</td>
</tr>
<tr>
<td>DME</td>
<td>Additional Phase I results reported; Phase II trial to start this year.</td>
</tr>
<tr>
<td>DME</td>
<td>LIGHTSITE III trial ongoing; completion scheduled 2022.</td>
</tr>
<tr>
<td>DME, nAMD, GA secondary to dry AMD</td>
<td>Phase IIb trial launch delayed from 2020; launch expected later in 2021.</td>
</tr>
<tr>
<td>DME (also uveitic macular edema)</td>
<td>Phase II (n=71) results reported.</td>
</tr>
<tr>
<td>GA secondary to dry AMD</td>
<td>Phase III trial (n=400) initiated; completion due in 2023. Second Phase III trial pending.</td>
</tr>
</tbody>
</table>

**NEW: CLS-AX (Clearside Biomedical)**

Axitinib is a small-molecule tyrosine kinase inhibitor (TKI) commonly used to treat renal cell carcinoma. CLS-AX is a proprietary suspension of axitinib for suprachoroidal injection. Enrollment started in January of the Phase I/IIa OASIS dose-escalation trial in nAMD (n=15, NCT04626128). Eligible patients had stable visual acuity following two or more previous anti-VEGF injections. Enrolled patients initially receive aflibercept at the first visit and a single dose of CLS-AX at the second visit one month later. Study completion is expected next year. Axitinib has intrinsic high potency and pan-VEGF inhibition through receptor blockade.

**Conbercept (Chengdu Kanghong Biotechnology)**

Conbercept is an anti-VEGF recombinant fusion protein that’s been approved in China since 2013. It
targets VEGF-A and -B along with placental growth factor (PLGF). Two Phase III trials, PANDA-1 and PANDA-2, have each enrolled 1,140 patients with nAMD (NCT03577899, NCT03630952). The trials recently completed 36-week primary endpoint visits of enrolled patients and both are scheduled for completion in early 2022. Sponsor Chengdu Kanghong says it expects a global launch in 2023.

**EYP-1901 (EyePoint Pharmaceuticals)**

EyePoint has dosed the first patient in the Phase I clinical trial of EYP-1901 as a potential twice-yearly, sustained-delivery anti-VEGF treatment in nAMD. EYP-1901 combines the bioerodable Durasert sustained-release insert with vorolanib, a multi-kinase inhibitor that’s shown potential in previous human trials in nAMD as an oral therapy. The trial isn’t listed yet on ClinicalTrials.gov.

**Elamipretide (Stealth BioTherapeutics)**

Elamipretide is a cell-permeable peptide delivered via a 40-mg subcutaneous injection that targets mitochondrial dysfunction. The Phase II ReCLAIM-2 study in AMD with noncentral GA (n=180; NCT03891875) is ongoing with a completion date set for March 2022.

In the past year, Stealth has pursued nonocular indications for elamipretide, namely cardiomyopathy in Barth syndrome, a genetic disorder characterized by dilated cardiomyopathy, skeletal myopathy, neutropenia and short stature, as well as primary mitochondrial myopathy.

The key endpoint of ReCLAIM-2 is low-luminance BCVA at 48 weeks, with secondary outcomes including change in GA area measured by fundus autofluorescence and/or optical coherence tomography at 48 weeks.

**Faricimab (Genentech/Roche)**

Faricimab is a bispecific antibody that binds and neutralizes both angiopoietin-2 (Ang-2) and VEGF-A. STAIRWAY (n=76, NCT03038880) was a 52-week Phase II trial of nAMD patients that compared faricimab 6 mg q16 weeks flexible dosing or q12-week fixed dosing, both after four monthly injections, and monthly ranibizumab 0.5 mg. Best-corrected VA improvements in both faricimab groups were comparable with ranibizumab, as was improvement in central subfield thickness.

Genentech has reported top-line results from two large, global, Phase III trials, TENAYA (n=671, NCT03823287) and LUCERNE (n=658, NCT03923300) comparing faricimab to aflibercept in nAMD. Faricimab injections at intervals of up to q16 weeks achieved comparable vision outcomes to aflibercept, and 45 percent of patients in both studies received faricimab every 16 weeks during the first year. Completion for both is scheduled for late next year.

Parallel Phase III trials, YOSEMITE (n= 940, NCT03622580) and RHINE (n= 951, NCT03622593), are evaluating faricimab for DME. Genentech reported that both studies met their primary endpoints and showed that faricimab at q8 weeks and q16-week flex dosing demonstrated comparable VA gains with aflibercept q8 weeks, and that faricimab was generally well-tolerated with no new safety signals identified. In addition, the Phase III Rhone-X study (n=1,500, NCT04432531) is investigating the long-term effect of faricimab in DME, with completion expected in 2023.

**NEW: FHTR2163 (Genentech/Roche)**

Also known as RG6147, this antibody, delivered by intravitreal injection, inhibits high-temperature requirement A1 (HtrA1), a serine protease gene associated with GA. HtrA1 has also been identified as a major risk factor for wet AMD. The Phase II GALLEGRO trial (n=360, NCT03972709) of patients with GA is evaluating outcomes over 76 weeks with completion due next year. A separate open-label Phase II trial (n=360, NCT04607148) comparing q4-week and q8-week dosing is due at the end of 2023.

**GB-102 (Graybug Vision)**

GB-102 is a proprietary micro-particle depot formulation of the pan-VEGF inhibitor sunitinib designed to be administered intravitreally twice yearly. Treatment in the Phase IIb ALTISSIMO trial (n=56, NCT03953079) in nAMD concluded in January. Graybug reports that 12-month topline data are expected to be announced in the second quarter and full results later in the year. A second open-label Phase I/IIa trial (n=32, NCT03249740) in nAMD provided evidence of durable biological activity for up to eight months from a single intravitreal injection with minor reports of depot migration.

An ongoing, open-label Phase IIa trial (n=21, NCT04085341) is evaluating GB-102 in DME and macular edema secondary to RVO. A three-month safety analysis reported further evidence demonstrating the safety of the 1-mg dose, with a reduced number of particle migration events compared to the ADAGIO trial, while the rate of drug-related adverse events in the 2-mg arm remained unchanged.
NEW: GEM103 (Gemini Therapeutics)

GEM103 was granted FDA fast-track designation for GA secondary to dry AMD. GEM103 is a recombinant, human complement factor H. After topline Phase I results confirmed the drug’s safety (n=12, NCT04246866), the Phase IIa ReGaTTa study (n=45, NCT04684394) enrolled its first patient last fall. Completion of the trial is scheduled for year end.

ICON-1 (Iconic Therapeutics)

Iconic describes ICON-1, also labeled hI-con1 in clinical trials, as a fusion protein that binds to tissue factor overexpressed in the retina and the choroid of patients with AMD.

A Phase II clinical trial for choroidal neovascularization and AMD, called EMERGE (n=88, NCT02358889), found ranibizumab alone to be superior to hI-con1 0.3 mg alone or in combination with ranibizumab for six-month improvement in central subfield thickness, but no significant difference between combination treatment and ranibizumab monotherapy for six-month VA improvement (patients on hI-con1 alone actually lost 2.1 letters at six months).

