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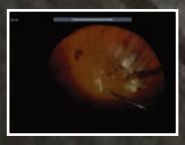
FIFTH ANNUAL PIPELINE REPORT

NEW ENTRIES EXCEED EXITS

A review of 66 candidates in clinical trials, including gene therapies, agents for inherited retinal diseases and biosimilars. *Page 18*



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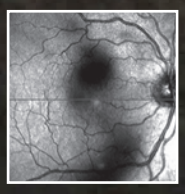

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THE PRE-LESION–WHERE COMPLEMENT OVERACTIVATION IS CAUSING THE NEXT WAVE OF DESTRUCTION IN GEOGRAPHIC ATROPHY[1,2]

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EDITORIAL

By Charles C. Wykoff, MD, PhD

2022: Banner year for clinical trials

Despite the pandemic upending our lives in countless ways, U.S. clinical trial enrollment accelerated through 2021, with many trials closing earlier than anticipated. Never before has a year dawned holding so many anticipated, important new data releases in our space, each with the potential to meaningfully impact how we manage patients.

In neovascular age-related macular degeneration, we'll see primary outcome data from DAZZLE, the Phase III noninferiority trial in which aflibercept is being compared to the anti-VEGF antibody biopolymer conjugate KSI-301 (Kodiak Sciences) given every 12, 16 or 20 weeks (there's no eight-week arm) after three loading doses. Second, the ARCHWAY Phase III trial of the recently approved Susvimo port-delivery system (Genentech/Roche) will yield two-year data.

In geographic atrophy, we'll see two-year data from the pegcetacoplan (Apellis) Phase III DERBY and OAKS trials, and one-year data from the Phase III GATHER2 trial of Zimura (avacincaptad, IVERIC bio).

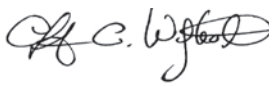
In addition, two therapeutics with multiple programs are expected to bear fruit. We will see data from the high-dose aflibercept 8 mg (Regeneron Pharmaceuticals) Phase III programs in both nAMD (PULSAR) and diabetic macular edema (PHOTON).

Finally, it will be a busy year for the recently approved Vabysmo (faricimab-svoa, Genentech/Roche). In addition to two-year data from the nAMD and DME Phase III programs (TENAYA and LUCERNE; YOSEMITE and RHINE), we may see data from the Phase III BALATON and CAMINO trials in retinal vein occlusion as well.

Beyond this alphabet soup of pivotal trials, there are a plethora of Phase I and II trials expected to produce new data, including multiple trials of gene therapy delivered by intravitreal, suprachoroidal or subretinal approaches, optogenetics programs, numerous tyrosine kinase inhibitor programs, and multiple drugs with completely novel mechanisms of action and unique delivery routes, such as oral, sub-cutaneous and drop formulations.

Consider communicating to your patients the breadth of ongoing, promising retina research. For patients with untreatable pathologies such as GA, hearing cautiously optimistic perspectives that new therapeutics that could slow their disease are in late-stage trials may give them a refreshing ray of hope. For patients receiving repeated injections, awareness of programs evaluating therapeutics with meaningfully increased durability may motivate them to hang in there until next-generation pharmacotherapies are available.

This year will witness several meaningful clinical trial readouts. I look forward to continuing to move our space forward with you, together.



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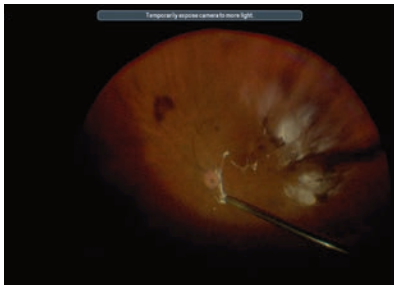

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Is Vabysmo the next $1 billion anti-VEGF?

With the Food and Drug Administration approval of what's now known as Vabysmo, retina specialists have the option of an intravitreal agent for neovascular age-related macular degeneration and diabetic macular edema that targets two disease pathways and can extend treatment intervals out to four months.

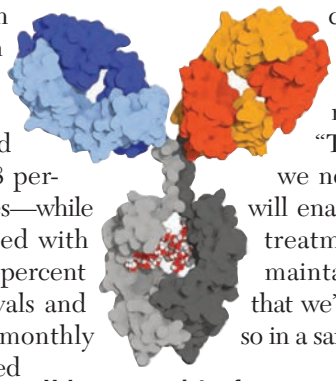
The approval of faricimab-svoa—formerly just faricimab—came days after the publication of one-year results from four Phase III trials.[1,2] Genentech says Vabysmo will be available in the United States "in the coming weeks." The London analytics firm Clarivate reports that Vabysmo is projected to have more than $1 billion in annual sales.

Faricimab is what's known as a bispecific antibody. That is, it targets two key pathways that contribute to retinal disease: vascular endothelial growth factor-A—the same VEGF complement that aflibercept (Eylea, Regeneron Pharmaceuticals) targets—and angiopoietin-2 (Ang-2).

Trial results

In nAMD, 45 percent of faricimab-treated patients between the TENAYA and LUCERNE trials[1] received treatment every 16 weeks after four monthly loading doses, one third continued with 12-week dosing and the rest every eight-week dosing.

In DME, more than half the patients in the YOSEMITE and RHINE studies combined[2] were treated every 16 weeks—51.8 percent across both studies—while 20.5 percent continued with 12-week dosing, 15.5 percent had eight-week intervals and 12 percent were on monthly dosing. The studies used two faricimab dosing intervals: up to 16 weeks after four monthly loading doses using a treat-and-extend approach; and eight-week intervals after six monthly loading doses.



Vabysmo consists of one molecule with two active arms: an anti-VEGF-A fragment antibody (Fab) (blue) and an anti-Ang-2 Fab (orange and red). The optimized fragment (gray) has no effective agent.

Jeffrey S. Heier, MD, lead author of the TENAYA and LUCERNE results, says faricimab potentially meets the need for extended treatment duration. "The treatment burden is something that we've all understood for 15 years now since the first approvals of anti-VEGF beginning with pegaptanib, but then continuing with the stronger anti-VEGFs ranibizumab and aflibercept," he says.

"But there's always been this challenge to maintain maximum benefit with a minimum of visits to the clinic; to minimize the treatment burden while maximizing the treatment benefit," he says. "The hope is here that we now have an agent that will enable us to extend those treatment intervals but still maintain the same benefits that we've seen to date and do so in a safe manner." Dr. Heier is copresident and medical director of Ophthalmic Consultants of Boston.

Targeting Ang-2

Charles C. Wykoff, MD, PhD, lead author of the YOSEMITE and RHINE report, explains the importance of targeting Ang-2, which neutralizes the vasoprotective effects of the Ang-1 and Tie2 signaling pathway. "There's a great deal of basic science data to support that activation of Tie2 transmembrane receptor tyrosine kinase receptor can bring additional value that's separate from inhibition of VEGF," he says.

"The approach now that has been

IN BRIEF

RegenxBio has initiated ASCENT, the second of two Phase III pivotal trials to of its potential one-time subretinal gene therapy candidate **RGX-314** for neovascular age-related macular degeneration. The primary trial endpoint is noninferiority to aflibercept based on improvement in visual acuity. The trial will enroll around 465 patients.

Nanoscope Therapeutics has received Investigational New Drug (IND) clearance from the Food and Drug Administration to begin a Phase II trial of its **MCO-010** ambient-light activatable optogenetic monotherapy to restore vision in Stargardt disease.

Applied Genetic Technologies Corp. reports exceeding the enrollment target in the SKYLINE Phase I/II trial of **AGTC-501**, a recombinant adeno-associated virus vector-based gene therapy for X-linked retinitis pigmentosa (XLRP). Fourteen patients have been enrolled; the planned target enrollment was 12.

The FDA has granted Fast Track Designation to **4D Molecular Therapeutics'** gene therapy candidate **4D-125** to treat inherited retinal dystrophies due to defects in the *RPGR* gene, including XLRP.

The FDA has accepted the IND application for **Ocugen** to start a clinical trial of **OCU400** (AAV-NR2E3), a modifier gene therapy candidate for retinitis pigmentosa.

validated with the Phase III trials is to inhibit angiopoietin-2, which then subsequently translates into activation of the TI2 receptor," Dr. Wykoff adds. He's chief medical editor of Retina Specialist, partner in Retina Consultants of Texas and deputy chair of ophthalmology at the Blanton Eye Institute, Houston Methodist Hospital.

Both Dr. Heier and Dr. Wykoff disclosed relationships with Genentech/Roche. F. Hoffmann-La Roche sponsored the trials.

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Study elucidates HCQ retinopathy risk

In the first year of the COVID-19 pandemic, hydroxychloroquine received a lot of attention for its purported therapeutic effects for treating the disease. However, it has long been used in rheumatology, and retina specialists have been well aware of its vision-threatening side effects.

Now researchers have potentially quantified the risks for retinopathy in patients taking HCQ for systemic lupus erythematosus and other rheumatoid disease. "We found that the HCQ dose relative to body weight was the major risk factor for the development of retinopathy and there was a dose-response relationship," April Jorge, MD, said at the American College of Rheumatology virtual meeting in November. She presented results of a case-control study of 4,899 patients who had been on HCQ for five years or longer.[1]

Dr. Jorge, a rheumatologist at Massachusetts General Hospital and an instructor at Harvard Medical School in Boston, said the odds of retinopathy were lowest for patients on ≤ 4 mg/kg HCQ daily, were higher in those using 5 to 6 mg/kg a day, and highest with ≥ 6 mg/kg a day.

"We also found that longer duration of use was another major risk factor contributing to retinopathy risk," Dr. Jorge said. "For every five years of use, the risk doubled."

Other significant risk factors were chronic kidney disease and Asian ancestry. The latter, Dr. Jorge said, came with a higher prevalence of the atypical pericentral pattern retinopathy that can be more difficult to detect.

The study evaluated a population of patients in the Kaiser Permanente Northern California system who had been on continuous HCQ therapy for at least five years between 1997 and 2020 and had regular retinopathy screenings after five years of therapy. In all, 164 had developed HCQ retinopathy—an incidence of 3.3 percent. Most cases (n=100) were mild, but 38 were moderate and 26 severe. A parafoveal pattern was noted in 131 and a pericentral pattern in 33.

"With regular screening, the majority of these cases are mild and therefore asymptomatic," Dr. Jorge said. Patients with additional risk factors need closer monitoring and dose adjustment, she said.

"The risk of HCQ retinopathy really needs to be weighed against the benefits of this medication," she said.

Dr. Jorge has no disclosures.

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1. Jorge A, Melles R, Conell C, et al. Risk factors for hydroxychloroquine retinopathy and its subtypes–prospective adjudication analysis of 4,899 incident users. Paper presented at virtual American College of Rheumatology Convergence 2021; November 7, 2021.

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Vision loss tied to cancer history

How imaging helped diagnose the cause of vision problems in a woman with endometrial adenocarcinoma.

By Meera D. Sivalingam, MD, and Jason Hsu, MD

Meera D. Sivalingam, MD

Jason Hsu, MD

A 69-year-old female was referred to our retina clinic for evaluation of floaters and blurred vision in both eyes for two weeks. Her medical history was significant for endometrial adenocarcinoma diagnosed 18 months earlier.

Work-up and imaging

Her visual acuity was 20/80 OD and 20/70 OS. Intraocular pressures were normal bilaterally. Her anterior segment exam revealed 1+ nuclear sclerosis in both eyes. Anterior chambers were quiet bilaterally. Fundus examination was significant for 1+ vitreous cell. The macula was flat.

