A PUBLICATION BY REVIEW of OPHTHALMOLOGY

RETINA SPECIALIST

VOL. 7, NO. 1 • JANUARY/FEBRUARY 2021

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

Also Inside

YOUR PATIENTS WITH DME ARE READY FOR A CHANGE

The power of EYLEA improved and sustained outcomes in the largest phase 3 anti-VEGF clinical trials completed to date in DME (N=862), with improved visual acuity at 52 and 100 weeks.[1]

IMPORTANT SAFETY INFORMATION AND INDICATIONS

CONTRAINDICATIONS

- EYLEA is contraindicated in patients with ocular or periocular infections, active intraocular inflammation, or known hypersensitivity to aflibercept or to any of the excipients in EYLEA.

WARNINGS AND PRECAUTIONS

- Intravitreal injections, including those with EYLEA, have been associated with endophthalmitis and retinal detachments. Proper aseptic injection technique must always be used when administering EYLEA. Patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment without delay and should be managed appropriately. Intraocular inflammation has been reported with the use of EYLEA.
- Acute increases in intraocular pressure have been seen with 60 minutes of intravitreal injection, including with EYLEA. Sustained increases in intraocular pressure have also been reported after repeated intravitreal dosing with VEGF inhibitors. Intraocular pressure and the perfusion of the optic nerve head should be monitored and managed appropriately.
- 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 IMPROVED AND SUSTAINED VISION GAINS THROUGH 52 AND 100 WEEKS IN DME[1-3]

	EYLEA 2 MG EVERY 4 WEEKS[§]	EYLEA 2 MG EVERY 8 WEEKS[‖]	CONTROL
VISTA	(n=154)	(n=151)	(n=154)
MEAN CHANGE IN BCVA (52 WEEKS,* 100 WEEKS[†])	+12.5, +11.5 LETTERS	+10.7, +11.1 LETTERS	+0.2, +0.9 LETTERS
PROPORTION GAINED ≥15 LETTERS (52 WEEKS,[‡] 100 WEEKS[†])	41.6%, 38.3%	31.1%, 33.1%	7.8%, 13.0%
VIVID	(n=136)	(n=135)	(n=132)
MEAN CHANGE IN BCVA (52 WEEKS,* 100 WEEKS[†])	+10.5, +11.4 LETTERS	+10.7, +9.4 LETTERS	+1.2, +0.7 LETTERS
PROPORTION GAINED ≥15 LETTERS (52 WEEKS,[‡] 100 WEEKS[†])	32.4%, 38.2%	33.3%, 31.1%	9.1%, 12.1%

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® (aflibercept) 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: 1. EYLEA® (aflibercept) Injection full U.S. Prescribing Information. Regeneron Pharmaceuticals, Inc. August 2019. **2.** Korobelnik JF, Do DV, Schmidt-Erfurth U, et al. Intravitreal aflibercept for diabetic macular edema. *Ophthalmology*. 2014;121(11):2247-2254. doi:10.1016/j.ophtha.2014.05.006 **3.** Brown DM, Schmidt-Erfurth U, Do DV, et al. Intravitreal aflibercept for diabetic macular edema: 100-week results from the VISTA and VIVID studies. *Ophthalmology*. 2015;122(10):2044-2052. doi:10.1016/j.ophtha. 2015.06.017

EYLEA®
(aflibercept) Injection
For Intravitreal Injection

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

08/2020
EYL.20.07.0057

EYLEA®
(aflibercept) Injection
For Intravitreal Injection

BRIEF SUMMARY—Please see the EYLEA full Prescribing Information available on HCP.EYLEA.US for additional product information.

1 INDICATIONS AND USAGE
EYLEA is a vascular endothelial growth factor (VEGF) inhibitor indicated for the treatment of:

Neovascular (Wet) Age-Related Macular Degeneration (AMD); Macular Edema Following Retinal Vein Occlusion (RVO); Diabetic Macular Edema (DME); Diabetic Retinopathy (DR).

4 CONTRAINDICATIONS

4.1 Ocular or Periocular Infections
EYLEA is contraindicated in patients with ocular or periocular infections.

4.2 Active Intraocular Inflammation
EYLEA is contraindicated in patients with active intraocular inflammation.

4.3 Hypersensitivity
EYLEA is contraindicated in patients with known hypersensitivity to aflibercept or any of the excipients in EYLEA. Hypersensitivity reactions may manifest as rash, pruritus, urticaria, severe anaphylactic/anaphylactoid reactions, or severe intraocular inflammation.

5 WARNINGS AND PRECAUTIONS

5.1 Endophthalmitis and Retinal Detachments.
Intravitreal injections, including those with EYLEA, have been associated with endophthalmitis and retinal detachments [*see Adverse Reactions (6.1)*]. Proper aseptic injection technique must always be used when administering EYLEA. Patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment without delay and should be managed appropriately [*see Patient Counseling Information (17)*].

5.2 Increase in Intraocular Pressure.
Acute increases in intraocular pressure have been seen within 60 minutes of intravitreal injection, including with EYLEA [*see Adverse Reactions (6.1)*]. Sustained increases in intraocular pressure have also been reported after repeated intravitreal dosing with vascular endothelial growth factor (VEGF) inhibitors. Intraocular pressure and the perfusion of the optic nerve head should be monitored and managed appropriately.

5.3 Thromboembolic Events.
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.

6 ADVERSE REACTIONS
The following potentially serious adverse reactions are described elsewhere in the labeling:
- Hypersensitivity [*see Contraindications (4.3)*]
- Endophthalmitis and retinal detachments [*see Warnings and Precautions (5.1)*]
- Increase in intraocular pressure [*see Warnings and Precautions (5.2)*]
- Thromboembolic events [*see Warnings and Precautions (5.3)*]

6.1 Clinical Trials Experience.
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in other clinical trials of the same or another drug and may not reflect the rates observed in practice.
A total of 2980 patients treated with EYLEA constituted the safety population in eight phase 3 studies. Among those, 2379 patients were treated with the recommended dose of 2 mg. 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.

Neovascular (Wet) Age-Related Macular Degeneration (AMD). The data described below reflect exposure to EYLEA in 1824 patients with wet AMD, including 1223 patients treated with the 2-mg dose, in 2 double-masked, controlled clinical studies (VIEW1 and VIEW2) for 24 months (with active control in year 1).
Safety data observed in the EYLEA group in a 52-week, double-masked, Phase 2 study were consistent with these results.

Table 1: Most Common Adverse Reactions (≥1%) in Wet AMD Studies

	Baseline to Week 52		Baseline to Week 96	
Adverse Reactions	EYLEA (N=1824)	Active Control (ranibizumab) (N=595)	EYLEA (N=1824)	Control (ranibizumab) (N=595)
Conjunctival hemorrhage	25%	28%	27%	30%
Eye pain	9%	9%	10%	10%
Cataract	7%	7%	13%	10%
Vitreous detachment	6%	6%	8%	8%
Vitreous floaters	6%	7%	8%	10%
Intraocular pressure increased	5%	7%	7%	11%
Ocular hyperemia	4%	8%	5%	10%
Corneal epithelium defect	4%	5%	5%	6%
Detachment of the retinal pigment epithelium	3%	3%	5%	5%
Injection site pain	3%	3%	3%	4%
Foreign body sensation in eyes	3%	4%	4%	4%
Lacrimation increased	3%	1%	4%	2%
Vision blurred	2%	2%	4%	3%
Intraocular inflammation	2%	3%	3%	4%
Retinal pigment epithelium tear	2%	1%	2%	2%
Injection site hemorrhage	1%	2%	2%	2%
Eyelid edema	1%	2%	2%	3%
Corneal edema	1%	1%	1%	1%
Retinal detachment	<1%	<1%	1%	1%

Less common serious adverse reactions reported in <1% of the patients treated with EYLEA were hypersensitivity, retinal tear, and endophthalmitis.

Macular Edema Following Retinal Vein Occlusion (RVO). The data described below reflect 6 months exposure to EYLEA with a monthly 2 mg dose in 218 patients following CRVO in 2 clinical studies (COPERNICUS and GALILEO) and 91 patients following BRVO in one clinical study (VIBRANT).

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

	CRVO		BRVO	
Adverse Reactions	EYLEA (N=218)	Control (N=142)	EYLEA (N=91)	Control (N=92)
Eye pain	13%	5%	4%	5%
Conjunctival hemorrhage	12%	11%	20%	4%
Intraocular pressure increased	8%	6%	2%	0%
Corneal epithelium defect	5%	4%	2%	0%
Vitreous floaters	5%	1%	1%	0%
Ocular hyperemia	5%	3%	2%	2%
Foreign body sensation in eyes	3%	5%	3%	0%
Vitreous detachment	3%	4%	2%	0%
Lacrimation increased	3%	4%	3%	0%
Injection site pain	3%	1%	1%	0%
Vision blurred	1%	<1%	1%	1%
Intraocular inflammation	1%	1%	0%	0%
Cataract	<1%	1%	5%	0%
Eyelid edema	<1%	1%	1%	0%

Less common adverse reactions reported in <1% of the patients treated with EYLEA in the CRVO studies were corneal edema, retinal tear, hypersensitivity, and endophthalmitis.

Diabetic Macular Edema (DME) and Diabetic Retinopathy (DR). The data described below reflect exposure to EYLEA in 578 patients with DME treated with the 2-mg dose in 2 double-masked, controlled clinical studies (VIVID and VISTA) from baseline to week 52 and from baseline to week 100.

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

	Baseline to Week 52		Baseline to Week 100	
Adverse Reactions	EYLEA (N=578)	Control (N=287)	EYLEA (N=578)	Control (N=287)
Conjunctival hemorrhage	28%	17%	31%	21%
Eye pain	9%	6%	11%	9%
Cataract	8%	9%	19%	17%
Vitreous floaters	6%	3%	8%	6%
Corneal epithelium defect	5%	3%	7%	5%
Intraocular pressure increased	5%	3%	9%	5%
Ocular hyperemia	5%	6%	5%	6%
Vitreous detachment	3%	3%	8%	6%
Foreign body sensation in eyes	3%	3%	3%	3%
Lacrimation increased	3%	2%	4%	2%
Vision blurred	2%	2%	3%	4%
Intraocular inflammation	2%	<1%	3%	1%
Injection site pain	2%	<1%	2%	<1%
Eyelid edema	<1%	1%	2%	1%

Less common adverse reactions reported in <1% of the patients treated with EYLEA were hypersensitivity, retinal detachment, retinal tear, corneal edema, and injection site hemorrhage.
Safety data observed in 269 patients with nonproliferative diabetic retinopathy (NPDR) through week 52 in the PANORAMA trial were consistent with those seen in the phase 3 VIVID and VISTA trials (see Table 3 above).

6.2 Immunogenicity.
As with all therapeutic proteins, there is a potential for an immune response in patients treated with EYLEA. The immunogenicity of EYLEA was evaluated in serum samples. The immunogenicity data reflect the percentage of patients whose test results were considered positive for antibodies to EYLEA in immunoassays. The detection of an immune response is highly dependent on the sensitivity and specificity of the assays used, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to EYLEA with the incidence of antibodies to other products may be misleading.
In the wet AMD, RVO, and DME studies, the pre-treatment incidence of immunoreactivity to EYLEA was approximately 1% to 3% across treatment groups. After dosing with EYLEA for 24-100 weeks, antibodies to EYLEA were detected in a similar percentage range of patients. There were no differences in efficacy or safety between patients with or without immunoreactivity.

8 USE IN SPECIFIC POPULATIONS.

8.1 Pregnancy
Risk Summary
Adequate and well-controlled studies with EYLEA have not been conducted in pregnant women. Aflibercept produced adverse embryofetal effects in rabbits, including external, visceral, and skeletal malformations. A fetal No Observed Adverse Effect Level (NOAEL) was not identified. At the lowest dose shown to produce adverse embryofetal effects, systemic exposures (based on AUC for free aflibercept) were approximately 6 times higher than AUC values observed in humans after a single intravitreal treatment at the recommended clinical dose [*see Animal Data*].
Animal reproduction studies are not always predictive of human response, and it is not known whether EYLEA can cause fetal harm when administered to a pregnant woman. Based on the anti-VEGF mechanism of action for aflibercept, treatment with EYLEA may pose a risk to human embryofetal development. EYLEA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.
All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. The background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data
Animal Data
In two embryofetal development studies, aflibercept produced adverse embryofetal effects when administered every three days during organogenesis to pregnant rabbits at intravenous doses ≥3 mg per kg, or every six days during organogenesis at subcutaneous doses ≥0.1 mg per kg.
Adverse embryofetal effects included increased incidences of postimplantation loss and fetal malformations, including anasarca, umbilical hernia, diaphragmatic hernia, gastroschisis, cleft palate, ectrodactyly, intestinal atresia, spina bifida, encephalomeningocele, heart and major vessel defects, and skeletal malformations (fused vertebrae, sternebrae, and ribs; supernumerary vertebral arches and ribs; and incomplete ossification). The maternal No Observed Adverse Effect Level (NOAEL) in these studies was 3 mg per kg. Aflibercept produced fetal malformations at all doses assessed in rabbits and the fetal NOAEL was not identified. At the lowest dose shown to produce adverse embryofetal effects in rabbits (0.1 mg per kg), systemic exposure (AUC) of free aflibercept was approximately 6 times higher than systemic exposure (AUC) observed in humans after a single intravitreal dose of 2 mg.