Results are pending in the second Phase II study (n=15, NCT03452527), called DECO (Dose Exploration and Continuation Option), which evaluated intravitreal ICON-1 0.6 mg in combination with aflibercept 2 mg for CNV in AMD.

NEW: IONIS-FB-LRx (Ionis Pharmaceuticals)

IONIS-FB-LRx is an antisense oligonucleotide (ASO) that inhibits complement factor B gene expression by binding with factor B mRNA. It’s the subject of a Phase II placebo-controlled trial (n=330, NCT03815825) in GA that will evaluate change in GA area at week 49. Study completion is expected in late 2022.

KSI-301 (Kodiak Sciences)

KSI-301 is the subject of clinical trials for three indications in exudative disease. In treatment-naïve nAMD, patient recruitment closed last fall in the Phase Ib/III DAZZLE study (n=550, NCT04049268) comparing KSI-301 and aflibercept. Completion is expected in late 2022. The primary endpoint is mean change in BCVA at one year.

In treatment-naïve DME, the Phase III GLEAM (n=450, NCT04611152) and GLIMMER (n=450, NCT04603937) studies are comparing KSI-301 on an individualized dosing regimen of q8 to q24 weeks after three loading doses and aflibercept q8 weeks after five loading doses.

Completion for both is expected toward late 2023. The Phase III BEACON study (n=550, NCT04592419) is evaluating KSI-301 in patients with treatment-naïve macular edema due to RVO. Completion is expected later next year.

NEW: LBS-008 (Belite Bio)

Belite Bio describes LBS-008 as a first-in-class oral, small-molecule, retinol-binding protein 4 (RBP4) specific antagonist for dry AMD. Results of a Phase I trial (n=71, NCT03734810) confirmed safety and tolerability and that oral administration achieved potentially therapeutic-level target engagement. Belite Bio says it expects to enter a global Phase III trial this year and is seeking an additional indication in Stargardt disease.

NEW: NGM621 (NGM Biopharmaceuticals)

NGM621 is a humanized IgG1 monoclonal antibody engineered to potently inhibit C3. NGM initiated the Phase II CATALINA trial (n=240, NCT04465955) in GA last fall. Completion is expected in 2023.

NEW: ONS-5010/Lytenava (bevacizumab-vikg, Outlook Therapeutics)

ONS-5010/Lytenava (bevacizumab-vikg) is an ophthalmic formulation of bevacizumab. Late last year, Outlook completed enrollment in its open-label Phase III safety study, NORSE THREE (n=195, NCT04516278) in nAMD. DME and branch RVO. Completion is expected this quarter.

A Phase III safety study in nAMD alone (n=227, NCT03834753) is scheduled for completion in the summer. The idea is to have a formulation of bevacizumab ready for injection without the need for repackaging by compounding pharmacies.

NEW: OpRegen (Lineage Cell Therapeutics)

This investigational cell therapy consists of allogeneic retinal pigment epithelium cells administered to the subretinal space for GA resulting from dry AMD. Interim results from a Phase I/IIa trial (n=24, NCT02286089) demonstrated improvement in VA and GA area among some treated patients. The study is scheduled for completion in late 2024.

OPT-302 (Ophthea)

Ophthea says it has “successfully completed” post-Phase II meetings with the FDA on its VEGF-C and -D inhibitor and expects to begin Phase III trials in nAMD early this year.
The ShORe trial would randomize patients to one of three study arms: q4-week treatment with ranibizumab in combination with either OPT-302 2 mg q4 weeks, OPT-302 2 mg on an extended q8-week regimen after three monthly doses, or sham q4 weeks.

The COAST trial would have three treatment arms: aflibercept 2 mg q8 weeks after three monthly loading doses in combination with the same two OPT-302 regimens in ShORe; and sham q4 weeks. Each trial would enroll at least 900 patients with a primary endpoint of mean change in VA after a year.

Results of a separate Phase Ib/IIa trial in DME refractory to anti-VEGF-A therapy were reported over the summer (n=153, NCT03397264). The Phase Ib component (n=9) was a dose-escalation study of OPT-302 in combination with aflibercept. The Phase IIa trial (n=144) was a dose-expansion study that randomized patients to either OPT-302/aflibercept combination therapy or aflibercept alone. That study reported that 52.8 percent of patients on combination therapy achieved a >5-letter improvement in VA at 12 weeks.

NEW: OTX-TKI (Ocular Therapeutix)

OTX-TKI is a reabsorbable intravitreal implant that delivers the small-molecule TKI axitinib in a sustained-release formulation to the vitreous. Interim Phase I data (n=26, NCT03630315) demonstrated a favorable safety profile and evidence of bioavailability with one patient demonstrating durability up to 11 months without rescue.7

PAN-90806 (PanOptica)

This once-daily topical drop that targets VEGF receptor 2 (VEGFR2) was the subject of Phase I/II trials in nAMD (n=51, NCT03479372), which were reported to have confirmed safety and tolerability. Results haven’t yet been posted.

Pegecetacoplan (APL-2, Apellis)

Eighteen-month data from the Phase Ib APL-2-103 study of pegecetacoplan in patients with advanced GA and low vision found that the growth rate of GA lesions was 52 percent slower in treated vs. untreated eyes.

The Phase I clinical trial (n=12, NCT03777332) assessed the safety of the pegecetacoplan formulation (15 mg/0.1 mL) that’s being used in the Phase III DERBY and OAKS studies (n=600, NCT03525600, NCT03525613), for which topline data are expected later in the year.

The patient population in the Phase Ib clinical trial is similar to those of the DERBY and OAKS studies, but includes patients with more advanced disease, a wider range of baseline lesion size and lower baseline visual acuity.

A post-hoc analysis of the Phase II FI LLY trial (n=246, NCT02503332) showed a 39-percent reduction in the rate of progression from nascent GA to GA in patients treated monthly vs. sham.

Port Delivery System (PDS) with ranibizumab (Genentech/ Roche)

Results from the Phase III Archway clinical trial (n=418, NCT03677934) reported last summer demonstrated that 98.4 percent of PDS patients went six months with no additional treatment and achieved vision outcomes equivalent to monthly ranibizumab eye injections.8 A Phase III extension study (n=1,000, NCT03683251) is also evaluating long-term safety and tolerability of PDS over 144 weeks with refill exchanges at q24 or q36 weeks. Completion of Archway is expected this spring. The extension study is scheduled for completion in 2025.

NEW: RO7250284 (Genentech/Roche)

This is a bispecific human anti-VEGF-A therapy that delivers the small-molecule TKI axitinib delivered via PDS that Roche is investigating for nAMD. A Phase I trial (n=50, NCT04567303) started recruiting patients in October 2020. Completion is expected in 2026.

Retilux (PhotoOptTx)

Worn like an eye patch, this device is designed to deliver laser therapy directly to the affected eye. PhotoOptTx describes photobiomodulation (PBM) as irradiation by light in the 630- to 690-nm range. Data are pending from a pilot study (n=134, NCT03666473) comparing PBM with sham in eyes with center-involved DME and good vision.