Marked arterial and venous sheathing was present in the periphery OU (*Figure 1*). Optical coherence tomography showed marked loss of the ellipsoid zone as well as significant loss of laminations of the outer plexiform and outer nuclear layers (*Figure 2*). Fundus autofluorescence revealed hyperautofluorescence of the posterior pole with mottled areas of hypoautofluorescence throughout the macula, as well as perivascular hyperautofluorescence OU (*Figure 3*).

Fluorescein angiogram showed mildly delayed arterial-venous transit time and peripheral nonperfusion OU. The left eye demonstrated a few small focal areas of periarterial leakage (*Figure 4, page 17*). Full-field electroretinogram (ERG) was isoelectric in the scotopic, combined flash, single flash photopic and 30-hertz flicker stimuli, consistent with marked rod and cone dysfunction. Humphrey visual field 24-2, Stim V revealed diffuse depression OU.

Magnetic resonance imaging of the brain and orbits with and without contrast was within normal limits.

Additional history and diagnosis

The patient was diagnosed with endometrial adenocarcinoma in October 2020. She received neoadjuvant chemotherapy with carboplatin and paclitaxel with surgical resection in March 2021. In May 2021, the patient received one cycle of pembrolizumab.

Given the patient's medical history and imaging findings, we diagnosed cancer-associated retinopathy (CAR).

Follow-up

The patient received sub-Tenon's triamcinolone injections in both eyes and was started on prednisolone acetate q.i.d. After discussion with her oncologist, she was started on prednisone 60 mg PO daily with calcium/vitamin D supplementation.

At two-week follow-up, the patient's VA declined to 20/200 OU. We discussed escalating immunotherapies, including rituximab, intravenous immunoglobulin

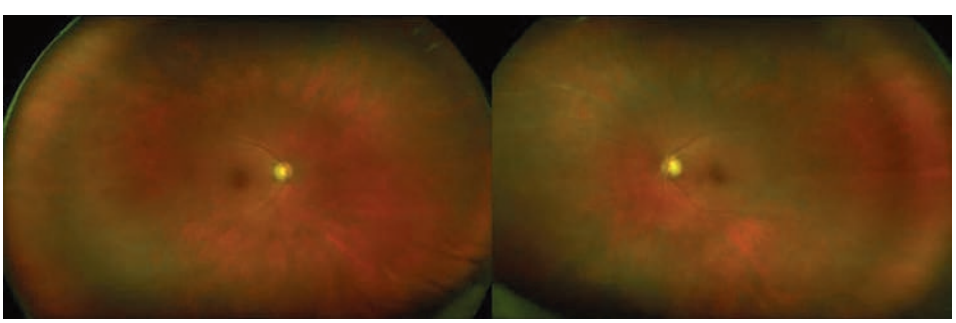

Figure 1. Color photography demonstrated marked arterial and venous sheathing in both eyes.

Bios

Dr. Sivalingam is a first-year vitreoretinal surgery fellow at Mid Atlantic Retina.

Dr. Hsu is with Mid Atlantic Retina/Retina Service, Wills Eye Hospital, Philadelphia.

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

(IVIg) and plasmapheresis (Plex) with her oncologist. The patient received five treatments of Plex on an every-other-day basis, followed by four weekly rituximab infusions.

VA at a three-month follow-up improved to 20/30 OD and 20/50 OS. However, at the four-month follow-up, the patient noted subjective decreased vision with a visual acuity of 20/50 OD and 20/70 OS. She received another course of Plex and rituximab. Unfortunately on follow-up one month later, her VA declined to light perception OU.

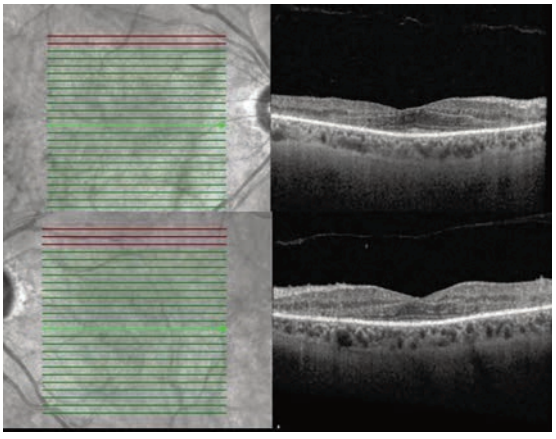

Figure 2. Optical coherence tomography showed marked loss of the ellipsoid zone outside the foveal center as well as significant loss of laminations of the outer plexiform and outer nuclear layers.

Features of CAR

CAR is one member of a spectrum of autoimmune retinopathies. This spectrum can be divided into neoplastic and non-neoplastic entities. Neoplastic entities include CAR and melanoma-associated retinopathy (MAR). CAR was first described by Ralph Sawyer, MD, and colleagues in 1976.[1] The pathogenesis of CAR occurs when tumor-associated antigens trigger production of autoantibodies that cross-react with retinal antigens, leading to retinal degeneration.[2]

CAR affects women twice as frequently as men, whereas MAR more commonly affects men.[3] Patients are most commonly affected in their fifth or sixth decade of life.

Small-cell carcinoma is the most commonly associated malignancy, followed by breast, uterine and cervical carcinoma.[4] The interval between diagnosis of malignancy and onset of visual symptoms varies. Visual symptoms typically precede the cancer diagnosis. Antirecoverin and antienolase antibodies are among the most frequently identified autoantibodies.[5] Recoverin is a protein present in photoreceptors involved in light and dark adaptation. Antienolase antibodies have been associated with breast and prostate cancer.[6]

Patients typically present with bilateral, subacute vision loss, scotomas, photopsias and nyctalopia.[7] There's no consensus on diagnostic criteria. The presence of autoimmune retinal antibodies isn't required, nor is it diagnostic, because they can be present in unaffected patients.

Fundus autofluorescence imaging can show stippled hyperautofluorescence in the posterior pole. Spectral-domain OCT

(Continued on page 17)

Patients with cancer-associated retinopathy typically present with bilateral, subacute vision loss, scotomas, photopsias and nyctalopia. There's no consensus on diagnostic criteria.

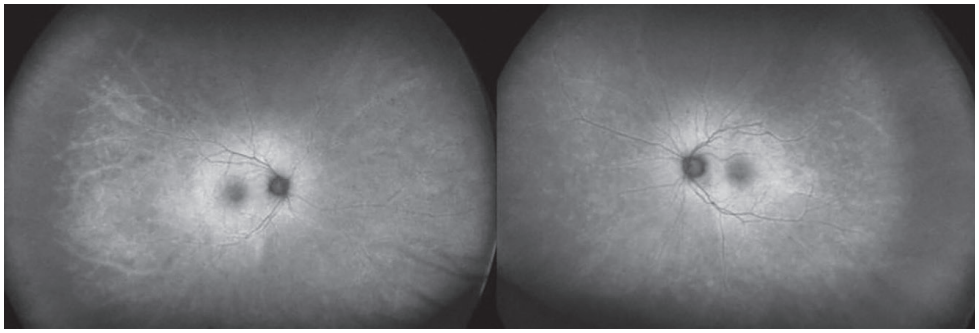

Figure 3. Fundus autofluorescence revealed hyperautofluorescence of the posterior pole with mottled areas of hypoautofluorescence throughout the macula as well as perivascular hyperautofluorescence in both eyes.

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

Uveitis risk of ICPIs for cancer

Immune checkpoint inhibitors are becoming more widely available, but they've been linked to uveitis in some patients.

By Alexander R. Shusko, MD, and Edmund Tsui, MD

Alexander R. Shusko, MD

Edmund Tsui, MD

Oncologic immunotherapies continue to be developed and transform the management choices of multiple types of cancer. Immune checkpoint inhibitors are a class of immunotherapy that disinhibits T-cells to promote the detection and elimination of abnormal host cells. The aim is to increase the antitumor response, but they also may cause systemic and ocular autoimmune side effects known as immune-related adverse events, or IRAEs.

There are seven approved immune checkpoint inhibitors (ICPIs) in the United States (*Table*). These medications target three different checkpoints:

- cytotoxic T-lymphocyte-associated protein 4 (CTLA-4);
- programmed cell death protein 1 (PD-1); and
- programmed death ligand 1 (PD-L1).

ICPIs are used for many types of cancers, but primarily for metastatic melanoma. Off-label uses for other types of cancers are starting to emerge as ICPIs become more widely available.

Ocular IRAEs

IRAEs in the eye most commonly affect the ocular surface, manifesting as conjunctivitis, episcleritis, scleritis, keratitis, corneal graft rejection and dry-eye syndrome.[1,2] Orbital complications include myasthenia gravis, exacerbation of thyroid ophthalmopathy, thyroid-like ophthalmopathy, cranial nerve palsies and myopathy.

ICPI-associated uveitis (ICPIU) is becoming more recognized with the increasing publication of case reports and case series. Figures 1 and 2 demonstrate examples of uveitis in patients undergoing treatment with ICPIs. The incidence of IRAEs with use of ICPIs was 1.2 percent in a large database study.[3] These authors noted a higher rate of ICPIU in patients with melanoma than other types of cancer.

ICPIU was more common with CTLA-4 inhibitors (ipilimumab) than other medication classes. Patients with a history of uveitis had higher rates of ICPIU. Patients affected by ICPIU were disproportionately Caucasian (82 percent), a disparity that may be due to the high prevalence of melanoma, the most common indication for ICPIs, in Caucasians.[4,5]

Characteristics of ICPIU

A literature review last year of 126 ICPIU cases reported that anterior uveitis was the most common type (37.7 percent)

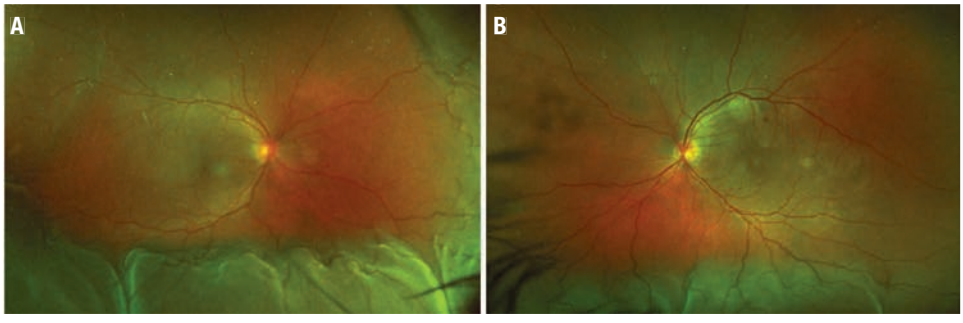

Figure 1. Posterior uveitis with choroidal effusions in a patient treated with a ipilimumab-nivolumab combination. A) Ultra-widefield color fundus photograph of the right eye shows choroidal effusion inferiorly, nasally, and temporally as well as subretinal fluid in the macula. B) Color photograph of the left eye also reveals an inferior choroidal effusion and macula-involving subretinal fluid. (*Adapted from Dow ER, et al. Ocul Immunol Inflamm. 2022;29:203-211. Used with permission*)

Bios

Dr. Shusko is a uveitis fellow at the Jules Stein Eye Institute, University of California Los Angeles.

Dr. Tsui is an assistant professor of ophthalmology in the uveitis service at the Jules Stein Eye Institute, David Geffen School of Medicine at UCLA.

DISCLOSURES: Dr. Shusko has no financial disclosures.

Dr. Tsui is a consultant for Kowa Company and EyePoint Pharmaceuticals.

followed by panuveitis (34 percent) and posterior uveitis (25.7 percent).[6] Intermediate uveitis (0.01 percent) was rarely reported. Most ICPIU cases followed these distribution patterns except in two cases.