8.2 Lactation
Risk Summary
There is no information regarding the presence of aflibercept in human milk, the effects of the drug on the breastfed infant, or the effects of the drug on milk production/excretion. Because many drugs are excreted in human milk, and because the potential for absorption and harm to infant growth and development exists, EYLEA is not recommended during breastfeeding.
The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for EYLEA and any potential adverse effects on the breastfed child from EYLEA.

8.3 Females and Males of Reproductive Potential
Contraception
Females of reproductive potential are advised to use effective contraception prior to the initial dose, during treatment, and for at least 3 months after the last intravitreal injection of EYLEA.

Infertility
There are no data regarding the effects of EYLEA on human fertility. Aflibercept adversely affected female and male reproductive systems in cynomolgus monkeys when administered by intravenous injection at a dose approximately 1500 times higher than the systemic level observed humans with an intravitreal dose of 2 mg. A No Observed Adverse Effect Level (NOAEL) was not identified. These findings were reversible within 20 weeks after cessation of treatment.

8.4 Pediatric Use.
The safety and effectiveness of EYLEA in pediatric patients have not been established.

8.5 Geriatric Use.
In the clinical studies, approximately 76% (2049/2701) of patients randomized to treatment with EYLEA were ≥65 years of age and approximately 46% (1250/2701) were ≥75 years of age. No significant differences in efficacy or safety were seen with increasing age in these studies.

17 PATIENT COUNSELING INFORMATION
In the days following EYLEA administration, patients are at risk of developing endophthalmitis or retinal detachment. If the eye becomes red, sensitive to light, painful, or develops a change in vision, advise patients to seek immediate care from an ophthalmologist [*see Warnings and Precautions (5.1)*].
Patients may experience temporary visual disturbances after an intravitreal injection with EYLEA and the associated eye examinations [*see Adverse Reactions (6)*]. Advise patients not to drive or use machinery until visual function has recovered sufficiently.

REGENERON

Manufactured by:
Regeneron Pharmaceuticals, Inc.
777 Old Saw Mill River Road
Tarrytown, NY 10591

Issue Date: 08/2019
Initial U.S. Approval: 2011

Based on the August 2019 EYLEA® (aflibercept) Injection full Prescribing Information.

EYL.19.07.0306

RETINA
SPECIALIST

19 Campus Blvd., Suite 101
Newtown Square, PA 19073
Telephone (610) 492-1000
Fax (610) 492-1039

Editorial inquiries (610) 492-1000
Advertising inquiries (610) 492-1011
E-mail retinaspecialist@jobson.com

Jobson Medical Information

EDITORIAL

By Charles C. Wykoff, MD, PhD

More balance

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.

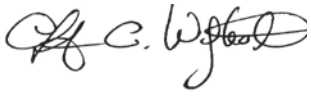
From a patient perspective, balance away from an environment of isolation and anxiety is needed. While we as physicians have become accustomed to a masked-culture in close quarters during clinic, many of our patients still spend most of their time alone and in fear, commonly not openly discussing it,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

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.

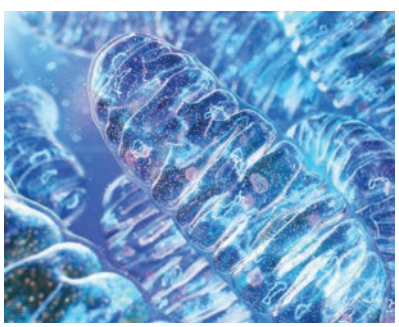
A second theme of the holiday cards was adopting a new pet. Most were dogs. On a whim last spring, we brought home two Duclair ducks. While not as cuddly or playful as your typical Goldendoodle or King Charles cavalier, the ducks have been quite entertaining and recently started producing delicious eggs.

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. RS

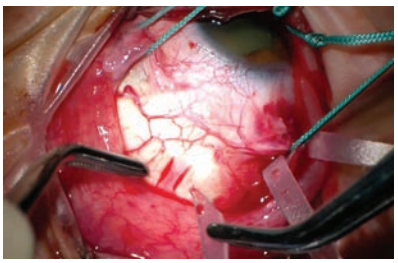


A PUBLICATION BY REVIEW of OPHTHALMOLOGY
RETINA SPECIALIST
JANUARY/FEBRUARY 2021 • VOL. 7, NO. 1

FEATURES



DEPARTMENTS



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.

Michael F. Chiang, MD, shown at the Casey Eye Institute, is two months into his term as director of the National Eye Institute. (*Courtesy Oregon Health and Science University*)

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)

IN BRIEF

The **Association for Research in Vision and Ophthalmology** granted **Yohei Tomita, MD, PhD**, the 2021 **Bert M. Glaser, MD, Award for Innovative Research in Retina**, which recognizes an early career investigator who has made a novel discovery that impacted the understanding and/or treatment of a retinal disease or condition. Dr. Tomita, a research fellow at Boston Children's Hospital and Harvard Medical School, is recognized with this award for his retinal translational research, with a focus on diabetic retinopathy and age-related macular degeneration.

Notal Vision has initiated the first U.S.-based study using its investigational home-based optical coherence tomography platform. The study will evaluate the ability of people with neovascular AMD to perform sequential daily self-imaging of their eyes with the self-operated Notal Home OCT device.

The first patients have been enrolled in the Phase I/IIa OASIS clinical trial of **CLS-AX** (axitinib injectable suspension) for nAMD. CLS-AX is a proprietary suspension of axitinib for suprachoroidal injection. **Clearside Biomedical** is sponsoring the trial.

Adverum Biotechnologies has completed patient enrollment in the INFINITY Phase II trial to evaluate a single intravitreal injection of **ADVM-022** for diabetic macular edema.

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.[1]

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.[2]

(Continued on page 10)

AMD Standard of Care is Not Enough

IRIS REGISTRY

20/83 VA

Average of first and second eyes at wet AMD diagnosis according to IRIS Registry real-world data[1]

HOME STUDY

≥20/40 VA

Average at wet AMD diagnosis with ForeseeHome[2]

Detect Early. Treat Early.

ForeseeHome is a **remote monitoring** program for at-risk dry AMD patients that helps **detect wet AMD earlier** and alerts you of changes.

ForeseeHOME™
AMD Monitoring Program

Remote patient monitoring supports better outcomes and stronger patient relationships

- Allows for earlier treatment initiation
- Helps provide better visual outcomes
- Safety net for wet AMD patients' fellow eyes
- Solidifies long-term relationships with your patients

Our Diagnostic Clinic is the Key to Successful Remote Monitoring

- Engagement & Education
- Benefits Verification & Authorization
- Continuous Monitoring

NOTAL VISION™
Diagnostic Clinic

- Practice Workflow Implementation
- Remote Patient Management
- Vision Alert Management

References: 1. Rao P et al. *Ophthalmology*. 2018;125(4):522-528. **2.** Domalpally A, Clemons TE, Bressler SB, et al. *Ophthalmol Retina*. 2019;3(4):326-335.

See website for FDA Indication for Use.

SM-000.00

GET STARTED TODAY

1-855-600-3112

Mon-Fri, 8 AM to 6 PM EST

www.foreseehome.com/hcp

A call to revise AAO hydroxychoroquine 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.[3]

Pre-COVID-19, around 30,000 new prescriptions for HCQ or chloroquine were written monthly, according to *Morbidity and Mortality Weekly Report*,[4] 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," says Dr. Browning. "Second would be our increasingly sensitive spectral-domain and swept-source optical coherence tomography."

Other tools are fundus autofluorescence, microperimetry 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 Yogokawa, 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

1. Browning DJ, Yokogawa N, Greenberg PB, Perlman E. Rethinking the hydroxychloroquine dosing and retinopathy screening guidelines. Am J Ophthalmol. 2020;219:101-106.
2. Braslow RA, Shiloach M, Macsai MS. Adherence to hydroxychloroquine dosing guidelines by rheumatologists: An electronic medical record-based study in an integrated health care system. Ophthalmology. 2017;124:604-608.
3. Myasoedova E, Crowson CS, Kremers HM, Therneau TM, Gabriel SE. Is the incidence of rheumatoid arthritis rising? Results from Olmsted County, Minnesota, 1955-2007. Arthritis Rheum. 2010;62:1576-1582.
4. Bull-Otterson L, Gray EB, Budnitz DS, et al. Hydroxychloroquine and chloroquine prescribing patterns by provider specialty following initial reports of potential benefit for COVID-19 treatment—United States, January–June 2020. Morbid Mortal Weekly Rep. 2020;69:1210-1215.

RETINA SPECIALIST

BUSINESS OFFICES
19 CAMPUS BOULEVARD, SUITE 101
NEWTOWN SQUARE, PA 19073
SUBSCRIPTION INQUIRIES (877) 529-1746
(USA ONLY); OUTSIDE USA, CALL (847) 763-9630

BUSINESS STAFF
PUBLISHER
MICHAEL HOSTER
(610) 492-1028 MHOSTER@JOBSON.COM

EXECUTIVE DIRECTOR
JAMES HENNE
(610) 492-1017 JHENNE@JOBSON.COM

REGIONAL SALES MANAGER
MICHELE BARRETT
(610) 492-1014 MBARRETT@JOBSON.COM

REGIONAL SALES MANAGER
JONATHAN DARDINE
(610) 492-1030 JDARDINE@JOBSON.COM

CLASSIFIED ADVERTISING
(888)-498-1460

PRODUCTION MANAGER
FARRAH APONTE
(212) 274-7057 FAPONTE@JOBSON.COM

SUBSCRIPTIONS
US ONE YEAR: $63.00
CANADIAN ONE YEAR: $99.00
FOREIGN ONE YEAR: $158.00
SUBSCRIPTIONS E-MAIL:
RETINASPECIALIST@CAMBEYWEST.COM

CIRCULATION
RETINA SPECIALIST
PO BOX 397
CONGERS, NY 10920-0397
CIRCULATION CUSTOMER SERVICE
PHONE: (877) 529-1746 (U.S)
OR (845) 267-3065 (OUTSIDE U.S)

SENIOR CIRCULATION MANAGER
JARED SONNERS
(973) 206-8091 jsonners@mdedge.com

CEO, INFORMATION GROUP SERVICES
MARC FERRARA

SENIOR VICE PRESIDENT, OPERATIONS
JEFF LEVITZ

VICE PRESIDENT, HUMAN RESOURCES
TAMMY GARCIA

VICE PRESIDENT, CREATIVE SERVICES & PRODUCTION
MONICA TETTAMANZI

SENIOR CORPORATE PRODUCTION DIRECTOR
JOHN ANTHONY CAGGIANO

VICE PRESIDENT, CIRCULATION
JARED SONNERS

Jobson Medical Information LLC,
395 Hudson Street, 3rd Floor, New York, NY 10014

WE'RE SEEING AMAZING RESULTS. AND SO ARE THEY.

At the Foundation Fighting Blindness our mission is everybody's vision. Our work shines a light on the darkness of inherited retinal diseases (IRDs).

We're the world's leading organization searching for treatments and cures. We need your help to fuel the discovery of innovations that will illuminate the future for so many. We have robust disease information, a national network of local chapters and support groups, local educational events, and our My Retina Tracker® Registry to help keep your patients connected with clinical and research advancements.

Help accelerate our mission by donating at ECPs4Cures.org.

FOUNDATION FIGHTING BLINDNESS

FightingBlindness.org

FAF, OCT demystify blurred vision cause

How multimodal imaging helped to elucidate an insidious nutritional deficiency.

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

Rebecca Russ Soares, MD, MPH

Jason Hsu, MD

Bios

Dr. Hsu is with Mid Atlantic Retina/Retina Service, Wills Eye Hospital, Philadelphia, where Dr. Soares is a fellow.

DISCLOSURES: Drs. Hsu and Soares have no relevant financial relationships to disclose.

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 excrescences localizing to the spots seen on the fundus examination.

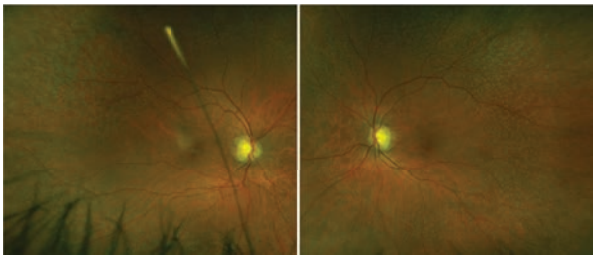


Figure 1. Fundus examination revealed innumerable yellow-white punctate dots throughout the posterior pole and mid-periphery in both eyes.