Risuteganib (Allegro Ophthalmics)

Results are still pending from a Phase II trial (n=42, NCT03626636) comparing the drug candidate formerly known as lumesnate with sham for nAMD. Allegro reports that preliminary results showed 48 percent of patients in the risuteganib group vs. 7 percent in the sham group met the primary endpoint of >8 letter gain in BCVA (p= 0.013) and that about 1,200 injections have been given outside the study with an acceptable safety profile.

The company this year is planning a larger Phase Ib/III clinical trial to confirm the Phase II study findings.
Gene therapies turn to exudative retinal disease

Developers of gene therapy candidates in ocular disease have shifted their focus from inherited retinal diseases, which often have limited treatment populations, to exudative diseases, including geographic atrophy secondary to age-related macular degeneration. They’re also investigating treatments in neovascular AMD and diabetic macular edema to reduce or eliminate the treatment burden of anti-VEGF therapies. The following is a list of investigative gene therapy candidates for exudative retinal disease.

ADVM-022 (Adverum Biotechnologies)
ADVM-022 is a single intravitreal injection that uses a propriety adeno-associated vector capsid, AAV7m8, carrying an aflibercept-coding sequence under the control of a proprietary expression cassette. It’s the subject of two clinical trials in nAMD and one in DME.

Partial data from cohorts in the OPTIC Phase I trial (n=30, NCT03748784) demonstrated durability of a single injection out to 92 weeks with no rescue and 99 and 85 percent reductions in annual anti-VEGF injections in high- and low-dose groups, respectively. Adverum says it will present longer-term OPTIC data in the first half of the year and initiate a pivotal trial by midyear.

In DME, Adverum says it expects to present data from the INFINITY Phase II (n=33, NCT0418427) trial in the second half of the year, and anticipates launching a pivotal trial in nAMD at midyear.

GT005 (Gyroscope Therapeutics)
A one-time therapy delivered subretinally, GT005 is designed to restore balance to an overactive complement system by inducing expression of complement factor I. The Food and Drug Administration last year approved the Orbit subretinal microinjection system and granted fast-track designation for GT005 in GA.

GT005 is being evaluated in three trials: Phase I/II FOCUS (n=45, NCT03846193), an open-label dose-escalation safety study of a single injection in GA; and the EXPLORE (n=75, NCT04437368) and HORIZON (n=150, NCT04566445) trials, both Phase II studies evaluating two doses in one injection in GA.

Gene therapies for exudative retinal disease in human trials

<table>
<thead>
<tr>
<th>Drug name (manufacturer)</th>
<th>Description/active agent</th>
<th>Indication</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADVM-022 (Adverum Biotechnologies)</td>
<td>Adeno-associated vector 7m8 of aflibercept</td>
<td>Neovascular age-related macular degeneration, diabetic macular edema</td>
<td>Patient enrollment completed in Phase II DME trial (n=33) with data readout this year; longer-term Phase I OPTIC (n=30) data due midyear.</td>
</tr>
<tr>
<td>GT005 (Gyroscope Therapeutics)</td>
<td>AAV-induced expression of complement factor I</td>
<td>Geographic atrophy secondary to dry AMD</td>
<td>Phase I/II FOCUS (n=45); Phase II EXPLORE (n=75); Phase II HORIZON (n=150) ongoing.</td>
</tr>
<tr>
<td>HMR59 (Hemera Biosciences)</td>
<td>Soluble form of CD59 protein found in cellular plasma membrane</td>
<td>GA secondary to dry AMD, nAMD</td>
<td>Phase I GA trial (n=17) declared inactive; Phase I nAMD trial (n=25) ongoing.</td>
</tr>
<tr>
<td>IBI302 (Innovent Biologics)</td>
<td>Bispecific anti-VEGF and anti-complement recombinant fully human fusion protein</td>
<td>nAMD</td>
<td>Results of Phase I dose-escalation trial (n=31) pending; Phase II comparator trial (n=18) due for completion midyear.</td>
</tr>
<tr>
<td>RGX-314 (RegensBio)</td>
<td>AAV8 vector containing anti-VEGF Fab transgene</td>
<td>Diabetic retinopathy without center-involved DME, nAMD</td>
<td>Initial Phase II CI-DME (n=40) data due this year; Interim Phase I/II (n=42) data in nAMD reported; Phase IIb/III nAMD trial (n=300) initiated; Phase II nAMD trial (n=40) due for completion 2022; second nAMD pivotal trial to launch later in year.</td>
</tr>
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Inherited retinal disease treatments move beyond gene therapies

Just as developers of gene therapy candidates have expanded their research beyond inherited retinal disease and into exudative retinal disease, some non-gene therapy candidates have emerged to treat IRD. The following IRD candidates are in human trials.

AAV-RPGR (MeiraGTx Holdings/Janssen Pharmaceuticals)
AAV-RPGR is designed to deliver functional copies of the RPGR gene to the subretinal space. Twelve-month data from the ongoing Phase I/II clinical trial (n=46, NCT03252847) in X-linked retinitis pigmentosa (XLRP) reported statistically significant vision improvement in the dose-escalation phase sustained for a year, although the numbers were small: six of seven patients in two dosing cohorts.14 These findings are being evaluated at additional time points.

AGTC-402 and rAAV2YF-PR1.7-hCNGB3 (Applied Genetic Technologies Corporation [AGTC])
Enrollment in two Phase I/II trials of gene therapies in achromatopsia have been completed: AGTC-402 for mutations in the ACHM CNGA3 gene (n=24, NCT02935517); and rAAV2YF-PR1.7-hCNGB3 for mutations in the ACHM CNGB3 gene (n=28, NCT02599922). Early results from dose-escalation cohorts of the trials showed positive signals in improving light discomfort and a favorable safety profile.

ALK-001 (Alkeus Pharmaceuticals)
A Phase II trial of this oral-modified form of vitamin A in Stargardt disease (n=140, NCT02402860) is underway. Vitamin A dimers have been linked to vision loss, and ALK-001 is designed to prevent formation of these toxic dimers and replace vitamin A.

Elamipretide (Stealth BioTherapeutics)
Elamipretide is a cell-permeable peptide delivered via a 40-mg subcutaneous injection that targets mitochondrial dysfunction. Results are pending of a Phase II study in Leber hereditary optic neuropathy (n=12, NCT02693119).

jCell (jCyte/Santen)
jCell is an intravitreal injection of human retinal progenitor cells (hRPC), now in a Phase II trial (n=84, NCT03073733) in RP. The treatment aims to preserve or restore vision independent of the mutated gene causing the disease. In the Phase IIb study, patients received 3 million cells, 6 million cells or a sham treatment in one eye. The high-dose group had a mean improvement in best-corrected visual acuity of 7.43 letters vs. 1.96 and 2.81 letters in the 3-million cell and sham groups. jCyte is planning a Phase III trial this year.

Lumevoq (GS010, GenSight)
Lumevoq is a single IVI of rAAV2/2-ND4. The Phase III RESCUE trial (n=39, NCT02652767) in LHON caused by a mutation in the ND4 mitochondrial gene reported 71 percent of patients had >15-letter improvement in at least one eye at 96 weeks.15 GenSight expects approval in Europe later in the year and topline results from the Phase III REFLECT trial (n=90, NCT03293524) in the second quarter.