Combination ipilimumab/nivolumab had an increased incidence of anterior uveitis (52.8 percent). Atezolizumab had no incidence of anterior uveitis, but it did have increased rates of posterior uveitis (80 percent). More specifically, IRAEs associated with atezolizumab were described as resembling acute macular neuroretinopathy (AMN) or paracentral acute middle maculopathy (PAMM) with retinal vasculitis or venulitis. No other ICPIs had a presentation like AMN or PAMM.

Vogt-Koyanagi-Harada-like disease was seen in 35 percent of patients who presented with panuveitis. The association between VKH disease and melanoma has been well-described.[7-11] An analysis of 48 cases of ICPIU presenting as VKH-like posterior inflammation showed the most common cancer association was melanoma (79 percent).[12]

Forty-four percent of VKH-like cases were associated with pembrolizumab, 23 percent with ipilimumab and 17 percent with nivolumab. Cases of VKH-like panuveitis were noted to have prodromal malaise and headache, serous retinal detachments, hearing loss, vitiligo and/or poliosis. Cross-reactivity between retinal and melanoma antigens may play a role in ICPIU.

Risk factors and management

A literature review of 40 patients found that the primary indication for ICPIs was lung cancer,[12] countering the studies that stated melanoma was the primary association. Patients with a history of ocular trauma, ocular surgery or use of pembrolizumab were more likely to experience intraocular inflammation.

Currently, the literature on ICPIU consists of only case reports, case series and survey studies. No standard recommendation exists for treatment of ICPIU.

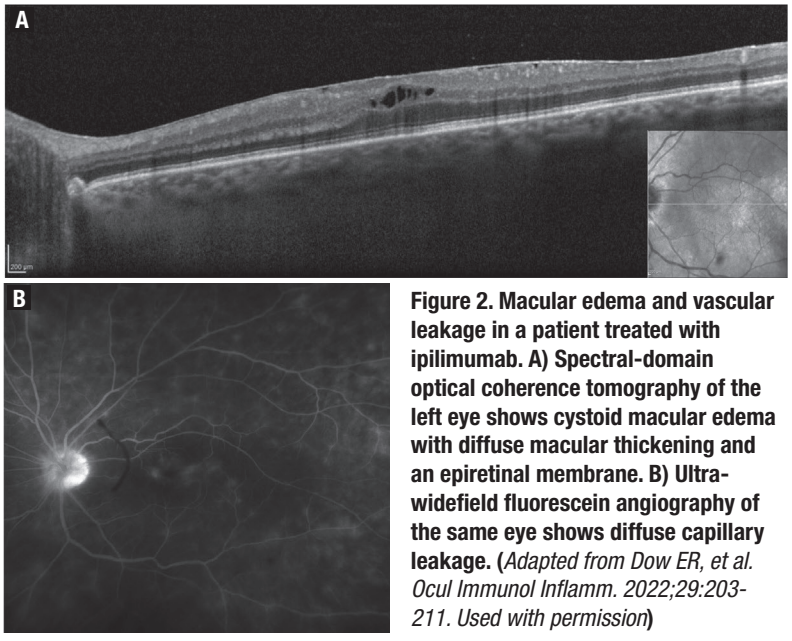

Figure 2. Macular edema and vascular leakage in a patient treated with ipilimumab. A) Spectral-domain optical coherence tomography of the left eye shows cystoid macular edema with diffuse macular thickening and an epiretinal membrane. B) Ultra-widefield fluorescein angiography of the same eye shows diffuse capillary leakage. (*Adapted from Dow ER, et al. Ocul Immunol Inflamm. 2022;29:203-211. Used with permission***)**

The most common treatment uses topical steroids. In a review of 49 ICPIU cases, 27 patients received topical steroids only, with resolution of the uveitis in most cases.[13] Topical steroids used included prednisolone acetate 1% and difluprednate 0.05%. Dosing frequency ranged from q.i.d. to hourly. Nine cases were treated with periocular steroid injections with or without topical steroids; the results were similar. Triamcinolone and dexamethasone were the most used periocular injections.

Thirteen patients received oral or intra-

(Continued on page 15)

Approved immune checkpoint inhibitors

Mechanism of action	Generic name	Trade name
CTLA-4 inhibitor	Ipilimumab	Yervoy (Bristol Myers Squibb)
PD-1 inhibitor	Pembrolizumab	Keytruda (Merck)
	Cemiplimab	Libtayo (Regeneron/Sanofi Genzyme)
	Nivolumab	Opdivo (Bristol Myers Squibb)
PD-L1 inhibitor	Atezolizumab	Tecentriq (Genentech/Roche)
	Avelumab	Bavencio (EMD Serono/ Pfizer)
	Durvalumab	Imfinzi (AstraZeneca)

WHAT ANATOMIC RESULTS COULD HE SEE THIS YEAR?

Of 134 patients treated in a DR clinical trial

80% SAW A ≥2-STEP DRSS IMPROVEMENT[1]

EYLEA®
(aflibercept) Injection
For Intravitreal Injection

Inspired by a real patient with DR.

PANORAMA study design: Multicenter, double-masked, controlled clinical study in which patients with moderately severe to severe NPDR (ETDRS-DRSS: 47 or 53) without CI-DME (N=402; age range: 25-85 years, with a mean of 56 years) were randomized to receive 1 of 2 EYLEA dosing regimens or sham. Protocol-specified visits occurred every 28±7 days for the first 5 visits, then every 8 weeks (56±7 days). During Year 2 (Weeks 52-96), patients randomized to one of the EYLEA arms received a different dosing regimen.[1]

IMPORTANT SAFETY INFORMATION

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 within 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.

STARTING EYLEA EARLIER MAY HELP PREVENT DR PROGRESSION

Primary Endpoint (Year 1)		Secondary Endpoint (Year 1)	
Proportion of patients with a ≥2-step DRSS improvement[1,2,*]		Reduction in the risk of developing PDR or ASNV or CI-DME[2,*,†]	
EYLEA Q8 (n=134)	EYLEA Q16 (n=135)	EYLEA Q8 (n=134)	EYLEA Q16 (n=135)
80% vs 15% in the sham group (n=133)	**65%** vs 15% in the sham group (n=133)	**79% Risk Reduction** **Event rate:** 11% vs 42% in the sham group (n=133)	**82% Risk Reduction** **Event rate:** 10% vs 42% in the sham group (n=133)

P<0.01 vs sham.

- The recommended dose for EYLEA in DR is 2 mg (0.05 mL) administered by intravitreal injection Q4 (≈every 28 days, monthly) for the first 5 injections, followed by 2 mg Q8 (every 2 months)[1]
- Although EYLEA may be dosed as frequently as 2 mg Q4 (≈every 25 days, monthly), additional efficacy was not demonstrated in most patients when EYLEA was dosed Q4 compared with Q8. Some patients may need Q4 (monthly) dosing after the first 20 weeks (5 months)[1]

*Full analysis set.
†Event rate was estimated using the Kaplan-Meier method. Composite endpoint of developing PDR, ASNV was diagnosed by either the reading center or investigator.

SEE WHAT EYLEA COULD DO FOR YOUR PATIENTS WITH DR AT HCP.EYLEA.US

anti-VEGF; anti–vascular endothelial growth factor; ASNV, anterior segment neovascularization; CI-DME, central-involved Diabetic Macular Edema; ETDRS-DRSS, Early Treatment Diabetic Retinopathy Study–Diabetic Retinopathy Severity Scale; PDR, proliferative diabetic retinopathy; Q4, every 4 weeks; Q8, every 8 weeks; Q16, every 16 weeks.

WARNINGS AND PRECAUTIONS (continued)

- 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.

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.
- Patients may experience temporary visual disturbances after an intravitreal injection with EYLEA and the associated eye examinations. Advise patients not to drive or use machinery until visual function has recovered sufficiently.

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.** Wykoff CC. Intravitreal aflibercept for moderately severe to severe non-proliferative diabetic retinopathy (NPDR): 2-year outcomes of the phase 3 PANORAMA study. Data presented at: Angiogenesis, Exudation, and Degeneration Annual Meeting; February 8, 2020; Miami, FL.

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

03/2021
EYL.21.02.0049

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 patients with:

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 central retinal vein occlusion (CRVO) in 2 clinical studies (COPERNICUS and GALILEO) and 91 patients following branch retinal vein occlusion (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.20.09.0052

venous steroids along with local therapy. The indication for initiating systemic steroids was ICPIU in eight of the 13 cases. ICPIs were discontinued in 18 cases, but only nine of them were due to ICPIU.

One case of nivolumab-associated ICPIU that was successfully treated with frequent topical steroids developed CME that required intravitreal triamcinolone.[14] The patient required an additional intravitreal triamcinolone treatment eight months after discontinuation of nivolumab. Cases have reported methotrexate use, but very few reports of steroid-sparing immunomodulatory agents for the treatment of ICPIU have been published.[11]

Framework for treatment

A recently published case series with a review of guidelines from the European Society of Medical Oncology and American Society of Clinical Oncology provides a framework for ICPIU treatment.[15] They reported eight cases of ocular IRAEs, including five cases of anterior uveitis and one of intermediate uveitis.

Each case of anterior uveitis was successfully managed with topical steroids alone while the patients continued ICPI treatment. The case of intermediate uveitis required oral prednisone and discontinuation of pembrolizumab. The patient was rechallenged with ipilimumab but had to abort therapy after two cycles due to severe colitis. The patient's metastatic disease had remained stable for 14 months at the time of publication.

Patients on ICPIs who experience ocular symptoms should be referred to an ophthalmologist early for further testing to grade the severity of the IRAEs. Both treatment of uveitis and ICPI use should be evaluated on an individual patient basis. Often, depending on the severity of the inflammation, local therapy may be sufficient to control it without stopping ICPI or using systemic corticosteroids. A multidisciplinary approach to managing ocular IRAEs should be weighed with the benefit of continuing the ICPI therapies.

Bottom Line

We're learning more about the immune-related adverse effects of immune checkpoint inhibitors as case reports and case series emerge. Ocular side effects most commonly involve the ocular surface, but ICPIU is a concern for patient morbidity.

Depending on the severity and response of the uveitis, topical or systemic steroids may be sufficient while continuing the ICPI. Any decision to suspend or discontinue ICPIs must involve the oncologist and ophthalmologist because these drugs may extend patient survival. RS

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Patients on immune checkpoint inhibitors who have ocular symptoms should be referred to an ophthalmologist early for further testing to grade the severity of the immune-related adverse events.

Strategies for PVD induction

A review of surgical methods to aid in posterior vitreous detachment induction.

By Tamara L. Lenis, MD, PhD, M. Abdallah Mahrous, MD, and Donald J. D'Amico, MD

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DISCLOSURES: Dr. Lenis and **Dr. Mahrous** have no relevant disclosures.

Dr. D'Amico is a consultant to Alcon.

Dr. Hahn is a conslutant to DORC.

The creation of a posterior vitreous detachment is critical in pars plana vitrectomy for most macular vitreoretinal interface disorders and retinal detachments. However, PVD induction can be a challenging surgical step in young patients as well as in older patients with particularly adherent posterior hyaloid or abnormal vitreoretinal interface.

Failure to successfully induce PVD can result in poor surgical outcomes such as persistent macular holes and proliferative vitreoretinopathy. Here, we review a variety of surgical methods that can be employed to aid in PVD induction.[1]

'Staining' vitreous

Enhancing visualization of the vitreous with intravitreal agents such as triamcinolone can help you see that the vitreous cutter (or soft-tip) is continuously engaging with the posterior hyaloid on aspiration. This is particularly useful to confirm that the cutter isn't above the hyaloid face, but, instead, is at an edge or below an edge (in a plane between the hyaloid and retina) allowing you to efficiently aspirate and then lift the hyaloid.