Serum laboratory studies were notable for normal chemistry panel and complete blood count. 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.[1] 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."[2]

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.[3–5] Other syndromes and surgical interventions that interfere with vitamin A absorption in the duodenum have also been associated with night blindness.[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.[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.[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.[11] Such accumulation is thought to "block" autofluorescence, yielding the hypoautofluorescence of these spots reported.[11] OCT findings further reveal the hyperreflective deposits under the ellipsoid zone band, again possibly shed photoreceptors.[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.[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.[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,[9] while others find a marked improvement.[10] Interestingly, OCT may also show reduced central sub-foveal thickness that resolves with treatment.[9] RS

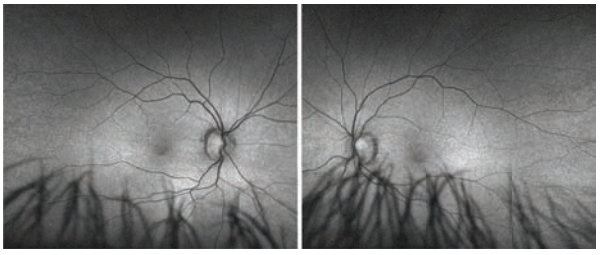


Figure 2. Fundus autofluorescence revealed bilateral stippled hyperautofluorescence correlating to the yellow-white dots on fundus examination.

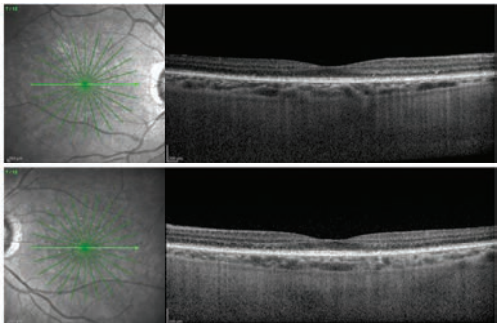


Figure 3. Optical coherence tomography revealed jagged irregularity of the ellipsoid zone with underlying hyperreflective deposits.

REFERENCES

1. Perusek L, Maeda T. Vitamin A derivatives as treatment options for retinal degenerative diseases. Nutrients 2013;5:2646–2666.
2. World Health Organization. Global prevalence of Vitamin A Deficiency. Micronutrient Deficiency Information System Working Paper No. 2. 1995. Available at: https://www.who.int/nutrition/publications/micronutrients/vitamin_a_deficiency/WHO_NUT_95.3/en/ Accessed November 8, 2020.
3. Slater GH, Ren CJ, Siegel N, et al. Serum fat-soluble vitamin deficiency and abnormal calcium metabolism after malabsorptive bariatric surgery. J Gastrointest Surg Off J Soc Surg Aliment Tract 2004;8:48–55; discussion 54-55.
4. Angrisani L, Santonicola A, Iovino P, et al. Bariatric Surgery Worldwide 2013. Obes Surg 2015;25:1822–1832.
5. Lee WB, Hamilton SM, Harris JP, Schwab IR. Ocular complications of hypovitaminosis a after bariatric surgery. Ophthalmology 2005;112:1031–1034.
6. Cheshire J, Kolli S. Vitamin A deficiency due to chronic malabsorption: An ophthalmic manifestation of a systemic condition. BMJ Case Rep 2017;2017.
7. Parafita-Fernández A, Escalona-Fermín MM, Sampil M, et al. Acquired night blindness due to bad eating patterns. Eur J Clin Nutr 2015;69:752–754.
8. Spits Y, De Laey J-J, Leroy BP. Rapid recovery of night blindness due to obesity surgery after vitamin A repletion therapy. Br J Ophthalmol 2004;88:583–585.
9. Saenz-de-Viteri M, Sádaba LM. Optical coherence tomography assessment before and after vitamin supplementation in a patient with vitamin A deficiency. Medicine (Baltimore). 2016;95:e2680.
10. Apushkin MA, Fishman GA. Improvement in visual function and fundus findings for a patient with vitamin A-deficient retinopathy. Retina. 2005;25:650–652.
11. Aleman TS, Garrity ST, Brucker AJ. Retinal structure in vitamin A deficiency as explored with multimodal imaging. Doc Ophthalmol. 2013;127:239–243.
12. Aasheim ET, Björkman S, Søvik TT, et al. Vitamin status after bariatric surgery: A randomized study of gastric bypass and duodenal switch. Am J Clin Nutr. 2009;90:15–22.
13. World Health Organization. Vitamin A supplements : A guide to their use in the treatment of vitamin A deficiency and xerophthalmia. 1997. Available at: https://apps.who.int/iris/handle/10665/41947 Accessed November 8, 2020.

Department Editor *Akshay S. Thomas, MD, MS*

Noninfectious uveitis in pregnancy

Knowing the options available for safely treating pregnant patients will empower retina specialists to confidently care for them.

By Rene Y. Choi, MD, PhD

Rene Y. Choi, MD, PhD

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.[1–5] 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.[4] More than 50 percent of this cohort experienced a uveitic flare within six months of delivery.

An Australian study reported similar results.[1] 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.[3] 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.[2] 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

Bios

Dr. Choi is an associate in vitreoretinal surgery and uveitis at Texas Retina Associates with offices in the Dallas-Fort Worth metroplex

Dr. Thomas is an associate in vitreoretinal surgery and uveitis at Tennessee Retina, with offices in central Tennessee and southern Kentucky.

DISCLOSURE: Drs. Choi and Thomas have no relevant financial relationships to disclose.

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 Pharamaceuticals). 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.[6,7] 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.[8–10]

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.[10–13]

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.[14–16]

Studies have shown the passage of TNF-inhibitors across the placenta appears to be the highest in the third trimester,[17,18]

(Continued on page 18)

Indications for medications to treat noninfectious uveitis during pregnancy

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

***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.

Pearls for scleral buckling with tunnels

These six tips can help you place the buckle more efficiently and safely.

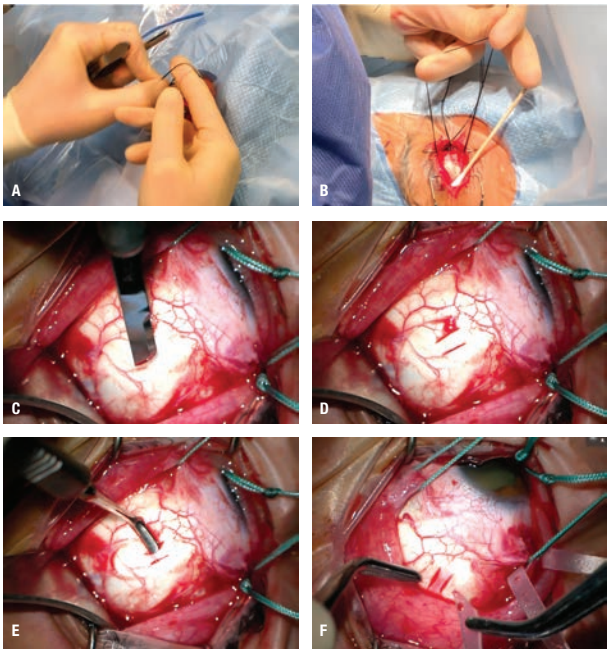
By Sarah Parker Read, MD PhD

Sarah Parker Read, MD, PhD

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.



Key steps for performing scleral buckle with tunnels: A) palm instruments when isolating muscles; B) use a cotton tip to self-detract the conjunctiva; C) use a 64 blade to make partial-thickness incisions; D) make two parallel incisions about 4 mm posterior to the muscle insertion; E) dissect the tunnel with Castroviejo scleral depressor; and F) bevel the band tip to thread through the tunnels.

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 mm ($C=2\varpi r$).[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)

View the Video

Watch as Dr. Read demonstrates pearls for scleral buckling with tunnels. Available at https://bit.ly/VideoPearl_021.

Bios

Dr. Read is a partner at Retina Consultants of Hawaii and a clinical assistant professor at University of Hawaii John A. Burns School of Medicine.

Dr. Hahn is a partner at New Jersey Retina in Teaneck.

DISCLOSURES: Dr. Read disclosed serving as a consultant to Carl Zeiss Meditec.

Dr. Hahn disclosed serving as a consultant to DORC.

"I was only seeing light flashes early on, but light FLASHES when you've not seen anything for so many years—it was wonderful"

—Keith H, retinal prosthesis recipient

WE'RE SEEING AMAZING RESULTS. AND SO ARE THEY.

At the Foundation Fighting Blindness our mission is everybody's vision. Our work shines a light on the darkness of inherited retinal diseases (IRDs).

We're the world's leading organization searching for treatments and cures. We need your help to fuel the discovery of innovations that will illuminate the future for so many. We have robust disease information, a national network of local chapters and support groups, local educational events, and our My Retina Tracker® Registry to help keep your patients connected with clinical and research advancements.

Help accelerate our mission by donating at **ECPs4Cures.org**.

FOUNDATION FIGHTING BLINDNESS

FightingBlindness.org

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, than 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. RS

REFERENCE

1. Skondra D, Westerfeld C, Vavvas DG, Modified controlled encircling scleral buckle for retinal detachment. J Vitreoretin Dis. 2017;1: 314–316.

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.[19]

Certolizumab pegol (Cimzia, UCB) is a TNF-inhibitor that has minimal to no placental transfer from mother to fetus, and has been shown to be an effective option to control intraocular inflammation.[20]

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.[21,22] Alkylating agents such as cyclophosphamide and chlorambucil are known teratogens and should be avoided during pregnancy.[23–25]

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 immunomodulatory 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. RS

REFERENCES

1. Chiam NP, Hall AJ, Stawell RJ, Busija L, Lim LL. The course of uveitis in pregnancy and postpartum. Br J Ophthalmol. 2013;97:1284-1288.
2. Chiam NP, Lim LL. Uveitis and gender: The course of uveitis in pregnancy. J Ophthalmol. 2014;2014:401915.
3. Kump LI, Cervantes-Castañeda RA, Androudi SN, Foster CS, Christen WG. Patterns of exacerbations of chronic non-infectious uveitis in pregnancy and puerperium. Ocul Immunol Inflamm. 2006;14:99-104.
4. Rabiah PK, Vitale AT. Noninfectious uveitis and pregnancy. Am J Ophthalmol. 2003;136:91-98.
5. Verhagen FH, Braakenburg AM, Kremer T, Drylewicz J, Rothova A, de Boer JH. Reduced number of relapses of human leucocyte antigen-B27-associated uveitis during pregnancy. Acta Ophthalmol. 2017;95:e798-e799.
6. Carmichael SL, Shaw GM. Maternal corticosteroid use and risk of selected congenital anomalies. Am J Med Genet. 1999;86:242-244.
7. Park-Wyllie L, Mazzotta P, Pastuszak A et al. Birth defects after maternal exposure to corticosteroids: Prospective cohort study and meta-analysis of epidemiological studies. Teratology. 2000;62:385-392.
8. Hoeltzenbein M, Elefant E, Vial T et al. Teratogenicity of mycophenolate confirmed in a prospective study of the European Network of Teratology Information Services. Am J Med Genet A. 2012;158A:588-596.
9. Perez-Aytes A, Ledo A, Boso V et al. In utero exposure to mycophenolate mofetil: A characteristic phenotype. Am J Med Genet A. 2008;146A:1-7.
10. Østensen M, Khamashta M, Lockshin M et al. Anti-inflammatory and immunosuppressive drugs and reproduction. Arthritis Res Ther. 2006;8:209.
11. Francella A, Dyan A, Bodian C, Rubin P, Chapman M, Present DH. The safety of 6-mercaptopurine for childbearing patients with inflammatory bowel disease: A retrospective cohort study. Gastroenterology. 2003;124:9-17.
12. Moskovitz DN, Bodian C, Chapman ML et al. The effect on the fetus of medications used to treat pregnant inflammatory bowel-disease patients. Am J Gastroenterol. 2004;99:656-661.
13. Polifka JE, Friedman JM. Teratogen update: Azathioprine and 6-mercaptopurine. Teratology. 2002;65:240-261.
14. Chambers CD, Johnson DL, Xu R et al. Birth outcomes in women who have taken adalimumab in pregnancy: A prospective cohort study. PLoS One. 2019;14:e0223603.
15. Roux CH, Brocq O, Breuil V, Albert C, Euller-Ziegler L. Pregnancy in rheumatology patients exposed to anti-tumour necrosis factor (TNF)-alpha therapy. Rheumatology (Oxford). 2007;46:695-698.
16. Vinet E, Pineau C, Gordon C, Clarke AE, Bernatsky S. Anti-TNF therapy and pregnancy outcomes in women with inflammatory arthritis. Expert Rev Clin Immunol. 2009;5:27-34.
17. Mahadevan U, Wolf DC, Dubinsky M et al. Placental transfer of anti-tumor necrosis factor agents in pregnant patients with inflammatory bowel disease. Clin Gastroenterol Hepatol. 2013;11:286-292.
18. Zelinkova Z, de Haar C, de Ridder L et al. High intra-uterine exposure to infliximab following maternal anti-TNF treatment during pregnancy. Aliment Pharmacol Ther. 2011;33:1053-1058.
19. O'Donnell S, O'Morain C. Review article: Use of antitumour necrosis factor therapy in inflammatory bowel disease during pregnancy and conception. Aliment Pharmacol Ther. 2008;27:885-894.
20. Prieto-Peña D, Calderón-Goercke M, Adán A et al. Efficacy and safety of certolizumab pegol in pregnant women with uveitis. Recommendations on the management with immunosuppressive and biologic therapies in uveitis during pregnancy. Clin Exp Rheumatol. Published online October 9, 2020.
21. Bar Oz B, Hackman R, Einarson T, Koren G. Pregnancy outcome after cyclosporine therapy during pregnancy: A meta-analysis. Transplantation. 2001;71:1051-1055.
22. Jain AB, Reyes J, Marcos A et al. Pregnancy after liver transplantation with tacrolimus immunosuppression: A single center's experience update at 13 years. Transplantation. 2003;76:827-832.
23. Botta JA, Hawkins HC, Weikel JH. Effects of cyclophosphamide on fertility and general reproductive performance of rats. Toxicol Appl Pharmacol. 1974;27:602-611.
24. Enns GM, Roeder E, Chan RT, Ali-Khan Catts Z, Cox VA, Golabi M. Apparent cyclophosphamide (cytoxan) embryopathy: A distinct phenotype. Am J Med Genet. 1999;86:237-241.
25. Steege JF, Caldwell DS. Renal agenesis after first trimester exposure to chlorambucil. South Med J. 1980;73:1414-1415.