OCU400 (Ocugen)
OCU400 has received orphan drug designation for the treatment of PDE6B gene mutation-associated retinal diseases. OCU400 consists of a functional copy of a nuclear hormone receptor gene, NR2E3, delivered to retina target cells via an adeno-associated viral vector. Expression of NR2E3 within the retina may help reset retinal homeostasis. A potential indication is RP caused by PDE6B mutation autosomal-dominant congenital stationary nystaglopia. Ocugen says it’s planning to initiate two parallel Phase I/II clinical trials this year.

rAAV2YF-GRK1-RPGR (AGTC)
Early results have been reported in the Phase II trial of this AAV-based therapy in XLRP (n=30, NCT03316560). A small group in the trial demonstrated improved visual sensitivity and stable or improving vision at 12 months. Last fall AGTC said it expects to initiate enrollment in the Vista trial in the first quarter this year.

Therapies for inherited retinal disease in human trials

<table>
<thead>
<tr>
<th>Drug name (manufacturer)</th>
<th>Description/active agent</th>
<th>Indication</th>
<th>Status</th>
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<tr>
<td>AAV-RPGR (MeiraGTx Holdings/Janssen Pharmaceuticals)</td>
<td>Subretinal delivery of functional copies of RPGR gene</td>
<td>X-linked retinitis pigmentosa</td>
<td>12-month Phase I/II (n=46) readout reported.</td>
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<tr>
<td>AGTC-402 and rAAV2YF-PR1.7-hCNGB3 (Applied Genetic Technologies Corporation)</td>
<td>Adeno-associated vector targeting mutations in the ACHM CNGA3 and CNGB3 genes</td>
<td>Achromatopsia</td>
<td>Enrollment completed in Phase I/II (n=24, 28, respectively); completion expected 2025.</td>
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<tr>
<td>ALK-001 (Alkeus Pharmaceuticals)</td>
<td>Oral modified vitamin A</td>
<td>Stargardt disease</td>
<td>Phase II trial (n=140) ongoing; completion scheduled March 2022.</td>
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<tr>
<td>Elamipretide (Stealth BioTherapeutics)</td>
<td>Subcutaneous mitochondria-targeting cell-permeable peptide</td>
<td>Leber hereditary optic neuropathy</td>
<td>Phase II trial (n=12) concluded; results pending.</td>
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<tr>
<td>jCell (jCyte/Santen)</td>
<td>Intravitreal human retinal progenitor cells.</td>
<td>Retinitis pigmentosa</td>
<td>Phase II trial (n=84) ongoing; Phase III to launch this year.</td>
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<tr>
<td>Lumevoq (GS010, GenSight)</td>
<td>Single intravitreal injection of rAAV2/2-ND4</td>
<td>LHON</td>
<td>Phase III RESCUE trial (n=39) results reported; topline Phase II REFLECT (n=80) results due this year.</td>
</tr>
<tr>
<td>OCU400 (Ocugen)</td>
<td>AAV of functional NR2E3 gene.</td>
<td>RP, autosomal dominant congenital nystaglopia</td>
<td>Two parallel Phase I/II trials to start this year.</td>
</tr>
<tr>
<td>rAAV2YF-GRK1-RPGR (Applied Genetic Technologies Corporation)</td>
<td>AAV-based treatment</td>
<td>XLRP</td>
<td>Early Phase I/II (n=30) results reported; Vista trial to start this year.</td>
</tr>
</tbody>
</table>
THR-149, THR-687 (Oxurion)

THR-149 is a plasma kallikrein inhibitor and THR-687 is a pan-arginylglycylaspartic acid (RGD) integrin antagonist. The indication for both is DME.

THR-149 is the subject of a Phase II trial, KALAHARI (n=122, NCT04527107), which will recruit patients with CI-DME refractory to anti-VEGF. Phase IIa will evaluate the optimal dose level, for which data are expected in midyear. Phase IIb will be a comparison study with aflibercept. Topline results are expected in 2023.

Updated data from the Phase I study of THR-687 (n=12, NCT03669233) confirmed safety and demonstrated early signs of efficacy. Following a single injection of the highest dose of THR-687, this activity was maintained at three months with a mean BCVA improvement of 12.5 letters. Oxurion says THR-687 is expected to enter Phase II development this year.

Valeda Light Delivery System (LumiThera)

This device also uses photobiomodulation. The LIGHTSITE III trial (n=96, NCT04065490) in dry AMD is ongoing with completion expected next year. Subjects will receive three PBM treatments a week for three weeks for a total of nine sessions.

LumiThera entered into a collaborative arrangement with Diopsys to conduct a pilot study in dry AMD that uses multi-focal electroretinogram function changes as a primary analysis. The device is approved in Europe.

Xiflam (OcuNexus Therapeutics)

OcuNexus was poised to launch a Phase Iib clinical trial of Xiflam in DME, nAMD and GA last year, but those plans were delayed. Now OcuNexus says it plans to file an IND application with the FDA in the second quarter and start the Phase II trial in the second half of the year. Xiflam is an oral small-molecule agent that blocks connexin43 hemichannels that have been shown to be overexpressed in exudative retinal disease.

NEW: Xipere (CLS-TA, Clearsider Biomedical)

Xipere, formerly known as CLS-TA, is a proprietary triamcinolone acetonide suspension formulated for Clearside’s suprachoroidal delivery platform. Besides trials in noninfectious uveitis, Xipere has been the subject of the Phase II TYBEE trial in DME (n=71, NCT03126786) comparing Xipere in combination with aflibercept and aflibercept alone. Following a single injection of the highest dose of THR-687, this activity was maintained at three months with a mean BCVA improvement of 12.5 letters. Oxurion says THR-687 is expected to enter Phase II development this year.

Zimura (avacincaptad pegol, IVERIC bio)

Zimura is a C5 inhibitor. Results from the Phase III GATHER1 trial (n=400, NCT04435366) in GA demonstrated that patients in the 2- and 4-mg treatment cohorts had a 27.4- and 27.8-percent reduction in average GA growth over a year, respectively, compared with sham. Iveric bio says a second Phase III trial in GA, known as GATHER2, will evaluate Zimura 2 mg over 24 months. Completion of GATHER1 is expected in 2023.

REFERENCES


The complement pathway in geographic atrophy

Examining the role of complement factors in advanced disease.

By Oleg Alekseev, MD, PhD, Eleonora M. Lad, MD, PhD, and Nathan Steinle, MD

**Take-home Points**

- The complement pathway is a complex multifactorial contributor of innate immunity and is directly involved in the pathogenesis of geographic atrophy.
- Activated complement components are found deposited within drusen and elevated in the serum of patients with age-related macular degeneration.
- Numerous polymorphisms in the complement pathway genes have been associated with AMD and specifically GA.
- Suppression of the complement pathway is an appealing therapeutic target to slow the progression of GA, and several complement factors and modulators are currently being investigated in promising late-phase clinical trials.

**Complement factor B**

CFB is an activating factor in the alternative pathway. It’s converted by CFD into its active subunit Bb, which then becomes an integral part of the C3 convertase. Activation products of CFB (Ba and Bb) are elevated in the serum of AMD patients.