Lack of internal limiting staining with vital dyes such as Brilliant Blue G (DORC) can also often indicate when the posterior hyaloid has not been sufficiently elevated.

Soft-tipped cannula

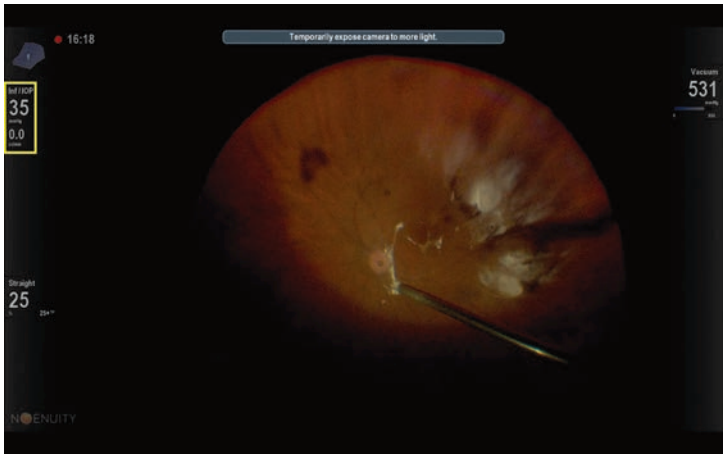
The use of a soft-tipped cannula can be an efficient alternative to the vitreous cutter, particularly if there's no obvious opening in the hyaloid face directly below the cutter. Often, if the "edge" can't be immediately found with the vitreous cutter, it may help to switch to the soft-tip to more directly engage with the posterior hyaloid.[2]

Sharp dissection of the hyaloid face

If needed, direct sharp dissection of the hyaloid face can also help to create a surgical opening in the posterior hyaloid, if one isn't already apparent. This technique has been described using a variety of instruments, including the diamond-dusted membrane scraper, micropick, microvitreoretinal blade and barbed needle.[3-6]

Visual cues on 3D heads-up display indicate occlusion

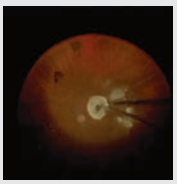
A built-in aid for PVD induction is to follow flow rates on the vitrectomy machine, taking advantage of the fact that the flow rate, often indicated adjacent to the set infusion pressure, will read near zero



A view of a posterior vitreous detachment using a soft-tipped cannula and the Ngenuity heads-up display (Alcon). Note the upper left inset (yellow box) indicates a flow rate of 0.0 cc/min when the instrument is completely occluded by the posterior hyaloid.

View the Video

Watch as Drs. Lenis and D'Amico use a vitreous cutter and soft-tipped cannula to aid in posterior vitreous detachment induction. Available at: https://bit.ly/VideoPearl_027



when the instrument is effectively occluded by the posterior hyaloid (*Figure*). This can be ascertained with an assistant giving verbal cues from a conventional display of any of the available vitrectomy platforms.

Alternatively, you can directly view the flow rate on a three-dimensional heads-up display (e.g., Ngenuity, Alcon). In inducing a PVD, when the flow rate drops to zero upon aspiration, simply remain in place while maintaining strong suction with the instrument port occluded for another two to three seconds; then elevation can begin.

A resumption of flow indicates a loss of suction, and the maneuver to reengage the hyaloid can be repeated as necessary. This technique allows you to more precisely and efficiently increase aspiration and lift the posterior hyaloid with confidence.

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Vision loss tied to cancer

(Continued from page 9)

commonly shows outer retinal loss and ellipsoid disruption.[2] Cystoid macular edema is also present in some cases. Full-field ERG can show variable abnormalities, depending on the degree of cone vs. rod function. Visual-field testing shows central or paracentral scotomas and constriction.[2]

Treatment

Visual deterioration in CAR can be severe. No standard treatment protocol exists. Treatment options include immunosuppression via systemic or local corticosteroids, including sub-Tenon's and intravitreal forms, as well as immunomodulatory therapy, including IVIg, plasmapheresis, cyclosporin, rituximab, infliximab, azathioprine and tocilizumab.[6]

The clinical course and therapy response are highly variable. Paramount in the discovery of CAR is a thorough systemic work-up and identification of the primary malignancy. Care of the retinopathy should be carefully coordinated with the patient's primary care physician and/or oncologist.

Bottom line

CAR is one entity in a complex category of autoimmune retinopathies that can have widely variable presentations. Careful examination in conjunction with ancillary testing is crucial for proper diagnosis. Co-management with the patient's primary care physician and oncologist is important to minimize morbidity and mortality.

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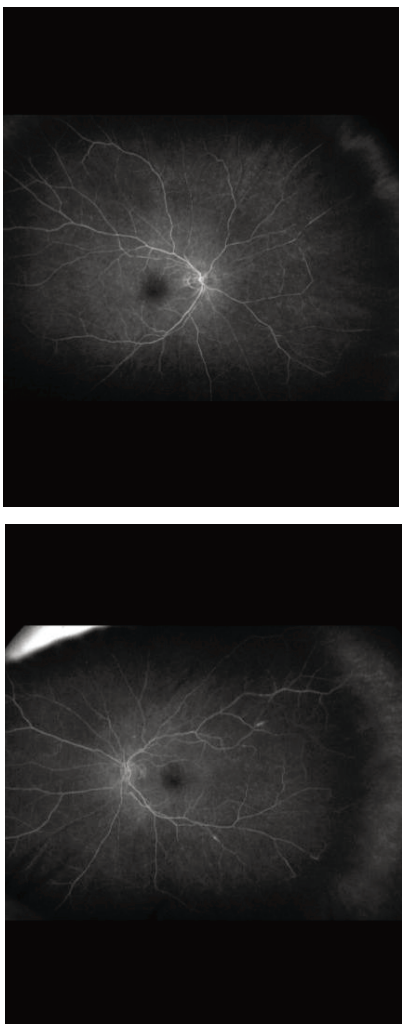

Figure 4. Fluorescein angiogram showed mildly delayed arterial-venous transit time and peripheral nonperfusion. The left eye (bottom) demonstrated a few small focal areas of periarterial leakage.

Fifth Annual Pipeline Report

New entries continue to exceed exits

Exits for discontinued programs (three over two years) exceed exits for approvals (two).

Richard Mark Kirkner
Editor

How the list was compiled

This listing was compiled from company press releases and regulatory filings, published reports in the literature, searches on ClinicalTrials.gov, and presentations at the American Academy of Ophthalmology Retina Subspecialty Day, American Society of Retina Specialists, Retina Society, Association for Research in Vision and Ophthalmology, EURETINA and the Ophthalmology Innovation Summit Retina Innovation Showcase. This year's listing includes investigational stem cell and gene therapies for exudative disease, gene therapies for exudative retinal disease, treatments for inherited retinal disorders and biosimilars.

By Richard Mark Kirkner

Take-home Points

- This year's listing includes 66 entries in four categories: biologics, steroids, cell therapies and light-activated treatments for exudative disease; gene therapies for exudative disease; treatments for inherited retinal disorders; and a new category for biosimilars.
- Ten new entries have been added to the primary and gene therapy and IRD lists, plus eight biosimilars not previously listed.
- Three candidates have been removed from the list, most notably Susvimo (Genentech/Roche), formerly known as the Port Delivery System with ranibizumab.

New investigative programs in retina have exceeded attrition over the past few years either because products were approved or programs discontinued. This year's version lists 58 programs, not including the eight biosimilar candidates. Last year's list had 51 entries.

Three exit the list

Notable exits since last year are brolucizumab (Beovu, Novartis), which was removed because it's already approved, although Novartis continues to pursue an additional indication for diabetic macular edema. The most notable is what was once called the Port Delivery System (PDS) with ranibizumab but, upon Food and Drug Administration approval last year, underwent a name change to Susvimo (Genentech/Roche).

Iconic Therapeutics' ICON-1 program in choroidal neovascularization has also been dropped. The company discontinued a Phase II trial last year to pursue a next-generation program for the same indication.

One approval remains on the list

One approval that happened earlier this year remains on the list, albeit under a new name: faricimab is now Vabysmo, the name Genentech/Roche adopted for the bispecific antibody upon its approval by the Food and Drug Administration. Because the approval came in January this year, and there are still meaningful Phase III trial readouts pending, it remains on our list.

New entries

One new entry on the main list is IBIf302 (Innovent Biologics), which has been reclassified from a gene therapy. The main list includes five other candidates that weren't listed last year: AR-13503 (Aerie Pharmaceuticals); ISTH0036 (Isarna Therapeutics); OCS-01 (Oculis); RBM-007 (Ribomic); and UBX1325 (Unity Biotechnology).

The list of gene therapy candidates for

exudative retinal disease includes one new entry: the dual transgene therapy 4D-150 (4D Molecular Therapeutics).

The listing of programs for inherited retinal disease includes four new entries: 4D-150 (again), but for X-linked retinitis pigmentosa; MCO-010 (Nanoscope Therapeutics) for Stargardt disease and RP; SAR439483 (Atsena Therapeutics) for Leber congenital amaurosis; and Visomitin (Mitotech) for Leber hereditary optic neuropathy.

This listing includes only therapies in human trials or soon to be in the clinic. It doesn't include preclinical candidates.

Abicipar pegol (Molecular Partners)

Last year, this was a collaborative venture with AbbVie. However, AbbVie pulled out, leaving Molecular Partners to pursue the candidate on its own. In 2020, the FDA issued a negative Complete Response Letter for abicipar pegol after the Phase III SEQUOIA (n=949, NCT02462486) and CEDAR (n=233, NCT02173496) trials reported high rates of intraocular inflammation (IOI)—15.1 and 15.7 percent in abicipar-treated patients compared with 0 to 0.6 percent in the ranibizumab comparator groups, respectively.[1]

Molecular Partners chief executive Patrick Amstutz expressed confidence in abicipar pegol after the separation from AbbVie, but the company hasn't reported any updates since. Both the SEQUOIA and CEDAR trials are listed as completed on ClinicalTrials.gov.

Aflibercept high dose (Regeneron Pharmaceuticals)

Ongoing pivotal trials are evaluating the 8-mg dose of aflibercept in DME (n=640, NCT04429503) and age-related eye disease (n=960, NCT04423718), using the standard 2-mg dose of Eylea as the comparator.

A separate Phase II trial (n=106, NCT04126317) in nAMD showed no new safety issues compared with the standard 2-mg dose. Regeneron reports that a higher proportion of patients in the aflibercept 8-mg group had no retinal fluid compared to patients in the 2-mg group, 43.4 vs. 26.4 percent (p=0.067) at week 16, at which point they had received three injections.

KST4290 (formerly ALK4290, Alkahest)

Alkahest completed a Phase IIb clinical trial, PHTHALO-205 (n=100, NCT04331730), last year, but results haven't yet been reported. The trial is evaluating visual acuity outcomes after three loading doses of aflibercept in treatment-naive nAMD patients.

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. Alkahest hasn't reported any updates in the past year.

ALK-001 (Alkeus Pharmaceuticals)

Recruiting ended last year in a Phase II/III trial (n=300, NCT03845582) of this oral modified form of vitamin A. ALK-001 aims to replace vitamin A and prevent formation of toxic vitamin A dimers in patients with geographic atrophy secondary to dry AMD. Alkeus is also pursuing concurrent trials in Stargardt disease.