A PUBLICATION BY REVIEW of Ophthalmology

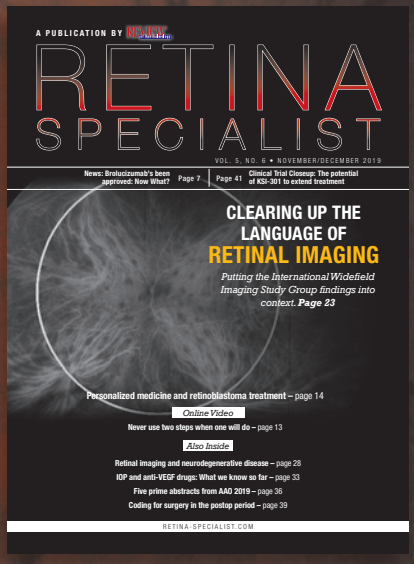
RETINA SPECIALIST

Retina Specialist focuses on the latest advances in the diagnosis, medical management and surgical treatment of diseases of the retina, along with practical, real-world advice from leading clinicians and other experts on managing the successful retina practice.

KEEP UP WITH CUTTING-EDGE SCIENCE IN RETINA.

Watch for issues in:

- JANUARY/FEBRUARY
- MARCH/APRIL
- MAY/JUNE
- JULY/AUGUST
- SEPTEMBER/OCTOBER
- NOVEMBER/DECEMBER



FOR INQUIRIES CONTACT

RETINASPECIALIST@JOBSON.COM

ADVERTISING OPPORTUNITIES

MICHAEL HOSTER • PUBLISHER • 610-492-1028 • MHOSTER@JOBSON.COM
JIM HENNE • 610-492-1017 • JHENNE@JOBSON.COM
MICHELE BARRETT • 215-519-1414 • MBARRETT@JOBSON.COM
JONATHAN DARDINE • 610-492-1030 • JDARDINE@JOBSON.COM

www.retina-specialist.com

@RetSpecMag RetinaSpecialistMag

Fourth Annual Pipeline Report

Many new entries, but no impactful exits

The list grows longer with new entries and categories and no trials resulting in approvals.

Richard Mark Kirkner
Editor

By Richard Mark Kirkner, Editor

Take-home Points

- This year's list includes 51 entries in three categories: biologics, steroids and light-activated treatments for exudative disease; gene therapies for exudative disease; and treatments for inherited retinal disorders.
- Fourteen new entries for exudative disease have been added to this year's listing.
- Expanded listing includes stem cell and gene therapies for exudative disease and treatments for inherited retinal disease.

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.

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 therapies for inherited retinal disease.

This year's report lists 51 entries, up from 23 last year. Besides the five gene therapy and eight IRD candidates added, 14 entries have been added to the list of biologic and other therapies for exudative disease.

Two candidates have been dropped from the list: AKB-9778 (Aerpio Therapeutics); and DE-122 (Santen/TRACON Pharmaceuticals).

AKB-9778, also known as razuprotafib, is patient self-administered like insulin. The Phase IIb trial in nonproliferative diabetic retinopathy failed to meet its primary end-

point. Sponsor Aerpio Therapeutics is pursuing its development in glaucoma. Santen Pharmaceutical and Tracon Pharmaceuticals last March discontinued development of the carotuximab endoglin antibody DE-122 after discouraging results of a Phase IIa trial in neovascular age-related macular degeneration.

This listing includes only therapies in human trials or soon to be in the clinic.

Abicipar pegol (AbbVie/Molecular Partners)

The SEQUOIA (n=949, Clinicaltrials.gov identifier NCT02462486) and CEDAR (n= 233, NCT02173496) Phase III trials reported rates of intraocular inflammation (IOI) of 15.1 to 15.7 percent in abicipar-treated patients compared with 0 to 0.6 percent in the ranibizumab treatment group.[1] Shortly after the FDA CRL, AbbVie and Molecular Partners—they're collaborating on development—withdrew the European Medicines Agency application for abicipar in nAMD. Trial readouts continued after the CRL, and the collaborating companies say they're committed to abicipar to fill an unmet need for treatment options in nAMD.

DARPin molecules are derived from naturally occurring binding proteins that consist of repeat sequences with capping structures at each end of the protein. They have three key properties that make them an important investigational class of binding protein for researchers: high binding affinity; low molecular weight; and customizable applications.

The Phase II Maple trial reported an overall IOI rate of 8.9 percent (11 of 123 eyes). A deep analysis of those 11 eyes found that all cases responded to treatment with topical or intraocular steroids and had resolved by the time the study was completed, and that vision improved in most eyes.[2] No cases of endophthalmitis or vasculitis were reported. Thomas A. Albini, MD, presenting the data at the Retina Society, said the results showed that a modified manufacturing process for abicipar demonstrated better safety than the formulation used in the Phase III studies.

Aflibercept (Regeneron Pharmaceuticals)

An 8-mg dose of aflibercept is the subject of a number of clinical trials. The Phase II/III PHOTON trial (n=640, NCT04429503) started enrolling patients in June. The Phase III PULSAR trial (n=960, NCT04423718) of patients with age-related vision problems started last summer. A separate Phase II trial (n=100, NCT04126317) in nAMD had started in 2019 and is scheduled for completion later this year.

Meanwhile, the standard 2-mg dose of aflibercept is the subject of the Phase III PANORAMA trial for moderately severe to severe nonproliferative DR without DME (n=402, NCT02718326). The study evaluated two treatment regimens with 2-mg aflibercept: q16 weeks after three monthly doses and one eight-week interval (n=135); and q8 weeks after five monthly doses (n=134). In the q16-week group, 65.2 percent had at least a two-step improvement in Diabetic Retinopathy Severity Score, as did 79 percent in the q8-week group vs. 15 percent in the sham group.[3]

AKST4290 (Alkahest Inc.)

Formerly known as ALK 4290, AKST4290 is an oral inhibitor of the chemokine C-C motif receptor 3 (CCR3) that blocks the action of eotaxin, an immunomodulatory protein that increases as humans age and contributes to specific age-related diseases. By targeting eotaxin and its downstream effects, AKST4290 may reduce the hallmark inflammation and neovascularization of AMD while also acting more broadly to reduce inflammation associated with many other age-related diseases.

Alkahest initiated a Phase IIb clinical trial, PHTHALO-205 (n=100, NCT04331730), to evaluate efficacy on visual acuity after three loading doses of aflibercept in treatment-naïve nAMD patients. Subjects have been randomized 1:1:1 to receive AKST4290 400 mg b.i.d., AKST4290 800 mg b.i.d. or placebo. Completion is scheduled for April.

NEW: ALK-001 (Alkeus Pharmaceuticals)

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 APX3300 in 100 people with moderately severe to severe NPDR

Biologics, steroids and light-activated treatments for exudative disease in human trials

Drug name (manufacturer)	Description/active agent
Abicipar pegol (AbbVie/Molecular Partners)	Designed ankyrin repeat protein (DARPin) therapy
Aflibercept high-dose (Regeneron Pharmaceuticals)	Anti-VEGF-A and anti-placental growth factor (PLGF)
AKST4290 (formerly ALK4290) (Alkahest Inc.)	Oral small-molecule CCR3 inhibitor
NEW: **ALK-001** (Alkeus Pharmaceuticals)	Oral formulation of modified vitamin A
NEW: **ANX007** (Annexon Biosciences)	Intravitreal antigen-binding fragment (Fab) to complement factor q1
NEW: **APX3330** (Ocuphire Pharma)	Twice-daily oral treatment targets Ref-1 protein
AR-1105 (Aerie Pharmaceuticals)	Biodegradable dexamethasone implant
NEW: **AXT107** (AsclepiX Therapeutics)	Intravitreal self-forming gel depot peptide
Brolucizumab (Novartis)	Humanized monoclonal antibody fragment
NEW: **CLS-AX** (Clearside Biomedical)	Small-molecule tyrosine kinase inhibitor (TKI) suspension for suprachoroidal injection
Conbercept (Chengdu Kanghong Biotechnology)	Recombinant fusion protein targeting vascular endothelial growth factor-A and -B and PLGF
EYP-1901 (EyePoint Pharmaceuticals)	Bioerodable implant using TKI vorolanib
Elamipretide (Stealth BioTherapeutics)	Mitochondria-targeting cell-permeable peptide for subcutaneous injection
Faricimab (Genentech/Roche)	Anti-VEGF and anti-angiopoietin-2 bispecific antibody
FHTR2163 (RG6147, Genentech/Roche)	Anti-high-temperature requirement A-1 (htrA-1) antibody
GB-102 (Graybug Vision)	Pan-VEGF antagonist sunitinib for intravitreal injection
NEW: **GEM103** (Gemini Therapeutics)	Recombinant, human complement factor H (CFH)
ICON-1 (Iconic Therapeutics)	Anti-tissue factor fusion protein
NEW: **IONIS-FB-LRx** (Ionis Pharmaceuticals)	Anti-sense oligonucleotide inhibiting CFB
KSI-301 (Kodiak Sciences)	Anti-VEGF bipolymer conjugate
NEW: **LBS-008** (Belite Bio)	Oral small-molecule retinol binding protein (RBP4) specific antagonist
NEW: **NGM621** (NGM Biopharmaceuticals)	Humanized IgG1 monoclonal antibody inhibiting CC3
NEW: **ONS-5010/Lytenava** (bevacizumab-vikg, Outlook Therapeutics)	Ophthalmic formulation of intravitreal bevacizumab
NEW: **OpRegen** (Lineage Cell Therapeutics)	Subretinally administered allogeneic retinal pigment epithelium cells
OPT-302 (Ophthea)	Anti-VEGF-C and -D
NEW: **OTX-TKI** (Ocular Therapeutix)	Hydrogel-based sustained-release intravitreal axitinib implant
PAN-90806 (PanOptica)	Topical agent targeting VEGFR-2
Pegcetacoplan (APL-2, Apellis)	CC3 inhibitor
Port Delivery System (PDS) with ranibizumab (Genentech/Roche)	Refillable ranibizumab 0.5% implant
NEW: **RO7250284** (Genentech/Roche)	Bispecific human antigen-binding fragment (Fab) form of faricimab delivered via PDS
Retilux (PhotoOpTx)	Worn laser therapy device using photobiomodulation
Risuteganib (Allegro Ophthalmics)	Luminate broad-spectrum anti-integrin peptide
THR-149 (Oxurion)	Plasma kallikrein inhibitor
THR-687 (Oxurion)	Pan-arginylglycylaspartic acid (RGD) integrin antagonist
Valeda Light Delivery System (LumiThera)	Light-delivery system using photobiomodulation
Xiflam (Ocunexus)	Oral small-molecule connexin43 hemichannel blocker
NEW: **Xipere** (CLS-TA, Clearside Biomedical)	Triamcinolone acetonide 40 mg/mL suspension for suprachoroidal injection
Zimura (iVERIC bio)	Avacincaptad pegol CFC5 inhibitor

and mild PDR (NCT04692688). APX3330 is a twice-daily oral tablet; dosing is five 120-mg tablets daily.