Two protective variants of CFB have been described: R32Q and L9H. The R32Q polymorphism also appears to slow GA progression. These polymorphisms may be protective due to the impaired activity of the resultant C3 convertase.

**Complement factor D**

CFD is directly upstream of CFB and also activates the alternative pathway. A
CFD-/- knockout mouse model of AMD showed decreased photoreceptor damage compared to wild type. One polymorphism (rs3826945) has been associated with AMD. In addition, serum levels of CFD have been shown to be elevated in AMD patients, a noteworthy finding since CFD is considered to be rate-limiting in the activation of the alternative pathway.

**Complement factor H**

CFH is a key regulatory factor responsible for complement cascade inactivation. CFH is the first and most researched complement factor to be linked to AMD. It prevents damage to healthy bystander cells, but not pathogens, by selective inhibition of complement activity on self-surfaces.

Genome-wide association studies have identified numerous risk-impacting, as well as disease-protective, CFH variants. Of these, Y402H is the most notable common variant; it’s present in 50 percent of AMD patients and correlates with the presence of GA.

This polymorphism compromises glycosaminoglycan-mediated interaction between CFH and the damaged retina, thereby attenuating inactivation of the complement cascade and allowing for chronic low-level inflammation.

In contrast, R1210C is an example of a rare but highly penetrant variant that imparts a more severe disease course, including earlier disease onset by approximately six years. Interestingly, CFH accumulates in drusen at the choroid-RPE interface, where it’s thought to expose retinal pigment epithelium cells to continuous membrane attack complex (MAC) damage. In addition to conferring general AMD risk, CFH variants impart higher risk of conversion from large drusen to GA.

**Complement factor I**

CFI is a C3b/C4b inactivator and the rate-limiting enzyme in complement termination. Interestingly, amyloid-beta, a component of drusen, binds to CFI and reduces its activity. While several high-risk CFI variants have been proposed, a meta-analysis has confirmed a strong association between AMD and CFI variants rs10033900T>C (protective) and rs2285714C>T (high-risk).

Subsequently, a large systematic functional testing study revealed numerous complement factors with known genetic associations with age-related macular degeneration are marked with A (CFB, CFD, CFH, CFI, C1 inhibitor, C2, C3, and C9). Those with known genetic associations specifically with geographic atrophy are marked with G (CFB, CFH, and C3). Complement regulators appear in orange boxes. Complement-targeting medications under current or former clinical trial investigation (Table, page 33) appear in dashed boxes. (Adapted from Khandhadia S, Cipriani V, Yates JR, Lotery AJ. Age-related macular degeneration and the complement system. Immunobiology. 2012;217:127-146.)

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**Bios**

Dr. Alekseev is a Heed fellow in medical retina at Duke University, Durham, North Carolina.

Dr. Lad is an associate professor at Duke University.

Dr. Steinle is a partner at California Retina Consultants in Southern California.

**DISCLOSURES:** Dr. Alekseev has no relevant relationships to disclose.

Dr. Lad disclosed relationships with Apellis, Roche, Novartis, Allegro, Galilmedix, Retrotepe, Gemini Therapeutics and LumiThera.

Dr. Steinle disclosed relationships with Alimera Sciences, Apellis, Carl Zeiss Meditec, Genentech, Notal Vision, Novartis, Regenerative Patch Technologies, Regeneron and RegenBio, and is an investor in Vortex Surgical.
rare CFI variants that likely contribute to AMD.18 A rare but particularly pathogenic polymorphism is G119R, which results in a hypoactive version of CFI and imparts a 20-fold increased risk of AMD.19

Complement factor P
CFP (properdin) is the only known positive regulator of the complement cascade, wherein it stabilizes the C3 and C5 convertases. While no properdin polymorphisms are known to associate with AMD, it presents an appealing therapeutic target (Table).

Complement component 1
The trigger of the classical pathway, C1 becomes activated by binding to antigen-antibody complexes. While no known AMD-causing variants of C1 have been identified, potential associations between AMD and variants in the C1-inhibitor gene, SERPING1,20 have been noted, although these findings remain contested.

Complement component 2
C2 is activated via the classical and lectin pathways to become a part of the C3 convertase. Two major protective variants of C2 are E318D and rs547154. However, since C2 and CFB are in extensive linkage disequilibrium, CFB/C2 is considered a single risk-modifying allele, wherein C2 variants likely do not have an independent molecular role in AMD.21

Complement component 3
C3 is the convergence point of the three complement pathways. It’s activated by C3 convertase to become C3α, which then becomes a core subunit of C5 convertase.

Activated C3 is often measured as a reflection of overall complement cascade activity. C3 is found deposited within drusen and elevated in plasma of AMD patients.3 C3 overexpression in mice induces retinal pathology that in many aspects recapitulates AMD, including photoreceptor and RPE atrophy.22 The most common AMD-linked C3 variants are R80G and R102G,4 whereas K155Q is a rare variant. Variant R102G is strongly associated specifically with GA.11

As a common relay point in the complement cascade, C3 is an attractive therapeutic target. A C3-neutralizing therapeutic (APL-2, also known as pegcetacoplan, Apellis Pharmaceuticals) has shown promising clinical results in a Phase II trial23 and is the subject of two fully enrolled ongoing Phase III trials24,25 (Table).

Additional agents, including a non-PEGylated compstatin (AMY-106)26 and a novel protease that cleaves and degrades C3 (CB 2782-PEG),27 are currently in preclinical development.

While most of the investigations into the role of complement in AMD focus on polymorphisms that cause complement dysfunction, it’s important to recognize the inciting pathology may lie outside the complement genes themselves. 

Complement component 5
C5 is activated by C5 convertase to become C5α, a pro-inflammatory mediator that acts as a nidus for MAC formation. Plasma levels of C5α are elevated in AMD patients11 and stimulation of the choroid C5α receptor causes ICAM-1 overexpression, which likely leads to monocyte recruitment.28 Nevertheless, no consistent and replicable associations between polymorphisms in C5 or C5α receptors and AMD have been reported.28,29 A C5-based therapeutic (avacincaptad pegol, also known as Zimura, Iveric bio) has already shown promising Phase II/III results,30 with a second Phase III trial ongoing31 (Table).

Complement component 9
C9 participates in the final stage of MAC formation, whereby polymerization of 12-18 molecules of C9 forms a cytolytic transmembrane pore in the target cell. A high-risk C9 variant (P167S) has been reported in a mixed population of GA and/or nAMD,32 although this study didn’t stratify specifically for correlation with GA.

Another variant, R95S, has only been reported in nAMD.33 While C9 is currently not being targeted for therapeutic purposes, an endogenous inhibitor of C9 polymerization, CD59, has inspired a gene-therapy-based MAC-inhibitory agent now in a Phase II trial (Table).
Outside the pathway

While most of the research into the role of complement in AMD focuses on polymorphisms that cause complement dysfunction, it’s important to recognize that the inciting pathology may lie outside the complement genes themselves. Inflammation, reactive oxygen species and complement-expressing macrophages all contribute to complement activation in AMD.