NEW: ANX007 (Annexon Biosciences)

Annexon initiated the Phase II ARCHER trial in GA (n=240, NCT04656561) last spring. The trial is evaluating changes in GA area using monthly and bimonthly dosing. Intravitreal ANX007 is a monoclonal antibody antigen-binding fragment designed to bind to complement factor 1q and inhibit activation of all downstream components of the classical complement cascade, including complement factors 3 and 5, without disrupting their normal function in other complement pathways. ARCHER is scheduled for completion at the end of next year.

APX3330 (Ocuphire Pharma)

APX3330 is dosed at five 120-mg tablets daily. Results of five Phase II trials, presented at the American Academy of Ophthalmology, reported adverse events in fewer than 5 percent of study patients, a rate similar to placebo.[1] Ocuphire is pursuing the Phase IIb ZETA-1 trial in DME (n=100, NCT04692688).

AR-1105; NEW: AR-13503 (Aerie Pharmaceuticals)

Aerie is preparing a Phase III trial of AR-1105, the bioerodable intravitreal dexamethasone implant, in DME. Phase II results in patients with macular edema associated with retinal vein occlusion (n=49, NCT03739593) demonstrated improvements in best-corrected visual acuity and macular edema with an adverse event profile similar to other corticosteroids.[2]

Meanwhile, Aerie initiated a program to develop AR-13503, an implant of an active metabolite of netarsudil, a Rho-kinase/protein kinase inhibitor that would be an

(Continued on page 22)

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

Drug name (manufacturer)	Description/active agent
Abicipar pegol (Molecular Partners)	Designed ankyrin repeat protein (DARPin) therapy
Aflibercept high-dose (Regeneron Pharmaceuticals)	8-mg dose of anti-VEGF-A and anti-placental growth factor (PLGF) agent
AKST4290 (formerly ALK4290) (Alkahest)	Oral small-molecule CCR3 inhibitor
ALK-001 (Alkeus Pharmaceuticals)	Oral formulation of modified vitamin A
ANX007 (Annexon Biosciences)	Intravitreal antigen-binding fragment (Fab) to complement factor q1
APX3330 (Ocuphire Pharma)	Twice-daily oral treatment targets Ref-1 protein
AR-1105 (Aerie Pharmaceuticals)	Bioerodable dexamethasone implant
NEW: **AR-13503** (Aerie Pharmaceuticals)	Bioerodable netarsudil implant
AXT107 (AsclepiX Therapeutics)	Intravitreal self-forming gel depot peptide
CLS-AX (Clearside Biomedical)	Small-molecule tyrosine kinase inhibitor suspension for suprachoroidal injection
Conbercept (Chengdu Kanghong Biotechnology)	Recombinant fusion protein targeting VEGF-A and -B and PLGF
Elamipretide (Stealth BioTherapeutics)	Mitochondria-targeting cell-permeable peptide for subcutaneous injection
EYP-1901 (EyePoint Pharmaceuticals)	Bioerodable implant using vorolanib
FHTR2163 (RG6147, Genentech/Roche)	Anti-high-temperature requirement A-1 antibody
GB-102 (Graybug Vision)	Pan-VEGF antagonist sunitnib for intravitreal injection
GEM103 (Gemini Therapeutics)	Recombinant, human complement factor H (CFH)
IBI302 (Innovent Biologics)	Bispecific anti-VEGF and anti-complement recombinant human fusion protein.
IONIS-FB-LRx (Ionis Pharmaceuticals)	Antisense oligonucleotide inhibiting CFB
NEW: **ISTH0036** (Isarna Therapeutics)	Antisense targeting transforming growth factor-beta (TFG-ß) protein
KSI-301 (Kodiak Sciences)	Anti-VEGF bipolymer conjugate
LBS-008 (Belite Bio)	Oral small-molecule retinol binding protein (RBP4) specific antagonist
NGM621 (NGM Biopharmaceuticals)	Humanized IgG1 monoclonal antibody inhibiting CC3
NEW: **OCS-01** (Oculis)	Topical formulation of high-concentration, preservative-free dexamethasone.
ONS-5010/Lytenava (bevacizumab-vikg, Outlook Therapeutics)	Ophthalmic formulation of intravitreal bevacizumab
OpRegen (Lineage Cell Therapeutics)	Subretinally administered allogenic retinal pigment epithelium cells
OPT-302 (Opthea)	Anti-VEGF-C and -D
OTX-TKI (Ocular Therapeutix)	Hydrogel-based sustained-release intravitreal axitinib implant
PAN-90806 (PanOptica)	Topical agent targeting VEGFR-2
Pegcetacoplan (APL-1, Apellis)	CC3 inhibitor
NEW: **RBM-007** (Ribomic)	Oligonucleotide-based aptamer with anti-FGF2 (fibroblast growth factor 2) activity.
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
NEW: **UBX1325** (Unity Biotechnology)	Small-molecule B-cell lymphoma-extra large (Bcl-xL) inhibitor.
Vabysmo (faricimab, Genentech/Roche)	Anti-vascular endothelial growth facotr and anti-angiopoietin-2 bispecific antibody
Valeda Light Delivery System (LumiThera)	Light-delivery system using photobiomodulation
Xiflam (InflammX)	Oral small-molecule connexin43 hemichannel blocker
Xipere (Formerly CLS-TA, Clearside Biomedical)	Triamcinolone acetonide 40 mg/mL suspension for suprachoroidal injection
Zimura (iVERIC bio)	Avacincaptad pegol CFC5 inhibitor

	Indication	Status
	Neovascular age-related macular degeneration	Phase III SEQUOIA and CEDAR trials completed.
	nAMD	Phase II/III (n=640) and Phase III trial (n=960) in diabetic macular edema and nAMD ongoing. Interim results of Phase II trial reported. Due for completion this year.
	nAMD	Phase IIb trial (n=100) completed. Results are pending.
	Geographic atrophy secondary to dry AMD (also Stargardt)	Patient enrollment completed in Phase II/III trial (n=300). Study completion due in 2023.
	GA secondary to dry AMD (also glaucoma)	Phase II trial (n=240) initiated. Completion due in 2023.
	Nonproliferative diabetic retinopathy, proliferative DR	Phase II results reported. Phase IIb trial in DME pending.
	Macular edema associated with retinal vein occlusion	Phase II (n=49) results reported. Phase III trial in preparation.
	nAMD, DME	Phase I (n=18) trial advanced to Stage 2.
	DME	Enrollment initiated in Phase I/IIa trial (n=18).
	nAMD	Early Phase I/IIa results reported (n=15). Extension study enrolling patients.
	nAMD, DME, RVO	Data pending from Phase III trials (n=1,140); FDA approval expected in 2022.
	GA secondary to dry AMD	GA subgroup (n=19) in Phase I trial (n=40) demonstrated vision improvement. Completion of Phase II (n=180) pending.
	nAMD	Interim Phase I results (n=17) reported.
	GA secondary to dry AMD	Phase I results report no safety/toxcity issues. Phase II Gallego trial (n=360) and Phase II open-label trial (n=360) ongoing.
	nAMD, DME, RVO	Results of Phase IIb ALTISSIMO (n=56, nAMD) trial reported. DR program discontinued.
	nAMD, GA secondary to dry AMD	Phase II (n=62) dry AMD and Phase IIa (n=50) nAMD results reported but studies ended. Company update pending.
	nAMD	Phase ib (n=18) results showed improvement in BCVA, CST.
	GA secondary to dry AMD	Phase II trial (n=330) recruiting patients. Completion expected this year.
	nAMD, DME	Phase IIa enrollment initiated.
	nAMD, DME, RVO	Phase Ib follow-up results reported. Phase III trials (n=1,550 combined) in all three indications ongoing.
	Dry AMD (also Stargardt disease)	Phase I trial (n=71) confirms safety, tolerability. Phase III trial planned for this year.
	GA secondary to dry AMD	Patient enrollment completed in Phase II trial (n=240).
	DME	Phase III trial (n=482) initiated enrollment. Phase IIb results reported in 2020.
	AMD, DME and branch RVO	Phase III (n=227) readout reported. Phase III trial (n=120) of prefilled syringe initiated.
	GA secondary to dry AMD	Early Phase I/IIa (n=24) results demonstrate efficacy signal.
	nAMD, DME	Phase III trials in nAMD (n=1,980) initiated. Fast-track designation granted.
	nAMD	Second Phase I trial (n=20) initiated enrollment.
	nAMD, DME, RVO	Readout of follow-up Phase I/II (n=51) results.
	GA secondary to dry AMD	Mixed readouts of Phase III trials (n=1,294).
	nAMD	Three Phase II trials ongoing. Topline data show mixed results vs. aflibercept.
	nAMD	Phase I (n=50) ongoing. Results due 2026.
	DME	Pilot study completed, early results reported.
	DME, dry AMD	Phase IIa (n=40) readout in dry AMD reported.
	DME	Phase IIa readout reported. Phase IIb results expected this year.
	DME	Phase II (n=330) enrollment completed. Topline Part B data due in 2023.
	nAMD, DME	Positive Phase I data reported. 24-week Phase I results and Phase II results pending.
	nAMD, DME	FDA approved indications for nAMD, DME. Readouts of four Phase III trials reported (n=3,230). Long-term Phase III results in DME (n=1,800) pending.
	dry AMD	Phase III (n-96) enrollment completed. Pilot study readouts reported.
	DME, nAMD, GA secondary to dry AMD	Reportedly in Phase IIb trials for DME, GA; no trials listed at ClinicalTrials.gov
	DME (also uveitic macular edema)	Phase II (n=71) results in DME reported.
	GA secondary to dry AMD	Second Phase III (n=448) enrollment completed. Topline data due later in year.

adjunct to anti-VEGF treatments. A six-month Phase I study in nAMD and DME (n=18, NCT03835884) advanced to Stage 2. The company is also pursuing a preclinical program of AR-14034 SR (axitinib) implant.

AXT107 (AsclepiX Therapeutics)

AsclepiX hasn't reported any updates since initiating enrollment in January 2021 in the Phase I/IIa CONGO trial to evaluate the safety and bioactivity of AXT107 in DME (n=18, NCT04697758). AXT107 aims to inhibit vascular endothelial growth factor A and VEGF-C, and activate the Tie2 pathway as well. AsclepiX is also pursuing programs in nAMD and RVO.

CLS-AX (Clearside Biomedical)

CLS-AX is a proprietary suspension of axitinib, a small-molecule tyrosine kinase inhibitor (TKI) used to treat renal cell carcinoma, formulated for suprachoroidal injection. Axitinib inhibits pan-VEGF through receptor blockade. Early results of the OASIS Phase I/IIa trial for nAMD (n=15, NCT04626128) report that the 0.1-mg dose was well-tolerated with no serious side effects. Ten patients in the first two cohorts treated with CLS-AX went at least two months, and four went three months, without needing retreatment. They averaged nine injections in the year before enrollment. Based on those findings, the dose for the next study cohort will go to 0.5 mg. An extension study to evaluate long-term outcomes is recruiting (n=10, NCT05131646).

Conbercept (Chengdu Kanghong Biotechnology)

The FDA last year granted the anti-VEGF fusion protein conbercept new indications for DME and RVO. Available in China since 2013, conbercept targets VEGF-A and -B along with placental growth factor (PLGF). Data are pending from two Phase III trials in nAMD, PANDA-1 and PANDA-2 (NCT03577899, NCT03630952), each enrolling 1,140 patients. However, the program hit a setback last March when the French government halted the clinical trial. Chengdu Kanghong has said it expects FDA approval this year and a global launch in 2023.