AR-1105 (Aerie Pharmaceuticals)

This bioerodable 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-

	Indication	Status
	Neovascular age-related macular degeneration	Trial readouts continue after negative complete response letter.
	nAMD	Phase II/III (n=640) commenced enrollment; Phase III (n=960) due for completion this year.
	nAMD	Phase IIb trial (n=100) initiated; completion due in April.
	Geographic atrophy secondary to dry AMD (also Stargardt)	Phase II/III trial (n=300) ongoing; completion due at year end.
	GA secondary to dry AMD (also glaucoma)	Phase II trial (n=240) to start in March.
	Nonproliferative diabetic retinopathy, proliferative DR	Phase II trial in DR/DME (n=100) scheduled to begin in first quarter.
	Macular edema associated with retinal vein occlusion	Phase II trial completed, results pending.
	Diabetic macular edema	First patient dosed in Phase I/IIa trial January 2021.
	DME	Topline Phase III results reported; results anticipated in Phase III KESTREL trial.
	nAMD	Enrollment started in Phase I/IIa trial; completion due in 2022.
	nAMD	Enrollment completed in two Phase III trials; results due in 2022.
	nAMD	First patient enrolled in Phase I trial in January 2021.
	GA secondary to dry AMD	Phase II ReCLAIM-2 trial ongoing; completion expected 2022.
	nAMD, DME	Phase II STAIRWAY trial results reported; Phase III trials ongoing for both indications.
	GA secondary to dry AMD	Phase II GALLEGO trial (n=360) and Phase II open-label trial (n=360) currently recruiting.
	nAMD, DME, RVO	Phase IIb ALTISSIMO (n=56, nAMD), Phase I/IIa (n=32, nAMD); and Phase IIa (n=21, DME, RVO) results pending.
	GA secondary to dry AMD	Phase I (n=12) results reported; Phase IIa (n=45) started enrollment in the fall.
	Choroidal neovascularization secondary to AMD.	Phase II results in combination with aflibercept (n=15) and ranibizumab (n=88) reported.
	GA secondary to dry AMD	Phase II trial (n=330) ongoing.
	nAMD, DME, retinal vein occlusion	Phase III trials (n=1,450 combined) in all three indications ongoing.
	Dry AMD (also Stargardt disease)	Phase I trial (n=71) confirms safety; Phase III trial planned for this year.
	GA secondary to dry AMD	Phase II CATALINA trial started July 2020.
	AMD, DME and branch RVO	Phase III safety studies due for completion this year.
	GA secondary to dry AMD	Interim Phase I/IIa data (n=24) reported.
	nAMD, DME	Phase Ib/IIa (n=153) results reported; Phase III trials to begin this year.
	nAMD	Interim Phase I data (n=26) report favorable safety profile.
	nAMD, DME, RVO	Results of Phase I/II trials (n=51) concluded in 2019 pending.
	GA secondary to dry AMD	Post-hoc Phase II results reported; topline Phase III results expected later in year.
	nAMD, DME, DR	Phase III Archway trial (n=418) expected to complete in spring; extension study ongoing.
	nAMD	Phase I trial (n=50) started recruitment October 2020. Results due 2026
	DME	Pilot study data pending.
	DME, dry AMD	Preliminary Phase II results reported; Phase IIb/III study planned for 2021.
	DME	Phase II KALAHARI trial started September; completion scheduled 2023.
	DME	Additional Phase I results reported; Phase II trial to start this year.
	Dry AMD	LIGHTSITE III trial ongoing; completion scheduled 2022.
	DME, nAMD, GA secondary to dry AMD	Phase IIb trail launch delayed from 2020; launch expected later in 2021.
	DME (also uveitic macular edema)	Phase II (n=71) results reported.
	GA secondary to dry AMD	Phase III trial (n=400) initiated; completion due in 2023. Second Phase III trial pending.

libercept 2 mg in mean BCVA change after a year (n=361, NCT03481660).

A second study in DME, KESTREL, reported similar outcomes of 6-mg brolucizumab—the dose approved for nAMD—relative to aflibercept (n=571, NCT03481634). More than half the patients in the brolucizumab 6-mg arm were maintained on a three-month dosing interval through year one following the loading phase. KESTREL also evaluated brolucizumab 3 mg. KESTREL anticipates results in the fall.

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.[4]

Genentech has reported topline 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=1,800, NCT04432831) 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.[5] HtrA1 has also been identified as a major risk factor for wet AMD.[6] The Phase II GALLEGO 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 microparticle 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, NC03815825) 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 IIb/III DAZZLE study (n=550, NCT04049266) 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, NTC04465955) 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.

Pegcetacoplan (APL-2, Apellis)

Eighteen-month data from the Phase Ib APL-2-103 study of pegcetacoplan 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 pegcetacoplan 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 FILLY 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 without needing 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 antigen-binding fragment (Fab) form of faricimab 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 (PhotoOpTx)

Worn like an eye patch, this device is designed to deliver laser therapy directly to the affected eye. PhotoOpTx describes photobiomodulation (PBM) as irradiation by light in the 630- to 690-nm range. Data are pending from a pilot study (n=134, NCT03866473) 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 luminate 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 IIb/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, AAV.7m8, 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, NCT04418427) 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.

HMR59 (Hemera Biosciences)

HMR59 is a soluble form of CD59, the protective protein normally found on the cellular plasma membrane. HMR-1001, a Phase I dose-escalation trial (n=17, NCT03144999) in GA, shut down last year. HMR-1002 is a Phase I proof-of-concept study (n=25, NCT03585556) in treatment-naïve patients with new onset nAMD. Patients will be treated with anti-VEGF followed by intravitreal AAV-CAGs CD59 a week later. They'll be followed for a year and receive anti-VEGF monthly as needed. Completion is expected next year.

IBI302 (Innovent Biologics)

China-based Innovent describes IBI302 as a bispecific anti-VEGF and anti-complement recombinant fully human fusion protein. The Phase I trial in nAMD (n=31, NCT03814291) of a single intravitreal injection found no serious adverse events or dose-limiting toxicity and demonstrated signs of improved vision and reduction of retinal edema.[12] At 28 days, all patients showed improvement in BCVA and central retinal thickness. Treatment duration in some patients lasted up to six weeks. A second Phase I trial (n=18, NCT04370379) is evaluating repeat treatment with high- and low-dose IBI302 with aflibercept as a comparator. Midyear completion is expected.

RGX-314 (RegenxBio)

RGX-314 is an AAV8 vector containing a transgene for anti-VEGF Fab that RegenxBio is investigating in diabetic retinopathy and nAMD. ALTITUDE, a Phase II trial (n=40, NCT04567550), is evaluating suprachoroidal delivery of RGX-314 using the SCS Microinjector in DR without center-involved DME. Initial data are due this year.

In nAMD, interim Phase I/IIa data (n=42, NCT03066258) demonstrated significant reduction in anti-VEGF injections after RGX-314 subretinal delivery, with 73 percent of patients in one cohort (8/11) remaining anti-VEGF free at a year.[13] Two trials in nAMD are planned. Enrollment started in the Phase IIb/III ATMOSPHERE study (n=300, NCT040704921) comparing RGX-314 and ranibizumab. A smaller Phase II trial, AAVIATE, (n=40, NCT04514653) is evaluating suprachoroidal delivery in nAMD. RegenxBio says it plans to start the second pivotal trial in nAMD in the second half of the year.

Gene therapies for exudative retinal disease in human trials

Drug name (manufacturer)	Description/active agent	Indication	Status
ADVM-022 (Adverum Biotechnologies)	Adeno-associated vector 7m8 of aflibercept	Neovascular age-related macular degeneration, diabetic macular edema	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.
GT005 (Gyroscope Therapeutics)	AAV-induced expression of complement factor I	Geographic atrophy secondary to dry AMD	Phase I/II FOCUS (n=45); Phase II EXPLORE (n=75); Phase II HORIZON (n=150) ongoing.
HMR59 (Hemera Biosciences)	Soluble form of CD59 protein found in cellular plasma membrane	GA secondary to dry AMD, nAMD	Phase I GA trial (n=17) declared inactive; Phase I nAMD trial (n=25) ongoing.
IBI302 (Innovent Biologics)	Bispecific anti-VEGF and anti-complement recombinant fully human fusion protein	nAMD	Results of Phase I dose-escalation trial (n=31) pending; Phase I comparator trial (n=18) due for completion midyear.
RGX-314 (RegenxBio)	AAV8 vector containing anti-VEGF Fab transgene	Diabetic retinopathy without center-involved DME, nAMD	Initial Phase II CI-DME (n=40) data due this year; Interim Phase I/IIa (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.

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 rAAV2tYF-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 rAAV2tYF-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, NCT02402660) 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 nyctalopia. Ocugen says it's planning to initiate two parallel Phase I/II clinical trials this year.

rAAV2tYF-GRK1-RPGR (AGTC)

Early results have been reported in the Phase I/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

Drug name (manufacturer)	Description/active agent	Indication	Status
AAV-RPGR (MeiraGTx Holdings/ Janssen Pharmaceuticals)	Subretinal delivery of functional copies of RPGR gene	X-linked retinitis pigmentosa	12-month Phase I/II (n=46) readout reported.
AGTC-402 and **rAAV2tYF-PR1.7-hCNGB3** (Applied Genetic Technologies Corporation)	Adeno-associated vector targeting mutations in the ACHM CNGA3 and ACHM CNGB3 genes	Achromatopsia	Enrollment completed in Phase I/II (n=24, 28, respectively); completion expected 2025.
ALK-001 (Alkeus Pharmaceuticals)	Oral modified vitamin A	Stargardt disease	Phase II trial (n=140) ongoing; completion scheduled March 2022.
Elamipretide (Stealth BioTherapeutics)	Subcutaneous mitochondria-targeting cell-permeable peptide	Leber hereditary optic neuropathy	Phase II trial (n=12) concluded; results pending.
jCell (jCyte, Santen)	Intravitreal human retinal progenitor cells.	Retinitis pigmentosa	Phase II trial (n=84) ongoing; Phase III to launch this year.
Lumevoq (GS010, GenSight)	Single intravitreal injection of rAAV2/s-ND4	LHON	Phase III RESCUE trial (n=39) results reported; topline Phase II REFLECT (n=90) results due this year.
OCU400 (Ocugen)	AAV of functional NR2E3 gene.	RP, autosomal dominant congenital nyctalopia	Two parallel Phase I/II trials to start this year.
rAAV2tYF-GRK1-RPGR (Applied Genetic Technologies Corporation)	AAV-based treatment	XLRP	Early Phase I/II (n=30) results reported; Vista trial to start this year.

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, NCT03666923) confirmed safety and demonstrated early signs of efficacy.[9] 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, Clearside 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 with aflibercept alone.[10]

The study found that the combination group had statistically significant improvement in CST and needed fewer treatments at 24 weeks, although BCVA changes between groups weren't statistically significantly different.

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

1. Khurana R. Abcipar for neovascular AMD: Two-year results from CEDAR and SEQUOIA Phase 3 clinical trials. Paper presented at American Academy of Ophthalmology Retina Subspecialty Day 2019; San Francisco, CA; October 11, 2019.
2. Albini T. Abicipar Phase 2 MAPLE trial demonstrates improved safety for patients with nAMD following a modified manufacturing process. Paper Presented at Retina Society 2020 VR Live; September 21, 2020.
3. Boyer E. Intravitreal aflibercept injection for nonproliferative diabetic retinopathy: Results from the PANORAMA study. Paper Presented at Retina Society 2020 VR Live; September 22, 2020.
4. Lad E, Lin H, Silverman D, Basu K, Ruiz CQ, Haskova Z. Effect of dual angiopoietin-2/VEGF-A inhibition with faricimab on macular anatomy in the STAIRWAY Phase 2 study of neovascular age-related macular degeneration (nAMD). Paper Presented at Retina Society 2020 VR Live; September 8, 2020.
5. Ciferri C, Lipari MT, Liang WC, et al. The trimeric serine protease HtrA1 forms a cage-like inhibition complex with an anti-HtrA1 antibody. Biochem J. 2015;472:169-181.
6. DeWan A, Liu M, Hartman S, et al. HTRA1 promoter polymorphism in wet age-related macular degeneration. Science. 2006;314;5801:989-992.
7. Boyer D. Safety and biological activity of intravitreal OTX-TKI implant in neovascular age-related macular degeneration (nAMD). Paper presented at American Academy of Ophthalmology Retina Subspecialty Day 2020; November 13, 2020.
8. Campochiaro P. Primary analysis results of the Phase III Archway trial of the Port Delivery System with ranibizumab for patients with neovascular AMD. Paper presented at American Society of Retina Specialists Annual Meeting; July 26, 2020.
9. Khanani A. Results of a Phase I study using the integrin antagonist THR-687 in patients with DME. Paper presented at Angiogenesis, Exudation and Degeneration 2020, Miami, FL; February 8, 2020.
10. Barakat M, Wykoff CC, Gonzalez V, et al. Suprachoroidal CLS-TA plus intravitreal aflibercept for diabetic macular edema: A randomized, double-masked, parallel-design, controlled study. Ophthalmol Retina. 2021;5:60-70.
11. Jafee GJ, Westby K, Csaky KG, et al. C5 inhibitor avacincaptad pegol for geographic atrophy due to age-related macular degeneration: A randomized pivotal Phase II/III trial. Ophthalmology. Published online August 31, 2020. Available at: https://doi.org/10.1016/j.ophtha.2020.08.027.
12. Wang F, Sun X, Zhang M, Lu S, Qian L. Phase I dose-escalation study of IBI302, a novel, bispecitive Fc-fusion protein targeting VEGF and complement system, in patients with nAMD. Poster presented at American Academy of Ophthalmology 2020; November 13, 2020.
13. Wykoff C. Gene therapy with RGX-314 for neovascular AMD: New results from the ongoing Phase I/IIa study. Paper Presented at Retina Society 2020 VR Live; September 22, 2020.
14. Michaelides M, Besirli C, Khan K, et al. AAV-RPGR gene therapy for RPGR-associated X-linked retinitis pigmentosa: 12-month results from a Phase I/2 clinical trial. Paper presented at American Academy of Ophthalmology virtual meeting; November 13, 2020.
15. Newman NJ, Yu-Wai-Man P, Carelli V, et al. Efficacy and safety of intravitreal gene therapy for Leber hereditary optic neuropathy treated with 6 months of disease outset. Ophthalmology. Published online January 12, 2021. https://doi.org/10.1016/j.ophtha.2020.12.012.

The complement pathway in geographic atrophy

Examining the role of complement factors in advanced disease.

Oleg Alekseev, MD, PhD

Eleonora M. Lad, MD, PhD

Nathan Steinle, MD

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.