Particularly interesting is the role of iron homeostasis, critical for retinal and RPE health. Directly relevant to the pathogenesis of GA, cultured RPE cells exposed to elevated iron levels upregulate C3 gene expression, protein levels and protein secretion.34 Mice with elevated iron in the RPE develop activated C3 deposits in Bruch’s membrane.35

Moreover, iron increases retinal production and deposition of amyloid-beta,36 which is known to inhibit CFI activity.16 These findings align with the elevated iron levels in the RPE of GA-affected eyes of AMD patients37 and highlight iron-chelation as a potential approach to suppress complement activity for treatment of GA.

Bottom line

When considering the role of complement factors in GA, it’s important to recognize the broad range of outcome measures from the gene-association studies. While most of these studies examine cross-sectional AMD populations of pooled disease stages, the underlying molecular pathology is undoubtedly more complex. The genetic and environmental risk signature is likely quite different between the onset of early AMD, progression to GA, enlargement of GA and development of nAMD.

Relatively few studies have focused on identifying complement gene variants specifically pertinent to GA. Given that this knowledge is of utmost prognostic value and could inform the development of novel therapeutics, a focused characterization of a GA-specific genetic signature would be highly useful academically and clinically.

Phase III trials are ongoing for complement inhibition at the C3 and C5 levels.24,25,31 The results of these large trials will continue to shape how we approach GA.

To date, only three clinical trials have shown reduction in geographic atrophy growth: MAHALO, FILLY and GATHER1. Results of the Phase II MAHALO study were subsequently invalidated by the larger CHROMA and SPECTRI trials. Based on positive results of the Phase II FILLY and Phase II/III GATHER1 trials, both APL-2 and avacincaptad pegol are in Phase III clinical trials.

Candidates targeting the complement cascade to treat geographic atrophy

<table>
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<tr>
<th>Target</th>
<th>Candidate</th>
<th>Mechanism</th>
<th>Phase</th>
<th>Clinicaltrials.gov identifier</th>
<th>Trial name</th>
<th>Effect on GA Growth</th>
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<td>CFB</td>
<td>IONIS-FB-LRx</td>
<td>Atisense oligonucleotide</td>
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<td>NCT03815825</td>
<td>GOLDEN</td>
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<td>No reduction</td>
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<td></td>
<td>Eculizimab mAb</td>
<td></td>
<td>II</td>
<td>NCT00958833</td>
<td>COMPLETE</td>
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<td></td>
<td>Avacincaptad pegol Aptamer</td>
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<td>II/III</td>
<td>NCT02686658</td>
<td>GATHER1</td>
<td>28-percent reduction at 12 months</td>
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<td>C59</td>
<td>HMR59 Adeno-associated virus</td>
<td></td>
<td>II</td>
<td>NCT04358471</td>
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To date, only three clinical trials have shown reduction in geographic atrophy growth: MAHALO, FILLY and GATHER1. Results of the Phase II MAHALO study were subsequently invalidated by the larger CHROMA and SPECTRI trials. Based on positive results of the Phase II FILLY and Phase II/III GATHER1 trials, both APL-2 and avacincaptad pegol are in Phase III clinical trials.

(Continued on page 38)
In advanced dry age-related macular degeneration, in which subfoveal photoreceptors and retinal pigment epithelial cells are lost, profound central vision loss results. However, even patients with earlier stages of dry AMD, such as high-risk drusen or noncentral geographic atrophy, experience significant visual dysfunction despite preserved best corrected visual acuity. Manifestations of visual dysfunction in this population include difficulty with low-light vision and reading, poor adaptation to changes in lighting and impaired low-light activities of daily living. These problems can be quantified as loss of low-luminance visual acuity (LLVA) and low-luminance reading acuity (LLRA). Recently, the mitochondrion has emerged as a promising therapeutic target for the treatment of dry AMD.

Mitochondria emerge as target

Mitochondria are the cellular organelles that provide energy in the form of adenosine triphosphate (ATP). While glycolysis generates the majority of cellular ATP, mitochondria are frequently required to provide ATP for specific, critical and/or high-energy cellular activities.

In addition to their role in cellular energetics, mitochondria act as signaling nodes in a variety of pathways, most notably reactive oxygen species (ROS) and calcium regulation. Mitochondrial dysfunction is associated with ATP loss, increased production of ROS, calcium dysregulation and, in some cases, cell death.

AMD is a complex disease with multiple risk factors contributing to disease in each individual. Well-documented risk factors include age, heredity and environmental risk factors, most famously cigarette smoking.

Several lines of reasoning point to mitochondrial dysfunction as a major mediator of dry AMD. Evidence of mitochondrial dysfunction in AMD ranges from analyses of postmortem tissues demonstrating a reduction in mitochondria and abnormal mitochondrial morphology in RPE isolated...
from patients with AMD compared with age-matched controls.\(^1\)

In addition, some inherited mitochondrial diseases, such as maternal-inherited diabetes and deafness, and mitochondrial encephalopathy, lactic acidosis and stroke-like episodes (MELAS), are known to manifest as macular atrophy and other findings also seen in AMD.\(^2,3\)

**Compelling preclinical evidence**

Compelling preclinical evidence from both tissue culture and animal models supports mitochondria as a target in AMD. For instance, higher rates of mutation in mitochondrial DNA, a common marker of mitochondrial injury, have been found in patients with AMD and the number of mutations is correlated with disease progression.\(^4\)

Cigarette smoking is a well-documented major environmental risk factor for development and progression of AMD. Hydroquinone is a major toxin contained in cigarette smoke, plastics and processed foods, and is well characterized as a mitochondrial toxicant. Both cigarette smoke and hydroquinone exposure have been found to cause the development of drusen-like deposits in mice, suggesting a causative role for mitochondrial injury in AMD pathogenesis.\(^5\)

Furthermore, mitochondrial dysfunction is a prominent feature in one of the best studied mouse models of dry AMD, the APOE4 \(^{-/-}\) mouse.\(^6\) On electroretinogram, RPE in these mice display multiple markers of mitochondrial dysfunction, development of sub-RPE deposits resembling drusen and visual dysfunction.

**Emerging therapeutic candidates**

Interestingly, treatment with subcutaneously elamipretide (Stealth Biotherapeutics), a drug currently in development for dry AMD, reversed RPE morphological changes, sub-RPE deposits and visual dysfunction.\(^6\) Elamipretide is a cell-permeable peptide delivered via a 40-mg subcutaneous injection that targets mitochondrial dysfunction.

Risuteganib (Allegro Ophthalmics) is another promising drug under investigation for dry AMD as well as other retinal indications such as diabetic macular edema. Risuteganib, an integrin antagonist, is reported to have multiple mechanisms of action including mitochondrial protection.

Risuteganib has been shown to prevent mitochondrial injury in cultured RPE cells exposed to hydroquinone, suggesting that mitochondrial protection is efficacious in an *in vitro* model of AMD.\(^7\) Additionally, risuteganib was found to reduce mitochondrial ROS and improve mitochondrial bioenergetics in cultured RPE.\(^8\)

On the basis of these preclinical data, both elamipretide and risuteganib have advanced to human trials and have completed early stage clinical studies showing promising signs of efficacy in patients with dry AMD.