EYP-1901 (EyePoint Pharmaceuticals)

EYP-1901 uses the bioerodable Durasert sustained-release insert with vorolanib, a TKI that has shown potential in previous human trials in nAMD as an oral therapy. Interim six-month results of the Phase I DAVIO trial in nAMD (n=17, NCT04747197) showed that 76 percent of patients didn't need rescue treatment at four months and 53 percent were rescue-free at six months.[3] At six months, BCVA was stable (-2.5 letters), as was central subfield thickness (-1.7 µm). EyePoint says it intends to start a Phase II trial this year.

Elamipretide (Stealth BioTherapeutics)

A subgroup with noncentral GA (n=19) in the Phase I ReCLAIM trial in intermediate AMD (n=40, NCT02848313) demonstrated vision improvements, including an average increase of 4.6 ±5.1 letters at week 24.[4] A third of patients demonstrated improvement of ≥10 letters at the same interval, and 6.7 percent showed a ≥15-letter improvement. On average, treatment reduced GA growth by 18 percent. Elamipretide, a cell-permeable peptide delivered

Gene therapies targeting GA, nAMD, DR

This listing includes one new entry: 4D-150 (4D Molecular Therapeutics). One entry from last year, IBIf302 (Innovent Biologics) has been reclassified as a biological agent.

NEW: 4D-150 (4D Molecular Therapeutics). 4D reports dosing the first patient in the Phase I/II trial evaluating this dual-transgene, intravitreal therapy in patients with neovascular age-related macular degeneration.

The dose-escalation, randomized, controlled, masked expansion trial is expected to enroll about 60 adults. It will involve multiple dose levels in an open-label, 3+3 design with an initial dose of 3×10^{10} vector genomes (vg)/eye. The dose-expansion phase will randomize 50 patients 2:2:1 to receive one of two dose levels of 4D-150 (n=20 for each dose level) or aflibercept (n=10). Primary endpoints are safety and tolerability. Secondary endpoints include the number of supplemental aflibercept injections received and change from baseline in best corrected visual acuity over time. The trial isn't listed at www.Clinicaltrials.gov.

ADVM-022 (Adverum Biotechnologies). Adverum reports it's finalizing the design of a Phase II trial in nAMD that will evaluate two doses of ADVM-022: a 2×10^{11} vg/eye dose and a lower 6×10^{11} vg/eye dose. ADVM-022 is a single intravitreal injection treatment that uses a proprietary adeno-associated vector capsid, AAV.7m8, carrying an aflibercept-coding sequence under the control of a proprietary expression cassette.

The nAMD trial will include three new enhanced steroid prophylaxis regimens, possibly a topical, intravitreal and a combination of systemic and local steroids. The trial is expected to enroll approximately 72 patients, with enrollment starting in the third quarter.

Data from the Phase I OPTIC trial in nAMD (n=30, NCT03748784) demonstrated a >80-percent reduction in yearly anti-VEGF injections following the 2E11 dose.[17] The Phase II INFINITY trial

in DME (n=36, NCT04418427) reported higher-than-expected rates of intraocular inflammation and iris-related events,[18] so the company discontinued the diabetic macular edema program.

GT005 (Gyroscope Therapeutics). A one-time therapy delivered subretinally, GT005 aims to induce complement factor I expression. Interim data from the Phase I/II FOCUS trial (n=45, NCT03846193) in GA reported no treatment-related serious adverse events in 28 patients, while biomarker data from 13 patients demonstrated sustained increased levels of vitreous complement factor I (CFI) as well as sustained decreases in downstream proteins associated with complement system activation.[19] A new analysis showed no increases in systemic CFI levels circulating in the blood. Completion of the trial is planned in 2025.

Two other trials are ongoing: Phase II EXPLORE trial (n=75, NCT04437368) evaluating two doses administered as a single injection in GA, due for completion in early 2023; and Phase II HORIZON (n=150, NCT04566445), also evaluating two doses in one injection in GA, with completion scheduled for early next year.

HMR59 (Hemera Biosciences). Results are pending from the HMR-1002 Phase I proof-of-concept study (n=25, NCT03585556) in treatment-naïve patients with new onset nAMD. HMR59 is a soluble form of CD59, the protective protein normally found on the cellular plasma membrane. Patients receive a single intravitreal injection of HMR59 a week after getting an anti-VEGF treatment. They're being followed for 12 months and treated with additional anti-VEGF monthly as needed.

RGX-314 (RegenxBio). RegenxBio has initiated the ASCENT trial, the second Phase III trial evaluating RGX-314 in nAMD. ASCENT is evaluating subretinal delivery across two dose arms—6.4 x 10^{10} genomic copies per eye (GC/eye) and 1.3 x 10^{11} GC/eye—vs. aflibercept. The primary endpoint is noninferiority to aflibercept-based BCVA change at one year. The trial will enroll around 465 patients. RGX-314 is an AAV8 vector that contains a transgene for anti-VEGF fab.

Two Phase II trials of suprachoroidal delivery are also ongoing: AAVIATE in nAMD (n=40, NCT04514653) and ALTITUDE in diabetic retinopathy without center-involved DME (n=40, NCT04567550). In AAVIATE, RGX-314-treated patients had an average six-month change in central retinal thickness of -33 µm compared to -12 µm for the ranibizumab group. RGX-314 patients also showed a 71.8-percent reduction in anti-VEGF treatment burden at six months.[19] Two-year results of a Phase I/IIa trial of subretinal delivery of RGX-314 in nAMD (n=42, NCT03066258) demonstrated the treatment was generally well tolerated across five dose cohorts with long-term durability out to three years.[20]

In ALTITUDE, 15 patients dosed with 2.5 x 10^{11} GC/eye of RGX-314 demonstrated stable BCVA of +2.6 letters, while five patients in the observational control arm demonstrated stable BCVA of -0.4 letters.[19] Five patients (33 percent) demonstrated a two-step or greater improvement in VA vs. none in the control group.[21]

Enrollment started at the beginning of the year in the pivotal Phase IIb/III ATMOSPHERE study (n=300, NCT040704921) comparing RGX-314 and ranibizumab in patients with nAMD. Completion is expected in 2024.

Gene therapies for exudative disease in human trials

Drug name (manufacturer)	Description/active agent	Indication	Status
NEW: 4D-150 (4D Molecular Therapeutics)	Dual-transgene intravitreal therapy	Neovascular age-related macular degeneration	Phase I/II trial initiated in 2022.
ADVM-022 (Adverum Biotechnologies)	Adeno-associated vector 7m8 of aflibercept	nAMD, diabetic macular edema	Phase II trial in planning stages. Results of Phase I (nAMD, n=30), Phase II (DME, n=36) trials reported. DME program discontinued.
GT005 (Gyroscope Therapeutics)	AAV-induced expression of complement factor I	GA secondary to dry AMD	Interim Phase I/II (n=45) readout. Two Phase II trials (n=225).
HMR59 (Hemera Biosciences)	Soluble form of CD59 protein	GA secondary to dry AMD, nAMD	Phase I nAMD trial (n=25) results pending.
RGX-314 (RegenxBio)	AAV8 vector containing anti-VEGF fab transgene	Diabetic retinopathy without center-involved DME, nAMD	Second Phase III trial in nAMD initiated. Readouts of Phase II trials of suprachoroidal delivery in DR without CI-DME (n=40) and nAMD reported. Two-year Phase I/IIa (n=42) data in nAMD reported. Phase II nAMD trial (n=40) due for completion 2022.

Investigational therapies for inherited retinal disease

This year's listing includes four new agents: 4D-125 (Molecular Therapeutics) targeting X-linked retinitis pigmentosa (XLRP); SAR439483 (Atsena Therapeutics), a gene therapy for Leber congenital amaurosis; MCO-010 (Nanoscope Therapeutics) for Stargardt and RP; and Visomitin (Mitotech), a topical treatment for Leber hereditary optic neuropathy.

There's also one name change: AGTC-501 (Applied Genetic Technologies Corporation) was listed as rAAV2tYF-GRK1-RPGR last year.

NEW: 4D-125 (4D Molecular Therapeutics)**.** The Food and Drug Administration granted Fast Track designation to this candidate for retinal dystrophies due to defects in the *RPGR* gene, including XLRP. 4D-125 aims to deliver a functional copy of the *RPGR* gene (retinitis pigmentosa GTPase regulator) to photoreceptors. 4DMT is currently enrolling patients in a Phase I/II clinical trial (n=43, NCT04517149). The study is using a standard 3+3 dose-escalation design, followed by dose expansion.

AAV-RPGR (MeiraGTx Holdings/Janssen Pharmaceuticals)**.** This recombinant AAV vector aims to deliver functional copies of the *RPGR* gene to the subretinal space. In the dose-escalation phase of a Phase I/II clinical trial (n=49, NCT03252847) in XLRP, patients treated with AAV5-RPGR gene therapy demonstrated changes in mean retinal sensitivity and volumetric analysis of the central 30 degrees of the retina that were maintained at 24 months.[22] A follow-up study (n=36, NCT04312672) is evaluating long-term safety of the AAV2-RPGR vector.

AGTC-402, rAAV2tYF-PR1.7-hCNGB3 and **AGTC-501** (formerly rAAV2tYF-GRK1-RPGR) (Applied Genetic Technologies Corporation)**.** AGTC presented 12-month findings of two Phase I/II trials of gene therapies in achromatopsia: AGTC-402 for mutations in the *CNGA3* gene (n=24, NCT02935517); and rAAV2tYF-PR1.7-hCNGB3 for mutations in the *CNGB3* gene (n=28, NCT02599922).[23] The agents demonstrated biologic activity based on improvements in visual sensitivity and light discomfort, along with a favorable safety profile. Three-month data from pediatric patients in both trials are due in the fourth quarter and an end-of-Phase II briefing packet to the FDA in the first half of 2022.

Meanwhile, AGTC reports it enrolled 14 patients in the SKYLINE trial of AGTC-501, a recombinant adeno-associated virus vector-based gene therapy for XLRP, exceeding the planned target enrollment of 12. SKYLINE is a multi-site expansion of the ongoing Phase I/II study (n=42, NCT03316560). The goal is to identify the proportion of treated eyes that show improvement in visual sensitivity and acuity, as well as functional outcomes.

ALK-001 (Alkeus Pharmaceuticals)**.** The FDA granted Breakthrough Therapy designation to ALK-001, an oral modified form of vitamin A, for Stargardt disease. A Phase II placebo-control study (n=140, NCT02402660) is recruiting patients. ALK-001 is designed to replace vitamin A and prevent formation of toxic vitamin A dimers that have been linked to vision loss. The trial is scheduled for completion in March.