The complement pathway, a key component of innate immunity, maintains immune homeostasis throughout the body, including in ocular tissues. It's composed of three pathways—classical, alternative and lectin—all eventually converging on C3 cleavage (*Figure*).

Endogenous inhibitory factors suppress activated complement to maintain immune equilibrium. Thus, autologous damage can arise due to overaction, whether through inappropriate activation or inadequate inhibition.

In the retina, the complement system, particularly the alternative pathway, has been implicated in the development of age-related macular degeneration and geographic atrophy. In all, six members of the complement cascade—CFB, CFH, CFI, C2, C3 and C9—are estimated to account for 40 to 60 percent of AMD heritability.[1]

Complement activation levels differ significantly between AMD disease stages, with higher activation corresponding with more advanced AMD and central GA.[2] Many complement components and regulators deposit within drusen, where they act as inflammatory foci.[3]

This review examines the role of complement factors in the pathogenesis of GA.

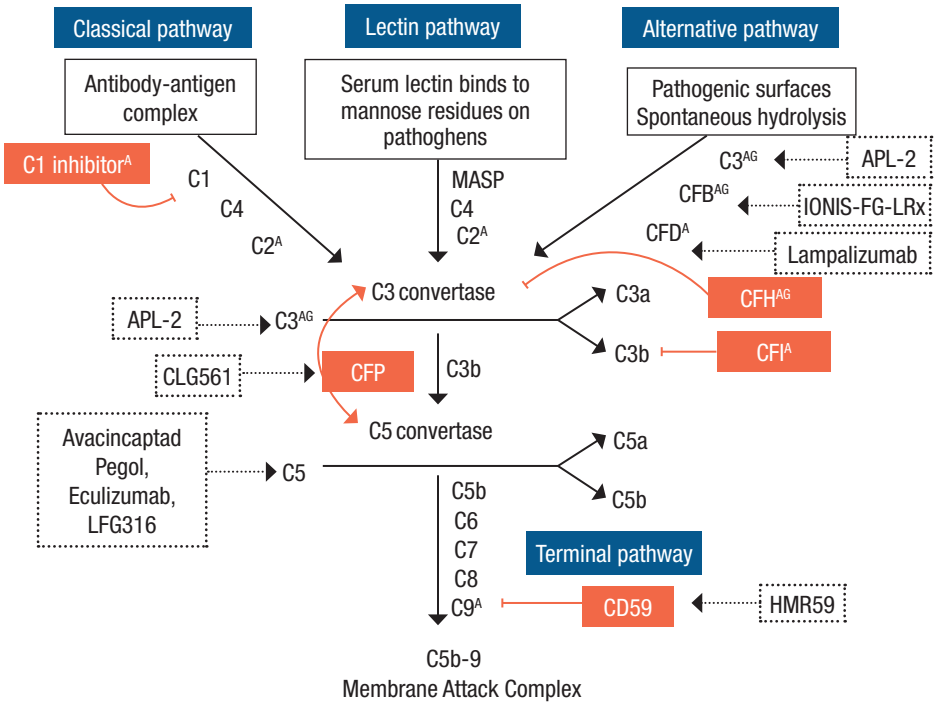
Complement factor B

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.[3]

Two protective variants of CFB have been described: R32Q and L9H.[4] The R32Q polymorphism also appears to slow GA progression.[5] 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



Three complement pathways—classical, lectin and alternative—converge on the common terminal pathway, eventually leading to formation of the membrane attack complex. 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.)

CFD-/- knockout mouse model of AMD showed decreased photoreceptor damage compared to wild type.[6] One polymorphism (rs3826945) has been associated with AMD.[7] In addition, serum levels of CFD have been shown to be elevated in AMD patients,[7] 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.[3] It prevents damage to healthy bystander cells, but not pathogens, by selective inhibition of complement activity on self-surfaces.[8]

Genome-wide association studies have identified numerous risk-imparting, 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[9] and correlates with the presence of GA.[10,11] 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.[12]

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.[13] 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.[9] In addition to conferring general AMD risk, CFH variants impart higher risk of conversion from large drusen to GA.[14,15]

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.[16] 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).[17]

Subsequently, a large systematic functional testing study revealed numerous

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, Gallimedix, Retrotope, Gemini Therapeutics and LumiThera.
Dr. Steinle disclosed relationships with Alimera Sciences, Apellis, Carl Zeiss Meditec, Genentech, Notal Vision, Novartis, Regenerative Patch Technologies, Regeneron and RegenxBio, and is an investor in Vortex Surgical.

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.

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 C3a, 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 trial[23] and is the subject of two fully enrolled ongoing Phase III trials[24,25] (*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.

Complement component 5

C5 is activated by C5 convertase to become C5a, a pro-inflammatory mediator that acts as a nidus for MAC formation. Plasma levels of C5a are elevated in AMD patients[11] and stimulation of the choroid C5a receptor causes ICAM-1 overexpression, which likely leads to monocyte recruitment.[28] Nevertheless, no consistent and replicable associations between polymorphisms in C5 or C5a 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 ongoing[31] (*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 patients[37] 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 pathobiology 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.

Candidates targeting the complement cascade to treat geographic atrophy

Target	Candidate	Mechanism	Phase	Clinicaltrials.gov identifier	Trial name	Effect on GA Growth
CFB	IONIS-FB-LRx	Atisense oligo-nucleotide	II	NCT03815825	GOLDEN	Ongoing
CFD	Lampalizumab	Monoclonal antibody	II	NCT02288559		Unpublished
			II	NCT01229215	MAHALO	20-percent reduction at 18 months
			III	NCT02247479	CHROMA	No reduction
			III	NCT02247531	SPECTRI	No reduction
CFP	CLG561	mAb	II	NCT02515942		Unpublished
C3	APL-2	Compstatin	II	NCT02503332	FILLY	29-percent reduction at 12 months
			III	NCT03525600	OAKS	Ongoing
			III	NCT03525613	DERBY	Ongoing
C5	LFG316	mAb	II	NCT01527500		No reduction
	Eculizimab	mAb	II	NCT00935883	COMPLETE	No reduction
	Avacincaptad pegol	Aptamer	II/III	NCT02686658	GATHER1	28-precent reduction at 12 months
			III	NCT04435366	GATHER2	Ongoing
CD59	HMR59	Adeno-associated virus	II	NCT04358471		Ongoing

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.

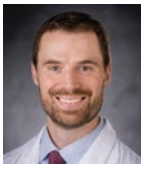
REFERENCES

1. Fritsche LG, Fariss RN, Stambolian D, Abecasis GR, Curcio CA, Swaroop A. Age-related macular degeneration: Genetics and biology coming together. Annu Rev Genomics Hum Genet. 2014;15:151-171.
2. Heesterbeek TJ, Lechanteur YTE, Lorés-Motta L, et al. Complement activation levels are related to disease stage in AMD. Invest Ophthalmol Vis Sci. 2020;61:18.
3. Khandhadia S, Cipriani V, Yates JR, Lotery AJ. Age-related macular degeneration and the complement system. Immunobiology. 2012;217:127-146.
4. Thakkinstian A, McEvoy M, Chakravarthy U, et al. The association between complement component 2/complement factor B polymorphisms and age-related macular degeneration: A HuGE review and meta-analysis. Am J Epidemiol. 2012;176:361-372.

(Continued on page 38)

The promise of targeting mitochondria in dry AMD

Mitochondrial therapies have shown the potential to improve visual function in patients with dry age-related macular degeneration.



Michael J. Allingham, MD, PhD

By Michael J. Allingham, MD, PhD

Take-home Points

- Patients with age-related macular degeneration experience visual dysfunction including poor low-luminance vision and reading in spite of preserved foveal photoreceptors and retinal pigment epithelium.
- Mitochondrial dysfunction is one of several potential mechanisms of vision loss in AMD.
- Several therapeutic candidates targeting mitochondria have been found to be safe and well-tolerated, and have shown promising efficacy signals.
- In addition to potentially reducing progression of geographic atrophy, mitochondrial therapies may boost visual function, particularly low-luminance vision, in patients with AMD.

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

Bio

Dr. Allingham is an assistant professor at Duke Eye Center, Durham, North Carolina

DISCLOSURES: Dr. Allingham has received research funding from Stealth Biotherapeutics and has served as a subinvestigator for the ReCLAIM-1 and ReCLAIM-2 trials of elamipretide.

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.

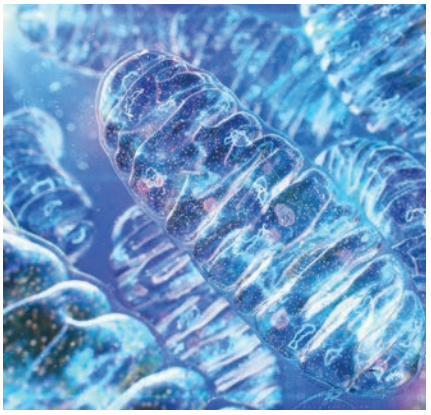
Risuteganib has been shown to prevent mitochondrial injury in cultured RPE cells exposed to hydroquinone, suggesting that mitochondrial protection is efficacious in an *in vitro* model of AMD.[7] Additionally, risuteganib was found to reduce mitochondrial ROS and improve mitochondrial bioenergetics in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



A rendering of the exterior of mitochondria. (*National Institutes of Health*)

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.

erythema and induration.

The NCGA subgroup demonstrated a mean increase in BCVA of 4.6±5.1 letters from baseline (p=0.003), with a mean increase in LLVA of 5.4±7.9 letters from baseline (p=0.025). This group also demonstrated a significant increase in LLRA of logMAR -0.52±0.75 (p<0.017), representing a 5-line gain from baseline. In this subgroup, the mean change in GA square-root area was 0.13±0.14 mm measured by optical coherence tomography. This was less than the 24-week rate of growth observed in natural history studies and placebo control arms of clinical trials for GA.

The HRD subgroup demonstrated a mean increase in BCVA of 3.6±6.4 letters from baseline (p=0.025), with a mean increase in LLVA of 5.6±7.8 letters from baseline (p=0.006). At week 24, these patients had a modest but significant mean increase in BCRA of logMAR -0.11±0.15 (p=0.005), corresponding to approximately a 1-line gain from baseline. Investigators also observed a significant mean increase in LLRA of logMAR -0.28±0.17 (p=0.0001), which equates to a 3-line gain vs. baseline.

Currently, ReCLAIM-2 (NCT03891875), a Phase IIb multicentered randomized trial, is underway to further evaluate elamipretide for slowing growth of GA lesion size as well as improving standard and low-luminance vision outcomes.

Early risuteganib outcomes

Risuteganib, also known as luminate, 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.

Bottom line

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. Two trials in patients with dry AMD have demonstrated improved visual function in addition to signals suggesting improvement in anatomic outcomes such as GA lesion size. Improvement in vision outcomes represents an important paradigm shift in therapy goals for dry AMD and would address a major unmet clinical need in a large body of patients for whom there is currently no effective therapy. RS

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.

REFERENCES

1. Bianchi E, Scarinci F, Ripandelli G, et al. Retinal pigment epithelium, age-related macular degeneration and neurotrophic keratouveitis. Int J Mol Med. 2013;31:232-242.
2. Rummelt V, Folberg R, Ionasescu V, Yi H, Moore KC. Ocular pathology of MELAS syndrome with mitochondrial DNA nucleotide 3243 point mutation. Ophthalmology. 1993;100:1757-1766.
3. Smith PR, Bain SC, Good PA, et al. Pigmentary retinal dystrophy and the syndrome of maternally inherited diabetes and deafness caused by the mitochondrial DNA 3243 tRNA(Leu) A to G mutation. Ophthalmology. 1999;106:1101-1108.
4. Terluk MR, Kapphahn RJ, Soukup LM, et al. Investigating mitochondria as a target for treating age-related macular degeneration. J Neurosci. 2015;35:7304-7311.
5. Espinosa-Heidmann DG, Suner IJ, Catanuto P, Hernandez EP, Marin-Castano ME, Cousins SW. Cigarette smoke-related oxidants and the development of sub-RPE deposits in an experimental animal model of dry AMD. Invest Ophthalmol Vis Sci. 2006;47:729-737.
6. Cousins SW, Saloupis P, Brahmajoti MV, Mettu PS. Mitochondrial dysfunction in experimental mouse models of subRPE deposit formation and reversal by the mito-reparative drug MTP-131. Invest Ophthalmol Vis Sci. 2016;57:2126.
7. Yang P, Shao Z, Besley NA, et al. Risuteganib protects against hydroquinone–induced injury in human RPE cells. Investig Opthalmology Vis Sci. 2020;61:35.
8. Zhou D, Chwa M, Shao Z, et al. Mechanism of action of risuteganib for retinal diseases through protection of retinal pigment epithelium (RPE) and enhancement of mitochondrial functions. Invest Ophthalmol Vis Sci. 2020;61:4949.