**Elamipretide results**

The ReCLAIM study (\(n=40,\) NCT02848313) was a Phase I, single-site, open-label clinical trial that evaluated the safety and tolerability of subcutaneous elamipretide in subjects with dry AMD. This study included two prespecified subgroups: patients with noncentral (NC) GA (\(n=19\)); and those with high-risk drusen (HRD) without GA (\(n=21\)). Subjects were required to demonstrate at least a 5-letter LLVA deficit and to endorse LL deficits on a LL questionnaire.

All subjects received daily subcutaneous elamipretide (40 mg). Outcomes were assessed at week 24 following initiation of the study drug. Subcutaneous elamipretide was generally safe and well-tolerated with no treatment-related serious adverse events. The most common adverse events were injection-site reactions including pruritis.
Mitochondrial Pathway

Considerable evidence from both preclinical studies and early stage clinical trials provides a compelling rationale for further investigation of mitochondria-targeted therapy for dry AMD.

Early risuteganib outcomes

Risuteganib, also known as luminite, is the subject of a completed Phase II randomized trial of patients with intermediate dry AMD (n=42). This 32-week study enrolled 40 subjects with 25 receiving intravitreal risuteganib 1 mg and 15 receiving sham treatment. Subjects had intermediate dry AMD.

The primary endpoint was the percent of subjects experiencing a clinically significant 8-letter gain in BCVA at week 24 for treated patients and at week 12 for sham. Secondary endpoints included low-luminance deficit, color vision, rate of conversion to exudative AMD, morphology on optical coherence tomography and microperimetry as well as mean BCVA between cohorts.

Risuteganib was well-tolerated with no drug-related serious adverse events reported. Preliminary results reported the study met its primary endpoint, demonstrating an 8-letter gain in BCVA in 48 percent of treated subjects compared with 7.1 percent in the sham control arm (p=0.013).

Risuteganib is not currently recruiting for an AMD indication, but given the positive Phase II findings, the company says it's planning a follow-on Phase III study.

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REFERENCES

Way back in 1989, Medicare used a strictly fee-for-service payment structure. Physicians were compensated based on the volume of claims they submitted. With that payment structure, Congress became concerned that physicians were profiting from self-referrals for use of clinical laboratory services. Consequently, Congress enacted Section 1877 of the Social Security Act, commonly known as the “Stark Law.” The law was subsequently expanded in 1993 and 1994 to encompass additional services. Currently, the self-referral provisions include prohibiting a physician from:

- making referrals for designated services that Medicare pays to an entity with which the physician or an immediate family member has a financial ownership; and/or
- submitting a claim to Medicare for those referred services.

### Services Stark covers

The list of designated services that Stark covers includes items that affect ophthalmologists, such as clinical laboratory services, radiology and other imaging services, outpatient prescription drugs and outpatient hospital services, among other services.

Over time, we’ve come to understand that the Stark laws can run counter to the overall goals the Centers for Medicare & Medicaid Services has established for patient care, so CMS has evolved. The goals of the current CMS program include ensuring:

- a patient’s ability to understand treatment plans and make empowered decisions;
- providers’ alignment on an end-to-end treatment approach (that is, coordination among providers along the patient’s full care journey);
- incentives for providers to coordinate and collaborate and provide patients with tools to get more involved; and
- information-sharing among providers, facilities and other stakeholders to enable efficient care while preserving and protecting patient access to data.

### Counter to collaboration

These goals, especially those related to incentivizing providers to collaborate, as well as other changes to Medicare, led CMS to add exceptions to the Stark law, with significant changes enacted last November. For instance, the revised final rule “permits parties to reconcile payment discrepancies in compensation arrangements without running afoul” of Stark. CMS also recognized that programs such as the Merit-Based Incentive Payment System (MIPS), which encourages shared care and value-based care, may result in referrals that could be considered violations under Stark. In response, CMS established routes to grant waivers to accountable care organizations under Stark law revisions.

The Federal Register states: “Congress also granted [the Secretary of Health and Human Services] broad authority to waive provisions of section 1877 of the Act and certain other Federal fraud and abuse laws when he determines it is necessary to implement the Shared Savings Program … or test models under the Innovation Center’s authority.”

Significantly, the Stark revisions address potential conflicts that arise from ACOs, otherwise known as “value-based” arrangements. The new exceptions for value-based arrangements include those:

- designed to achieve at least one value-based purpose, including a provision of item or service;
- that provide at least one value-based activity for a target patient population.

### By Ellen R. Adams, MBA

A look at how the latest revisions to self-referral regulations meant to facilitate collaborative care may impact your practice.

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**Bio**

Ms. Adams is a consultant with Corcoran Consulting Group. She can be reached at 1-800-399-6565 or at www.corcoranccg.com.

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COMMENTARY

Fixing unintended consequences

The Stark revisions also address other areas of the law that had unintended consequences for patients and physicians. In addition to addressing issues regarding fair market value, group practice concerns, profit sharing and electronic security, provisions in the revised law address concerns regarding in-network patient referrals.

Correcting issues in the original law regarding network referrals has significant impact on physicians working in some referral- and hospital-based employment arrangements. The law requires significant contractual support to avoid violation of Stark.

Non-monetary referral arrangements, such as paid travel or fee waivers, can be considered Stark violations. In addition, payments to a group practice that then flow to individual physicians may also violate the law.

Despite revisions in the law, it’s important to note that Stark is a “strict liability statute.” That means that proof of specific intent to violate the law is not required. Violation of Stark can include fines and/or exclusion from participation in federal health-care programs.

The Stark law is longstanding and thus has had many revisions and changes, including the latest updates. It behooves a physician to have a qualified health-care attorney review any nonmonetized referral schemes, accountable care arrangements, lease agreements or computer-related service agreements to avoid running afoul of the Stark laws.

REFERENCES


COMPENDIUM

Complement pathway in GA

(Continued from page 33)


6.2 Clinical Studies Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in one clinical trial cannot be directly compared with rates in other clinical trials. The data below reflect exposure to 0.5 mg LUCENTIS in 440 patients with neovascular AMD treated in 10 placebo-controlled clinical trials with LUCENTIS followed by ranibizumab injection FUV (5.1) in the full prescribing information.

The data reflect adverse reactions observed in 533 patients treated with 0.5 mg LUCENTIS and 250 patients treated with 0.3 mg LUCENTIS. The ATE rate was 4.2% (11 of 260) with 0.5 mg LUCENTIS and 2.4% (6 of 250) with 0.3 mg LUCENTIS. Based on these data, the ATE rate at 2 years was 7.2% (18 of 250) with 0.5 mg LUCENTIS and 4.8% (12 of 250) with 0.3 mg LUCENTIS. Although there was a low rate of arterial thromboembolic events (ATEs) observed in some studies.

6.3 Immunogenicity

As with other anti-VEGF agents, there is the potential for an immune response in patients treated with LUCENTIS. The immunogenicity data reflect the percentage of patients whose test results were considered positive for antibodies to ranibizumab in immunosuppressed and non-immunosuppressed patients.

The ATE rate at 2 years was 7.2% (18 of 250) across treatment groups. After monthly dosing with LUCENTIS for 6 to 24 months in patients treated with ranibizumab, antibodies to ranibizumab were detected in approximately 15% of patients.