Elamipretide (Stealth BioTherapeutics). Phase II results in LHON (n=12, NCT02693119) showed that two of 16 treated eyes had visual impairment and higher rates of mild ocular surface problems than vehicle. Six treated eyes also had mild cataract, as did five vehicle-treated eyes before switching to elamipretide. Elami-

Therapies for inherited retinal disease in human trials

Drug name (manufacturer)	Description/active agent	Indication	Status
NEW: **4D-125** (Molecular Therapeutics)	Subretinal delivery of functional copies of RPGR gene	X-linked retinitis pigmentosa (XLRP)	Phase I/II trial (n=43) enrolling with dose-expansion to follow.
AAV-RPGR (MeiraGTx Holdings/ Janssen Pharmaceuticals)	Subretinal delivery of functional copies of RPGR gene	XLRP	24-month Phase I/II trial (n=49) reports maintenance of improvements.
AGTC-402 and **rAAV2tYF-PR1.7-hCNGB3** (Applied Genetic Technologies Corporation)	Adeno-associated virus (AAV) vector targeting mutations in the CNGA3 and CNGB3 genes	Achromatopsia	Phase I/II trials (n=24, 28, respectively) report biological signal, favorable safety profile.
AGTC-502 (formerly rAAVtYF-GRK1-RPGR, AGTC)	Recombinant AAV vector-based gene therapy	XLRP	Multisite expansion of Phase I/II trial (n=12) under way.
ALK-001 (Alkeus Pharmaceuticals)	Oral modified vitamin A	Stargardt disease	Breakthrough Therapy designation granted; Phase II trial (n=140) scheduled for completion in March.
Elamipretide (Stealth BioTherapeutics)	Subcutaneous mitochondria-targeting cell-permeable peptide	Leber hereditary optic neuropathy	Phase II trial (n=12) reported higher rates of mild ocular events than vehicle.
jCell (jCyte, Santen)	Intravitreal human retinal progenitor cells.	Retinitis pigmentosa	Phase IIb trial (n=30) showed sustained visual acuity improvement.
Lumevoq (GS010, GenSight Biologics)	Single intravitreal injection of rAAV2/2-ND4	LHON	Multiple Phase III trials report VA improvement in treated eyes. Four-year data are pending.
NEW: **MCO-010** (Nanoscope Therapeutics)	Ambient-light activatable optogenetic therapy	RP, Stargardt disease	Phase IIb RP trial ongoing; Phase II Stargardt trial cleared.
OCU400 (Ocugen)	AAV of functional *NR2E3* gene.	RP, Leber congenital amaurosis	Investigational New Drug application accepted. Clinical trials pending.
NEW: **SAR439483** (Atsena Therapeutics)	AAV-based therapy targeting *GUCY2D* gene mutations	LCA	Phase I/II trial (n=15) initiated.
NEW: **Visomitin** (Mitotech)	Topical cardiolipin peroxidation inhibitor	LHON	Phase II trial pending.

pretide is a cell-permeable peptide that targets mitochondrial dysfunction and is delivered subcutaneously.

jCell (jCyte, Santen)**.** jCell is an intravitreal injection of human retinal progenitor cells (hRPC) into the vitreous that aims to preserve or potentially restore some vision in RP and related conditions. One-year Phase IIb results (n=30, NCT04604899) showed that patients treated with a 6-million cell dose had a sustained average improvement of +16.27 letters vs. +1.85 letters in the sham group (p=0.003).[24] A separate analysis found a correlation between improvements in central foveal thickness and visual function.[25] The Phase IIb and Phase II trials (n=84, NCT03073733) in RP are ongoing.

Lumevoq (GS010, GenSight)**.** The Phase III REFLECT trial (n=98, NCT03293524) in LHON caused by a defect in the *ND4* gene demonstrated that 73 percent of bilaterally treated eyes had VA improvement of ≥15 letters two years after treatment. Lumevoq (lenadogene nolparvovec) is a single intravitreal injection of rAAV2/2-ND4. Three-year data from RESTORE (n=61, NCT03406104), a follow-up trial of the Phase III RESCUE (n=39, NCT02652767) and REVERSE (n=37, NCT02652780) trials, showed sustained VA improvement in treated patients.[26] Four-year data are pending.

NEW: MCO-010 (Nanoscope Therapeutics). The FDA has approved an Investigational New Drug (IND) application to begin a Phase II trial in Stargardt disease, and a Phase IIb trial in RP is ongoing. MCO-010 is an ambient-light activatable optogenetic monotherapy.

OCU400 (Ocugen)**.** The FDA accepted the company's application for a human clinical trial of OCU400 (AAV-NR2E3), a modifier gene therapy that targets nuclear hormone receptors (NHR). The FDA has granted four orphan drug designations for OCU400, and the European Medicines Agency granted two in 2021 for RP and LCA. Ocugen says the platform could be indicated for multiple IRDs. One potential indication is RP caused by *PDE6B* mutation autosomal-dominant congenital stationary nyctalopia and resulting from genetic mutations found in *NR2E3* and rhodopsin. OCU400 consists of a functional copy of the *NR2E3* gene.

NEW: SAR439483 (Atsena Therapeutics)**.** Atsena received orphan drug designation for its unnamed investigational AAV-based therapy for LCA caused by biallelic mutations in the *GUCY2D* gene. The safety and efficacy of the therapy are being evaluated in a Phase I/II clinical trial (n=15, NCT03920007). Study completion is scheduled for February. Atsena is also pursuing human trials for its gene therapy program for X-linked retinoschisis.

NEW: Visomitin (Mitotech). The FDA granted orphan drug designation for treatment of LHON. Visomitin is a topical cardiolipin peroxidation inhibitor. Mitotech says it plans this year to start a Phase II trial for the indication, and reports that a three-year open-label Phase IIa study conducted outside the United States showed improvements in a range of underlying mutations.

via a 40-mg subcutaneous injection, is the subject of the ongoing Phase II ReCLAIM-2 study in AMD with noncentral GA (n=180; NCT03891875), completion of which is set for March.

FHTR2163 (Genentech)

FHTR2163, also known as RG6147, is an antigen-binding fragment (Fab) that targets the high-temperature requirement protein A1 (HtrA1), a serine protease gene associated with GA that's a potential risk factor for nAMD. Phase I results in patients with GA secondary to dry AMD found no dose-limiting toxicities or serious ocular adverse events in 15 patients, including 13 who had three 20-mg injections over 12 weeks.[5] FHTR2163 is the subject of two ongoing Phase II trials in GA: GALLEGO (n=360, NCT03972709), which is evaluating outcomes over 76 weeks with completion due later in the year; and an open-label Phase II trial (n=360, NCT04607148) comparing q4-week and q8-week dosing, due at the end of next year.

GB-102 (Graybug Vision)

This proprietary microparticle depot formulation of the pan-VEGF inhibitor sunitinib is intended for twice-yearly injection. The Phase IIb ALTISSIMO trial (n=56, NCT03953079) randomized previously treated nAMD patients into three arms: GB-102 1 mg (n=21), GB-102 2 mg (n=22), both dosed every six months; or bimonthly aflibercept (n=13). Fifty patients completed the 12-month treatment phase of the study. GB-102 2 mg was discontinued after an interim safety analysis. These patients were re-dosed with GB-102 1 mg for the second injection at six months. Median time to first rescue therapy with GB-102 was five months, but 48 percent of patients didn't need rescue for at least six months. However, the average change in BCVA was lower in the GB-102 arm than the aflibercept arm, although CST was comparable in both arms.[6]

Graybug had been developing GB-103, a once-yearly formulation of GB-102 for DR, but halted further development based on results of an 18-month, Phase IIb trial. Graybug reports in a regulatory filing that without a funding partner, further development of GB-102 for nAMD or DME, or GB-103 for DR is unlikely.[7]

GEM103 (Gemini Therapeutics)

GEM103 is a recombinant, human complement factor H. Gemini reports that the Phase II ReGAtta trial in dry AMD (N=62, NCT04643886) showed that GEM103 has been generally well-tolerated at more than nine months, with a signal to reduce complement activation biomarkers while maintaining supraphysiological levels of CFH over multiple intravitreal injections.

Six-month data of a Phase IIa add-on study in nAMD (n=50, NCT04684394) showed bimonthly treatment of GEM103 plus aflibercept vs. sham plus aflibercept resulted in similar safety

Biosimilars poised to have an impact

With ranibizumab (Lucentis, Genentech/Roche) already off patent in the United States and losing its European patent protection this year, and aflibercept (Eylea, Regeneron Pharmaceuticals) coming off patent in 2023 in the United States and in 2025 in Europe, clinical trials of biosimilar candidates are moving forward—but there's also a candidate for a biosimilar referencing ophthalmic bevacizumab (Avastin, Genentech/Roche). This listing breaks the candidates down by their respective reference products.

Bevacizumab biosimilar

HLX04-O (Shanghai Henlius Biotech). This candidate probably has more appeal outside the United States, where access to quality compounding pharmacies can be dodgy. Neovascular age-related macular degeneration is the indication for this ophthalmic formulation of the bevacizumab biosimilar HLX04. The first patients were dosed in a single-arm Phase I trial (n=20, NCT04993352). Two Phase III trials in nAMD using ranibizumab are also listed: one that started recruiting last year (n=388, NCT04740671) and a second that has yet to begin recruiting (n=388, NCT 05003245). Last year regulators in China approved the biosimilar for cancer indications.

Ranibizumab biosimilars

Byooviz (Biogen)**.** Also known as SB11, this product last year became the first ophthalmology biosimilar to get Food and Drug Administration approval. It's indicated for nAMD, macular edema following retinal vein occlusion and myopic choroidal neovascularization. It will be launched in the United States after June, according to terms of a global license agreement with Genentech. Last year Samsung Biologics and Biogen, then partners in Samsung Bioepis, completed a Phase III comparator trial (n=705, NCT03150589). Biogen sold rights to other biosimilars to Samsung Biologics but retained the rights to Byooviz.

CHS-201 (Coherus BioSciences). The FDA accepted the Biologic License Application (BLA) for review of this agent, also known FYB201, in October, setting a Biosimilar User Fee action date for August. A Phase III trial (n=712, NCT02611778) was completed late last year with results pending. Coherus says it plans to launch the biosimilar in the second half of the year. Coherus obtained the U.S. license from Bioeq.

Xlucane (Xbrane Biopharma). Bausch + Lomb entered into an agreement with STADA Arzneimittel of Germany and its development partner, Xbrane Biopharma of Sweden, to commercialize Xlucane in the United States and Canada. Xbrane reported a Phase III trial demonstrated equivalency with the reference product (n=580, NCT03805100). The European Medicines Agency accepted the Marketing Authorization Application in September. The company said last June that it would file a BLA with the FDA in the fourth quarter of 2021, but that couldn't be confirmed at press time.

Aflibercept biosimilars

ALT-L9 (Alteogen). South Korea-based Alteogen reported in April that it completed a Phase I comparator trial (n=28, NCT-04058535) that showed equivalent efficacy in nAMD. Alteogen says the findings may provide a path to a shorter Phase III trial. Alteogen is developing ALT-L9 in collaboration with Kissei Pharmaceutical of Japan.

CT-P42 (Celltrion Healthcare). Celltrion initiated a Phase III trial in diabetic macular edema (n=300, NCT04739306).

LY9004 (Boan Biology). Luye Pharma's biotech subsidiary has licensed this candidate, also known as OT-702, to Ocumension Therapeutics. It's in Phase III trials in China, but not in the United States.

SOK583A1 (Sandoz). The Novartis division initiated the Phase III MYLIGHT trial (n=460, NCT04864834) comparing this previously unnamed agent with the reference product.

Anti-VEGF biosimilars in human trials

Biosimilar name (manufacturer)	Indication	Status
Reference product: Bevacizumab		
HLX04-O (Shanghai Henlius Biotech)	Neovascular age-related macular degeneration	Phase I trial (n=20) initiated. Two Phase III trials (n=388 each) using ranibizumab as comparator.
Reference product: Ranibizumab		
Byooviz (Biogen)	nAMD, macular edema post-retinal vein occlusion, myopic choroidal neovascularization	U.S. approval granted. June U.S. launch planned.
CHS-201 (Coherus BioSciences)	nAMD	U.S. action date set for August. Phase III results pending.
Xlucane (Xbrane Biopharma)	nAMD	U.S. Biologics License Application pending.
Reference product: Aflibercept		
ALT-L9 (Alteogen)	nAMD	Phase I (n=28) trial completed.
CT-P42 (Celltrion Healthcare)	Diabetic macular edema	Phase III (n=300) trial initiated.
LY9004 (Ocumension Therapeutics)	nAMD	Phase III trial in China.
SOK583A1 (Sandoz)	nAMD	Phase III trial (n=460) initiated.

profiles, with biological CFH levels five times above baseline through six months. The company ended both studies and says it will provide an update on next steps this quarter.