The Stark (law) truth

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

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.[1]

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.[1]

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."[1]

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

Have a question for "Coding Commentary"? Tweet it to us at **@RetSpecMag**

Bio

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

- enterprises in which participants collaborate to achieve at least one value-based purpose, an exception that requires financial and operational oversight;
- that coordinate and manage care, improve care, appropriately reduce cost and transition to quality-of-care-based payment mechanisms.[1]

The overarching rationale for the Stark exceptions is to encourage innovation in the shift from fee-for-service to value-based payment models. For example, depending on the structure, some current shared-savings/shared-loss arrangements may be unable to meet current self-referral law requirements due to referral provisions, requirements to refrain from ordering unnecessary care and pay-for-performance.

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.[2]

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 monetized referral schemes, accountable care arrangements, lease agreements or computer-related service agreements to avoid running afoul of the Stark laws. RS

REFERENCES

1. Medicare Program; Modernizing and Clarifying the Physician Self-Referral Regulations. Federal Register. December 2, 2020;77492-77682; 2020-26140. Available at: https://www.federalregister.gov/documents/2020/12/02/2020-26140/medicare-program-modernizing-and-clarifying-the-physician-self-referral-regulations
2. Office of the Inspector General, U.S. Department of Health and Human Services. A roadmap for new physicians: Fraud and abuse laws. Undated. Available at: https://oig.hhs.gov/compliance/physician-education/01laws.asp

Complement pathway in GA

(Continued from page 33)

5. Caire J, Recalde S, Velazquez-Villoria A, et al. Growth of geographic atrophy on fundus autofluorescence and polymorphisms of CFH, CFB, C3, FHR1-3, and ARMS2 in age-related macular degeneration. JAMA Ophthamol. 2014;132:528-534.
6. Rohrer B, Guo Y, Kunchithapautham K, Gilkeson GS. Eliminating complement factor D reduces photoreceptor susceptibility to light-induced damage. Invest Ophthalmol Vis Sci. 2007;48:5282-5289.
7. Stanton CM, Yates JR, den Hollander AI, et al. Complement factor D in age-related macular degeneration. Invest Ophthalmol Vis Sci. 2011;52:8828-8834.
8. Herbert AP, Makou E, Chen ZA, et al. Complement evasion mediated by enhancement of captured factor H: implications for protection of self-surfaces from complement. J Immunol. 2015;195:4986-4998.
9. Hageman GS, Anderson DH, Johnson LV, et al. A common haplotype in the complement regulatory gene factor H (HF1/CFH) predisposes individuals to age-related macular degeneration. Proc Natl Acad Sci USA. 2005;102:7227-7232.
10. Sepp T, Khan JC, Thurlby DA, et al. Complement factor H variant Y402H is a major risk determinant for geographic atrophy and choroidal neovascularization in smokers and nonsmokers. Invest Ophthalmol Vis Sci. 2006;47:536-540.
11. Scholl HP, Fleckenstein M, Fritsche LG, et al. CFH, C3 and ARMS2 are significant risk loci for susceptibility but not for disease progression of geographic atrophy due to AMD. PloS one. 2009;4:e7418.
12. Park DH, Connor KM, Lambris JD. The challenges and promise of complement therapeutics for ocular diseases. Front Immunol. 2019;10:1007.
13. Raychaudhuri S, Iartchouk O, Chin K, et al. A rare penetrant mutation in CFH confers high risk of age-related macular degeneration. Nat Genet. 2011;43:1232-1236.
14. Seddon JM, Francis PJ, George S, Schultz DW, Rosner B, Klein ML. Association of CFH Y402H and LOC387715 A69S with progression of age-related macular degeneration. JAMA. 2007;297:1793-1800.
15. Yu Y, Reynolds R, Rosner B, Daly MJ, Seddon JM. Prospective assessment of genetic effects on progression to different stages of age-related macular degeneration using multistate Markov models. Invest Ophthalmol Vis Sci. 2012;53:1548-1556.
16. Wang J, Ohno-Matsui K, Yoshida T, et al. Altered function of factor I caused by amyloid beta: implication for pathogenesis of age-related macular degeneration from drusen. J Immunol. 2008;181:712-720.
17. Wang Q, Zhao HS, Li L. Association between complement factor I gene polymorphisms and the risk of age-related macular degeneration: A Meta-analysis of literature. Int H Ophthalmol. 2016;9:298-305.
18. Tan PL, Garrett ME, Willer JR, et al. Systematic functional testing of rare variants: Contributions of CFI to age-related macular degeneration. Invest Ophthalmol Vis Sci. 2017;58:1570-1576.
19. van de Ven JP, Nilsson SC, Tan PL, et al. A functional variant in the CFI gene confers a high risk of age-related macular degeneration. Nat Genet. 2013;45:813-817.
20. Ennis S, Jomary C, Mullins R, et al. Association between the SERPING1 gene and age-related macular degeneration: A two-stage case-control study. Lancet. 2008;372:1828-1834.
21. Gold B, Merriam JE, Zernant J, et al. Variation in factor B (BF) and complement component 2 (C2) genes is associated with age-related macular degeneration. Nat Genet. 2006;38:458-462.
22. Cashman SM, Desai A, Ramo K, Kumar-Singh R. Expression of complement component 3 (C3) from an adenovirus leads to pathology in the murine retina. Invest Ophthalmol Vis Sci. 2011;52:3436-3445.
23. Liao DS, Grossi FV, El Mehdi D, et al. Complement C3 Inhibitor pegcetacoplan for geographic atrophy secondary to age-related macular degeneration: A randomized Phase 2 trial. Ophthalmology. 2020;127:186-195.
24. Study to compare the efficacy and safety of intravitreal APL-2 therapy with sham injections in patients with geographic atrophy (GA) secondary to age-related macular degeneration. ClinicalTrials.gov Identifier: NCT03525600. https://clinicaltrials.gov/ct2/show/record/NCT03525600. Accessed December 14, 2020.
25. A study to compare the efficacy and safety of intravitreal APL-2 therapy with sham injections in patients with geographic atrophy (GA) secondary to age-related macular degeneration. ClinicalTrials.gov Identifier: NCT03525613. https://clinicaltrials.gov/ct2/show/NCT03525613. Accessed December 14, 2020.
26. Hughes S, Gumas J, Lee R, et al. Prolonged intraocular residence and retinal tissue distribution of a fourth-generation compstatin-based C3 inhibitor in non-human primates. Clin immunol. 2020;214:108391.
27. Furfine E, Rao A, Baker S, et al. Pegylated CB2782: a complement factor C3-inactivating protease and potential long-acting treatment for dry AMD. Invest Ophthalmol Vis Sci. 2019;60:374-374.
28. Skeie JM, Fingert JH, Russell SR, Stone EM, Mullins RF. Complement component C5a activates ICAM-1 expression on human choroidal endothelial cells. Invest Ophthalmol Vis Sci. 2010;51:5336-5342.
29. Baas DC, Ho L, Ennis S, et al. The complement component 5 gene and age-related macular degeneration. Ophthalmology. 2010;117:500-511.
30. Jaffe GJ, Westby K, Csaky KG, et al. C5 inhibitor avacincaptad pegol for geographic atrophy due to age-related macular degeneration: A randomized pivotal Phase 2/3 trial. Ophthalmology. Published online September 1, 2020.
31. A Phase 3 safety and efficacy study of intravitreal administration of Zimura (complement C5 inhibitor). ClinicalTrials.gov Identifier: NCT04435366. https://clinicaltrials.gov/ct2/show/NCT04435366. Accessed December 14, 2020.
32. Seddon JM, Yu Y, Miller EC, et al. Rare variants in CFI, C3 and C9 are associated with high risk of advanced age-related macular degeneration. Nat Genet. 2013;45:1366-1370.
33. Nishiguchi KM, Yasuma TR, Tomida D, et al. C9-R95X polymorphism in patients with neovascular age-related macular degeneration. Invest Ophthalmol Vis Sci. 2012;53:508-512.
34. Li Y, Song D, Song Y, et al. Iron-induced local complement component 3 (c3) up-regulation via non-canonical transforming growth factor (TGF)-βsignaling in the retinal pigment epithelium. J Biol Chem. 2015;290:11918-11934.
35. Hadziahmetovic M, Dentchev T, Song Y, et al. Ceruloplasmin/hephaestin knockout mice model morphologic and molecular features of AMD. Invest Ophthalmol Vis Sci. 2008;49:2728-2736.
36. Guo LY, Alekseev O, Li Y, Song Y, Dunaief JL. Iron increases APP translation and amyloid-beta production in the retina. Exp Eye Res. 2014;129:31-37.
37. Hahn P, Milam AH, Dunaief JL. Maculas affected by age-related macular degeneration contain increased chelatable iron in the retinal pigment epithelium and Bruch's membrane. Arch Ophthalmol. 2003;121:1099-1105.

LUCENTIS®
RANIBIZUMAB INJECTION

Brief summary–please see the LUCENTIS® package insert for full prescribing information.

1 INDICATIONS AND USAGE
LUCENTIS is indicated for the treatment of patients with:

1.1 Neovascular (Wet) Age-Related Macular Degeneration (AMD)

1.2 Macular Edema Following Retinal Vein Occlusion (RVO)

1.3 Diabetic Macular Edema (DME)

1.4 Diabetic Retinopathy (DR)

1.5 Myopic Choroidal Neovascularization (mCNV)

4 CONTRAINDICATIONS
4.1 Ocular or Periocular Infections
LUCENTIS is contraindicated in patients with ocular or periocular infections.

4.2 Hypersensitivity
LUCENTIS is contraindicated in patients with known hypersensitivity to ranibizumab or any of the excipients in LUCENTIS. Hypersensitivity reactions may manifest as severe intraocular inflammation.

5 WARNINGS AND PRECAUTIONS
5.1 Endophthalmitis and Retinal Detachments
Intravitreal injections, including those with LUCENTIS, have been associated with endophthalmitis and retinal detachments. Proper aseptic injection technique should always be used when administering LUCENTIS. In addition, patients should be monitored following the injection to permit early treatment should an infection occur *[see Dosage and Administration (2.6, 2.7) in the full prescribing information and Patient Counseling Information (17)]*.

5.2 Increases in Intraocular Pressure
Increases in intraocular pressure have been noted both pre-injection and post-injection (at 60 minutes) while being treated with LUCENTIS. Monitor intraocular pressure prior to and following intravitreal injection with LUCENTIS and manage appropriately *[see Dosage and Administration (2.7 in the full prescribing information)]*.

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 unknown cause).

Neovascular (Wet) Age-Related Macular Degeneration
The ATE rate in the three controlled neovascular AMD studies (AMD-1, AMD-2, AMD-3) during the first year was 1.9% (17 of 874) in the combined group of patients treated with 0.3 mg or 0.5 mg LUCENTIS compared with 1.1% (5 of 441) in patients from the control arms *[see Clinical Studies (14.1 in the full prescribing information)]*. In the second year of Studies AMD-1 and AMD-2, the ATE rate was 2.6% (19 of 721) in the combined group of LUCENTIS-treated patients compared with 2.9% (10 of 344) in patients from the control arms. In Study AMD-4, the ATE rates observed in the 0.5 mg arms during the first and second year were similar to rates observed in Studies AMD-1, AMD-2, and AMD-3.

In a pooled analysis of 2-year controlled studies (AMD-1, AMD-2, and a study of LUCENTIS used adjunctively with verteporfin photodynamic therapy), the stroke rate (including both ischemic and hemorrhagic stroke) was 2.7% (13 of 484) in patients treated with 0.5 mg LUCENTIS compared to 1.1% (5 of 435) in patients in the control arms (odds ratio 2.2 (95% confidence interval (0.8-7.1))).

Macular Edema Following Retinal Vein Occlusion
The ATE rate in the two controlled RVO studies during the first 6 months was 0.8% in both the LUCENTIS and control arms of the studies (4 of 525 in the combined group of patients treated with 0.3 mg or 0.5 mg LUCENTIS and 2 of 260 in the control arms) *[see Clinical Studies (14.2 in the full prescribing information)]*. The stroke rate was 0.2% (1 of 525) in the combined group of LUCENTIS-treated patients compared to 0.4% (1 of 260) in the control arms.

Diabetic Macular Edema and Diabetic Retinopathy
Safety data are derived from studies D-1 and D-2. All enrolled patients had DME and DR at baseline *[see Clinical Studies (14.3, 14.4 in the full prescribing information)]*.

In a pooled analysis of Studies D-1 and D-2 *[see Clinical Studies (14.3 in the full prescribing information)]*, the ATE rate at 2 years was 7.2% (18 of 250) with 0.5 mg LUCENTIS, 5.6% (14 of 250) with 0.3 mg LUCENTIS, and 5.2% (13 of 250) with control. The stroke rate at 2 years was 3.2% (8 of 250) with 0.5 mg LUCENTIS, 1.2% (3 of 250) with 0.3 mg LUCENTIS, and 1.6% (4 of 250) with control. At 3 years, the ATE rate was 10.4% (26 of 249) with 0.5 mg LUCENTIS and 10.8% (27 of 250) with 0.3 mg LUCENTIS; the stroke rate was 4.8% (12 of 249) with 0.5 mg LUCENTIS and 2.0% (5 of 250) with 0.3 mg LUCENTIS.

5.4 Fatal Events in Patients with DME and DR at baseline
Diabetic Macular Edema and Diabetic Retinopathy
Safety data are derived from studies D-1 and D-2. All enrolled patients had DME and DR at baseline *[see Clinical Studies (14.3, 14.4 in the full prescribing information)]*.