5.2 Increases in Intraocular Pressure

No increases in intraocular pressure have been observed in patients who have been treated with LUCENTIS. Increases in intraocular pressure have been observed in healthy volunteers treated with VEGF inhibitors. The increases in intraocular pressure are similar to those observed in healthy volunteers treated with VEGF inhibitors.

5.3 Thromboembolic Events

Although there was a low rate of arterial thromboembolic events (ATEs) observed in the LUCENTIS clinical trials, there is a potential risk of ATEs following intravitreal use of VEGF inhibitors. ATEs are defined as nonfatal stroke, nonfatal myocardial infarction, or vascular death (including deaths of unclear cause).

5.4 Fetal Overgrowth

In a preclinical study using Syrian hamster embryos (5.4.1), LUCENTIS was administered to pregnant hamsters on days 6 through 14 of gestation. The results of the study showed no evidence of fetal overgrowth in hamsters exposed to rats or mice treated with 0.5 mg LUCENTIS compared to control. Based on the results of preclinical studies, the potential for fetal overgrowth in humans is unknown. LUCENTIS should be given to pregnant women only if clearly needed.

5.5 Ocular Reactions in the DME and DR, AMD, and RVO Studies

No unexpected adverse reactions were observed in any of the trials. The development and distribution of the lesions are similar to those observed in healthy volunteers treated with VEGF inhibitors.

5.6 Headache

The incidence of headache was similar in patients treated with LUCENTIS and control. The development and distribution of the lesions are similar to those observed in healthy volunteers treated with VEGF inhibitors.

5.7 Hypersensitivity

Adverse events associated with hypersensitivity reactions in clinical studies are reported to the FDA MedWatch Program. Information on patients with hypersensitivity reactions to LUCENTIS should be reported to the FDA MedWatch Program at 1-800-FDA-1088 or www.fda.gov/medwatch. Information on patients with hypersensitivity reactions to ranibizumab should be reported to the FDA MedWatch Program at 1-800-FDA-1088 or www.fda.gov/medwatch.

6.1 Injection Procedure

Sensations related to the injection procedure have occurred in ~ 0.5% of intravitreal injections, including endophthalmitis (see Warnings and Precautions 5.3). Hemorrhagic retinal detachment, and intraretinal traumatic cataract.

5 WARNINGS AND PRECAUTIONS

5.1 Endophthalmitis and Retinal Detachments

Investigational and marketed products that have been associated with endophthalmitis and retinal detachments. Proper aseptic injection techniques should always be used when administering LUCENTIS. In clinical trials, 0.5 mg LUCENTIS was administered to patients who had been monitored following the injection to permit early treatment should any infection occur (see Dosage and Administration [7.7.5] in the full prescribing information and Patient Counseling Information (17)].

5.2 Increases in Intraocular Pressure

Intraocular pressure increases should be monitored in patients treated with 0.5 mg LUCENTIS. No local increase in pressure has been observed in patients treated with LUCENTIS. Increases in intraocular pressure have been observed in healthy volunteers treated with VEGF inhibitors. The increases in intraocular pressure are similar to those observed in healthy volunteers treated with VEGF inhibitors.

5.3 Thromboembolic Events

Although there was a low rate of arterial thromboembolic events (ATEs) observed in the LUCENTIS clinical trials, there is a potential risk of ATEs following intravitreal use of VEGF inhibitors. ATEs are defined as nonfatal stroke, nonfatal myocardial infarction, or vascular death (including deaths of unclear cause).

5.4 Fetal Overgrowth

In a preclinical study using Syrian hamster embryos (5.4.1), LUCENTIS was administered to pregnant hamsters on days 6 through 14 of gestation. The results of the study showed no evidence of fetal overgrowth in hamsters exposed to rats or mice treated with 0.5 mg LUCENTIS compared to control. Based on the results of preclinical studies, the potential for fetal overgrowth in humans is unknown. LUCENTIS should be given to pregnant women only if clearly needed.

5.5 Ocular Reactions in the DME and DR, AMD, and RVO Studies

No unexpected adverse reactions were observed in any of the trials. The development and distribution of the lesions are similar to those observed in healthy volunteers treated with VEGF inhibitors.

5.6 Headache

The incidence of headache was similar in patients treated with LUCENTIS and control. The development and distribution of the lesions are similar to those observed in healthy volunteers treated with VEGF inhibitors.

5.7 Hypersensitivity

Adverse events associated with hypersensitivity reactions in clinical studies are reported to the FDA MedWatch Program. Information on patients with hypersensitivity reactions to LUCENTIS should be reported to the FDA MedWatch Program at 1-800-FDA-1088 or www.fda.gov/medwatch. Information on patients with hypersensitivity reactions to ranibizumab should be reported to the FDA MedWatch Program at 1-800-FDA-1088 or www.fda.gov/medwatch.

6.1 Injection Procedure

Sensations related to the injection procedure have occurred in ~ 0.5% of intravitreal injections, including endophthalmitis (see Warnings and Precautions 5.3). Hemorrhagic retinal detachment, and intraretinal traumatic cataract.
INDICATIONS
LUCENTIS® (ranibizumab injection) is indicated for the treatment of patients with:
• Neovascular (wet) age-related macular degeneration (wAMD)
• Macular edema following retinal vein occlusion (RVO)
• Diabetic macular edema (DME)
• Diabetic retinopathy (DR)
• Myopic choroidal neovascularization (mCNV)

IMPORTANT SAFETY INFORMATION
• LUCENTIS is contraindicated in patients with ocular or periocular infections or known hypersensitivity to ranibizumab or any of the excipients in LUCENTIS. Hypersensitivity reactions may manifest as severe intraocular inflammation
• Intravitreal injections, including those with LUCENTIS, have been associated with endophthalmitis, retinal detachment, and iatrogenic traumatic cataract
• Increases in intraocular pressure (IOP) have been noted both pre-injection and post-injection with LUCENTIS
• Although there was a low rate of arterial thromboembolic events (ATEs) observed in the LUCENTIS clinical trials, there is a potential risk of ATEs following intravitreal use of VEGF inhibitors. ATEs are defined as nonfatal stroke, nonfatal myocardial infarction, or vascular death (including deaths of unknown cause)
• Fatal events occurred more frequently in patients with DME and DR at baseline treated monthly with LUCENTIS compared with control. Although the rate of fatal events was low and included causes of death typical of patients with advanced diabetic complications, a potential relationship between these events and intravitreal use of VEGF inhibitors cannot be excluded
• In the LUCENTIS Phase III clinical trials, the most common ocular side effects included conjunctival hemorrhage, eye pain, vitreous floaters, and increased intraocular pressure. The most common non-ocular side effects included nasopharyngitis, anemia, nausea, and cough

Please see Brief Summary of LUCENTIS full Prescribing Information on following page.
You may report side effects to the FDA at (800) FDA-1088 or www.fda.gov/medwatch. You may also report side effects to Genentech at (888) 835-2555.

Randomized, double-masked clinical trials conducted for the 5 LUCENTIS indications included the following: wAMD; MARINA, ANCHOR, PIER, HARBOR; DR and DME: RISE, RIDE; mCNV: RADIANCE; RVO; BRAVO, CRUISE.

REFERENCES:

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