A pooled analysis of Studies D-1 and D-2 *[see Clinical Studies (14.3 in the full prescribing information)]*, showed that fatalities in the first 2 years occurred in 4.4% (11 of 250) of patients treated with 0.5 mg LUCENTIS, in 2.8% (7 of 250) of patients treated with 0.3 mg LUCENTIS, and in 1.2% (3 of 250) of control patients. Over 3 years, fatalities occurred in 6.4% (16 of 249) of patients treated with 0.5 mg LUCENTIS and in 4.4% (11 of 250) of patients treated with 0.3 mg LUCENTIS. 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.

6 ADVERSE REACTIONS
The following adverse reactions are discussed in greater detail in other sections of the label:
- Endophthalmitis and Retinal Detachments *[see Warnings and Precautions (5.1)]*
- Increases in Intraocular Pressure *[see Warnings and Precautions (5.2)]*
- Thromboembolic Events *[see Warnings and Precautions (5.3)]*
- Fatal Events in patients with DME and DR at baseline *[see Warnings and Precautions (5.4)]*

6.1 Injection Procedure
Serious adverse reactions related to the injection procedure have occurred in < 0.1% of intravitreal injections, including endophthalmitis *[see Warnings and Precautions (5.1)]*, rhegmatogenous retinal detachment, and iatrogenic traumatic cataract.

6.2 Clinical Studies Experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in one clinical trial of a drug cannot be directly compared with rates in the clinical trials of the same or another drug and may not reflect the rates observed in practice.

The data below reflect exposure to 0.5 mg LUCENTIS in 440 patients with neovascular AMD in Studies AMD-1, AMD-2, and AMD-3; in 259 patients with macular edema following RVO. The data also reflect exposure to 0.3 mg LUCENTIS in 250 patients with DME and DR at baseline *[see Clinical Studies (14 in the full prescribing information)]*.

Safety data observed in Study AMD-4, D-3, and in 224 patients with mCNV were consistent with these results. On average, the rates and types of adverse reactions in patients were not significantly affected by dosing regimen.

Ocular Reactions
Table 1 shows frequently reported ocular adverse reactions in LUCENTIS-treated patients compared with the control group.

Table 1 Ocular Reactions in the DME and DR, AMD, and RVO Studies

	DME and DR 2-year		AMD 2-year		AMD 1-year		RVO 6-month	
	LUCENTIS 0.3 mg	Control	LUCENTIS 0.5 mg	Control	LUCENTIS 0.5 mg	Control	LUCENTIS 0.5 mg	Control
Adverse Reaction	n=250	n=250	n=379	n=379	n=440	n=441	n=259	n=260
Conjunctival hemorrhage	47%	32%	74%	60%	64%	50%	48%	37%
Eye pain	17%	13%	35%	30%	26%	20%	17%	12%
Vitreous floaters	10%	4%	27%	8%	19%	5%	7%	2%
Intraocular pressure increased	18%	7%	24%	7%	17%	5%	7%	2%
Vitreous detachment	11%	15%	21%	19%	15%	15%	4%	2%
Intraocular inflammation	4%	3%	18%	8%	13%	7%	1%	3%
Cataract	28%	32%	17%	14%	11%	9%	2%	2%
Foreign body sensation in eyes	10%	5%	16%	14%	13%	10%	7%	5%
Eye irritation	8%	5%	15%	15%	13%	12%	7%	6%
Lacrimation increased	5%	4%	14%	12%	8%	8%	2%	3%
Blepharitis	3%	2%	12%	8%	8%	5%	0%	1%
Dry eye	5%	3%	12%	7%	7%	7%	3%	3%
Visual disturbance or vision blurred	8%	4%	18%	15%	13%	10%	5%	3%
Eye pruritus	4%	4%	12%	11%	9%	7%	1%	2%
Ocular hyperemia	9%	9%	11%	8%	7%	4%	5%	3%
Retinal disorder	2%	2%	10%	7%	8%	4%	2%	1%
Maculopathy	5%	7%	9%	9%	6%	6%	11%	7%
Retinal degeneration	1%	0%	8%	6%	5%	3%	1%	0%
Ocular discomfort	2%	1%	7%	4%	5%	2%	2%	2%
Conjunctival hyperemia	1%	2%	7%	6%	5%	4%	0%	0%
Posterior capsule opacification	4%	3%	7%	4%	2%	2%	0%	1%
Injection site hemorrhage	1%	0%	5%	2%	3%	1%	0%	0%

Non-Ocular Reactions
Non-ocular adverse reactions with an incidence of ≥ 5% in patients receiving LUCENTIS for DR, DME, AMD, and/or RVO and which occurred at a ≥ 1% higher frequency in patients treated with LUCENTIS compared to control are shown in Table 2. Though less common, wound healing complications were also observed in some studies.

Table 2 Non-Ocular Reactions in the DME and DR, AMD, and RVO Studies

	DME and DR 2-year		AMD 2-year		AMD 1-year		RVO 6-month	
	LUCENTIS 0.3 mg	Control	LUCENTIS 0.5 mg	Control	LUCENTIS 0.5 mg	Control	LUCENTIS 0.5 mg	Control
Adverse Reaction	n=250	n=250	n=379	n=379	n=440	n=441	n=259	n=260
Nasopharyngitis	12%	6%	16%	13%	8%	9%	5%	4%
Anemia	11%	10%	8%	7%	4%	3%	1%	1%
Nausea	10%	9%	9%	6%	5%	5%	1%	2%
Cough	9%	4%	9%	8%	5%	4%	1%	2%
Constipation	8%	4%	5%	7%	3%	4%	0%	1%
Seasonal allergy	8%	4%	4%	4%	2%	2%	0%	2%
Hypercholesterolemia	7%	5%	5%	5%	3%	2%	1%	1%
Influenza	7%	3%	7%	5%	3%	2%	3%	2%
Renal failure	7%	6%	1%	1%	0%	0%	0%	0%
Upper respiratory tract infection	7%	7%	9%	8%	5%	5%	2%	2%
Gastroesophageal reflux disease	6%	4%	4%	6%	3%	4%	1%	0%
Headache	6%	8%	12%	9%	6%	5%	3%	3%
Edema peripheral	6%	4%	3%	5%	2%	3%	0%	1%
Renal failure chronic	6%	2%	0%	1%	0%	0%	0%	0%
Neuropathy peripheral	5%	3%	1%	1%	1%	0%	0%	0%
Sinusitis	5%	8%	8%	7%	5%	5%	3%	2%
Bronchitis	4%	4%	11%	9%	6%	5%	0%	2%
Atrial fibrillation	3%	3%	5%	4%	2%	2%	1%	0%
Arthralgia	3%	3%	11%	9%	5%	5%	2%	1%
Chronic obstructive pulmonary disease	1%	1%	6%	3%	3%	1%	0%	0%
Wound healing complications	1%	0%	1%	1%	1%	0%	0%	0%

6.3 Immunogenicity
As with all therapeutic proteins, 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 LUCENTIS in immunoassays and are highly dependent on the sensitivity and specificity of the assays.

The pre-treatment incidence of immunoreactivity to LUCENTIS was 0%-5% across treatment groups. After monthly dosing with LUCENTIS for 6 to 24 months, antibodies to LUCENTIS were detected in approximately 1%-9% of patients.

The clinical significance of immunoreactivity to LUCENTIS is unclear at this time. Among neovascular AMD patients with the highest levels of immunoreactivity, some were noted to have iritis or vitritis. Intraocular inflammation was not observed in patients with DME and DR at baseline, or RVO patients with the highest levels of immunoreactivity.

6.4 Postmarketing Experience
The following adverse reaction has been identified during post-approval use of LUCENTIS. Because this reaction was reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate the frequency or establish a causal relationship to drug exposure.
- Ocular: Tear of retinal pigment epithelium among patients with neovascular AMD

7 DRUG INTERACTIONS
Drug interaction studies have not been conducted with LUCENTIS.

LUCENTIS intravitreal injection has been used adjunctively with verteporfin photodynamic therapy (PDT). Twelve (12) of 105 (11%) patients with neovascular AMD developed serious intraocular inflammation; in 10 of the 12 patients, this occurred when LUCENTIS was administered 7 days (± 2 days) after verteporfin PDT.

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
Risk Summary
There are no adequate and well-controlled studies of LUCENTIS administration in pregnant women.

Administration of ranibizumab to pregnant monkeys throughout the period of organogenesis resulted in a low incidence of skeletal abnormalities at intravitreal doses 13-times the predicted human exposure (based on maximal serum trough levels [C_{max}]) after a single eye treatment at the recommended clinical dose. No skeletal abnormalities were observed at serum trough levels equivalent to the predicted human exposure after a single eye treatment at the recommended clinical dose *[see Animal Data]*.

Animal reproduction studies are not always predictive of human response, and it is not known whether ranibizumab can cause fetal harm when administered to a pregnant woman. Based on the anti-VEGF mechanism of action for ranibizumab *[see Clinical Pharmacology (12.1 in the full prescribing information)]*, treatment with LUCENTIS may pose a risk to human embryofetal development.

LUCENTIS should be given to a pregnant woman only if clearly needed.

Data
Animal Data
An embryo-fetal developmental toxicity study was performed on pregnant cynomolgus monkeys. Pregnant animals received intravitreal injections of ranibizumab every 14 days starting on Day 20 of gestation, until Day 62 at doses of 0, 0.125, and 1 mg/eye. Skeletal abnormalities including incomplete and/or irregular ossification of bones in the skull, vertebral column, and hindlimbs and shortened supernumerary ribs were seen at a low incidence in fetuses from animals treated with 1 mg/eye of ranibizumab. The 1 mg/eye dose resulted in trough serum ranibizumab levels up to 13 times higher than predicted C_{max} levels with single eye treatment in humans. No skeletal abnormalities were seen at the lower dose of 0.125 mg/eye, a dose which resulted in trough exposures equivalent to single eye treatment in humans. No effect on the weight or structure of the placenta, maternal toxicity, or embryotoxicity was observed.

8.2 Lactation
Risk Summary
There are no data available on the presence of ranibizumab in human milk, the effects of ranibizumab on the breastfed infant or the effects of ranibizumab on milk production/excretion.

Because many drugs are excreted in human milk, and because the potential for absorption and harm to infant growth and development exists, caution should be exercised when LUCENTIS is administered to a nursing woman.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for LUCENTIS and any potential adverse effects on the breastfed child from ranibizumab.

8.3 Females and Males of Reproductive Potential
Infertility
No studies on the effects of ranibizumab on fertility have been conducted and it is not known whether ranibizumab can affect reproduction capacity. Based on the anti-VEGF mechanism of action for ranibizumab, treatment with LUCENTIS may pose a risk to reproductive capacity.

8.4 Pediatric Use
The safety and effectiveness of LUCENTIS in pediatric patients have not been established.

8.5 Geriatric Use
In the clinical studies, approximately 76% (2449 of 3227) of patients randomized to treatment with LUCENTIS were ≥ 65 years of age and approximately 51% (1644 of 3227) were ≥ 75 years of age *[see Clinical Studies (14 in the full prescribing information)]*. No notable differences in efficacy or safety were seen with increasing age in these studies. Age did not have a significant effect on systemic exposure.

10 OVERDOSAGE
More concentrated doses as high as 2 mg ranibizumab in 0.05 mL have been administered to patients. No additional unexpected adverse reactions were seen.

17 PATIENT COUNSELING INFORMATION
Advise patients that in the days following LUCENTIS administration, patients are at risk of developing endophthalmitis. If the eye becomes red, sensitive to light, painful, or develops a change in vision, advise the patient to seek immediate care from an ophthalmologist *[see Warnings and Precautions (5.1)]*.

LUCENTIS®
[ranibizumab injection]
Manufactured by:
Genentech, Inc.
A Member of the Roche Group
1 DNA Way
South San Francisco, CA
94080-4990

Initial US Approval: June 2006
Revision Date: M-US-00002319(v1.0) 2019

LUCENTIS®
RANIBIZUMAB INJECTION

STRENGTH IN VISION

LUCENTIS has been extensively studied and FDA approved in 5 retinal indications.

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*.[1-10]

REFERENCES: 1. Rosenfeld PJ, et al; MARINA Study Group. *N Engl J Med*. 2006;355:1419-1431. **2.** Brown DM, et al; ANCHOR Study Group. *Ophthalmology*. 2009;116:57-65. **3.** Busbee BG, et al; HARBOR Study Group. *Ophthalmology*. 2013;120:1046-1056. **4.** Regillo CD, et al; PIER Study Group. *Am J Ophthalmol*. 2008;145:239-248. **5.** Brown DM, et al; RISE and RIDE Research Group. *Ophthalmology*. 2013;120:2013-2022. **6.** Data on file. Genentech, Inc. South San Francisco, CA. **7.** Campochiaro PA, et al; BRAVO Investigators. *Ophthalmology*. 2010;117:1102-1112. **8.** Brown DM, et al; CRUISE Investigators. *Ophthalmology*. 2010;117:1124-1133. **9.** Nguyen QD, et al; RISE and RIDE Research Group. *Ophthalmology*. 2012;119:789-801. **10.** Ho AC, et al; HARBOR Study Group. *Ophthalmology*. 2014;121:2181-2192.

Genentech
A Member of the Roche Group