NEW: IBI302 (Innovent Biologics)

IBI302 is a bispecific anti-VEGF and anti-complement recombinant fully human fusion protein. The Phase Ib clinical trial in nAMD (n=18, NCT04370379) involved multiple intravitreal injections of IBI302 or aflibercept. In the 12 subjects in the IBI302 group, BCVA improved 6.4 letters on average from baseline and central zone retinal thickness decreased 129.3 µm from baseline on average. In the 4-mg IBI302 group, visual acuity improved by 8 letters and mean CRT improved by 134.3 µm. There were no reported treatment-related adverse events. A Phase II trial in nAMD (n=231, NCT04820452) started recruiting last spring.

IONIS-FB-LRx (Ionis Pharmaceuticals)

The Phase II GOLDEN study for GA secondary to AMD (n=330, NCT03815825) is recruiting patients. It's a placebo-controlled trial that will evaluate change in GA area at week 49. Study completion is expected late in the year. IONIS-FB-LRx is an antisense oligonucleotide (ASO) that inhibits complement factor B gene expression by binding with factor B mRNA.

NEW: ISTH0036 (Isarna Therapeutics)

ISTH0036 is an antisense therapy that targets the transforming growth factor-beta (TFG-ß), a protein that's been found to be elevated in retinal disease. Isarna announced the enrollment of the first patient in BETTER, a parallel, two-segment Phase IIa clinical study to evaluate ISTH0036, in up to 24 patients with nAMD and DME, but the trial hasn't been listed at ClinicalTrials.gov. The primary endpoint is retinal fluid and central macular thickness reduction, with improvement of VA as a secondary endpoint. The trial aims to explore the prevention of fibrosis and epithelial-mesenchymal transition as a key differentiator to anti-VEGF therapies.

KSI-301 (Kodiak Sciences)

KS-301, an intravitreal anti-VEGF antibody biopolymer conjugate, is in clinical trials for three indications: nAMD, DME and RVO. One-year data from the Phase Ib trial (n=121, NCT03790852) showed that two-thirds of patients in each disease cohort achieved a six-month or longer treatment-free interval after a year. More than half—54 percent of nAMD patients—required one retreatment and 50 percent of DME patients didn't need any retreatment at one year.

The Phase IIb/III DAZZLE study (n=550, NCT04049266), comparing KSI-301 and aflibercept in treatment-naive nAMD, is ongoing, as are the Phase III GLEAM (n=450, NCT04611152) and GLIMMER (n=450, NCT04603937) studies, also comparing KSI-301 and aflibercept, in treatment-naive DME.

Meanwhile, Kodiak has completed enrollment in the Phase III BEACON study (n=550, NCT04592419) of KSI-301 in patients with treatment-naive macular edema due to RVO. Completion is expected later in the year.

LBS-008 (Belite Bio)

LBS-008 is an oral, small-molecule retinol binding protein 4 (RBP4) specific antagonist for dry AMD. Belite Bio says it expects to initiate a Phase III trial for the indication this year. A Phase I trial (n=71, NCT03735810) confirmed safety and tolerability of the drug and that oral administration achieved potentially therapeutic-level target engagement. A global Phase III trial in Stargardt disease started last summer.

NGM621 (NGM Biopharmaceuticals)

NGM621 is an intravitreal formulation of a humanized IgG1 monoclonal antibody engineered to potently inhibit C3. Patient enrollment was completed last summer in the Phase II CATALINA trial (n=240, NTC04465955) for GA. Study completion is expected in 2023.

NEW: OCS-01 (Oculis)

OCS-01 is a topical high-concentration formulation of preservative-free dexamethasone now in Phase III study in patients with DME. The first patients were enrolled in the DIAMOND trial (n=482, NCT05066997) in November. Phase IIb results (n=144), first presented in 2020, showed OSC-01 improved VA and reduced CMT compared to vehicle.[8]

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

Based on results of the Phase III NORSE TWO (n=227, NCT03834753) trial, Outlook says it plans to submit a BLA with the FDA in the first quarter of the year for this ophthalmic formulation of bevacizumab. Results showed that 68.5 percent of patients gained ≥5 letters of vision (p=0.0116) and 41.7 percent gained ≥15 letters (p=0.0052).[9]

Indications would cover nAMD, DME and branch RVO. Late last year Outlook started the Phase III NORSE SEVEN trial (n=120, NCT05112861) to evaluate the agent in vials and a prefilled syringe. Completion is expected by the end of the year. Recruitment in the Phase III NORSE 3 safety trial (n=195, NCT04516278) closed last year.

OpRegen (Lineage Cell Therapeutics)

This cell therapy consists of allogeneic retinal pigment epithelium cells administered to the subretinal space. Enrollment has been completed in the Phase I/IIa trial in GA secondary to dry AMD (n=24, NCT02286089), which demonstrated improvement in VA and GA area among some treated patients. Study completion is scheduled for year-end 2024. Lineage Cell Therapeutics signed an agreement with Genentech/Roche in December to collaborate on the development of OpRegen.

OPT-302 (Opthea)

Opthea initiated enrollment in Phase III trials of OPT-302 for nAMD. The ShORe (n=990, NCT04757610) and COAST (n=990, NCT04757636) studies are evaluating intravitreal 2-mg OPT 302 in combination with either 0.5 mg ranibizumab or 2.0 mg aflibercept, respectively, for nAMD.

Topline 52-week results are expected next year, after which Opthea says it will submit applications for approval in both the United States and Europe. The FDA last year granted Fast Track status for OPT-302 in combination with anti-VEGF-A therapy for nAMD.

OTX-TKI (Ocular Therapeutix)

The Phase I clinical trial of this intravitreal axitinib implant for nAMD started enrolling patients last summer (n=20, NCT04989699). Axitinib is the same small-molecule TKI used in CLS-AX. The prospective, randomized, controlled, multicenter trial is evaluating a single OTX-TKI implant containing a 600-µg dose of axitinib, compared with a 2-mg dose of aflibercept administered every eight weeks in subjects previously treated with anti-VEGF therapy.

PAN-90806 (PanOptica)

PanOptica describes this as a selective inhibitor of VEGF receptor 2, and reports that more than half of patients in the Phase I/II trial in nAMD (n=51, NCT03479372) who took the topical drop once daily completed the trial without needing intravitreal anti-VEGF rescue therapy Of those, 88 percent either had clinical improvement or disease stability.

Pegcetacoplan (APL-2, Apellis)

Based on feedback it received from the FDA, Apellis says it plans to submit a New Drug Application for pegcetacoplan for GA in the first half of this year. Results of the Phase III DERBY (n=621, NCT03525600) and OAKS studies (n=673, NCT03525613) showed mixed results.[10] OAKS met its primary endpoint, reducing lesion growth by 22 percent with monthly (n=202) and by 16 percent with bimonthly (n=205) treatment at 12 months vs. sham in patients with extrafoveal lesions (n=206).

However, DERBY failed to meet its primary endpoint, although it did reduce lesion growth in these patients: 12 and 11 percent for monthly (n=201) and bimonthly treatment (n=200), respectively, vs. sham. Combined results showed a 17-percent reduction with monthly (n=405) and 14-percent reduction with bimonthly (n=403) treatment. Thirteen patients (1.5 percent) had intraocular inflammation.

NEW: RBM-007 (Ribomic)

RBM-007 is an oligonucleotide-based aptamer with potent anti-fibroblast growth factor 2 (FGF2) activity, which has been linked to fibrosis in nAMD, among other diseases. Ribomic says the candidate has dual anti-angiogenic and anti-scarring actions that make it a potential additive therapy to anti-VEGF treatments for nAMD.

Three studies are evaluating RBM-007 for nAMD: TOFU (n=86, NCT04200248), a Phase II trial evaluating the candidate in combination with aflibercept in previously treated patients; RAMEN (NCT04640272), a single-arm, open-label extension trial; and TEMPURA (NCT04895293), an investigator-sponsored trial in treatment-naïve nAMD patients.

The trials have yielded mixed early results. Topline TOFU data showed RBM-007 in combination with aflibercept didn't demonstrate any vision improvement over aflibercept alone. However, preliminary interim results of TEMPURA have shown improvement in vision and retinal anatomy.

Retilux (PhotoOpTx)

This device is worn like an eye patch. It delivers laser therapy directly to the affected eye using photobiomodulation (PBM), which uses light in the 630-to-900-nm range. The pilot study (n=135, NCT03866473) compared PBM with sham in eyes with center-involved DME and good vision. PBM patients had twice-daily treatments for 90 seconds at 670 nm for four months. Average change in CST at four months was 13 µm

WET AMD EYE

ANTI-VEGF

Therapy yields better long-term VA results when wet AMD detected with good VA[1]

FELLOW EYE

20/79 VA

Mean VA of fellow eyes at wet AMD diagnosis according to real-world data[1]

Over 60% of wet AMD "fellow eyes" lose too much vision[1]– even with frequent treatment visits

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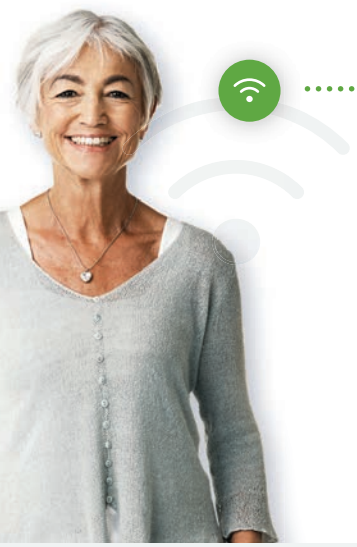

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- Continuous Monitoring

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- Remote Patient Management
- Vision Alert Management

References: 1. Ho AC, Kleinman DM, Lum FC, et al. Baseline Visual Acuity at Wet AMD Diagnosis Predicts Long-Term Vision Outcomes: An Analysis of the IRIS Registry. *Ophthalmic Surg Lasers Imaging Retina*. 2020;51:633-639. **2.** Real-World Performance of a Self-Operated Home Monitoring System for Early Detection of Neovascular AMD (ForeseeHome device), presented by Allen Ho, American Society of Retina Specialist Meeting 2020.

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(SD 53) for the treatment group and 15 µm (SD 57) in the placebo group. Rescue therapy was administered in 4.4 percent of the PBM patients and 1.5 percent of the placebo group. PhotoOpTx hasn't made any announcements on the program since results were posted to ClinicalTrials.gov.

Risuteganib (Allegro Ophthalmics)

Risuteganib is a small-peptide oxidative stress stabilizer. Results of the Phase IIa trial in nonexudative AMD (n=40, NCT03626636) were published in August.[11] Risuteganib 1 mg in patients with intermediate disease met the study's primary endpoint—an ≥8-letter improvement in best corrected visual acuity—in 48 percent of patients in the risuteganib group at week 28 and 7 percent of patients in the sham group at week 12 (p=0.013). No drug-related serious adverse events were reported in the risuteganib group.

RO7250284 (Genentech/Roche)

The Phase I trial (n=50, NCT04567303) in nAMD is recruiting patients. Completion is expected in 2026. This is a bispecific human Fab form of faricimab delivered via the port delivery system.

THR-149, THR-687 (Oxurion)

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

THR-149 is the subject of a Phase II trial, KALAHARI (n=122, NCT04527107), which is recruiting patients with CI-DME refractory to anti-VEGF. The trial is now in Phase IIb comparing the agent with aflibercept. Topline results are expected in 2023. Phase IIa data reported last year that THR-149 had a favorable safety profile. Part B is comparing three monthly injections of THR-149 and three monthly injections of aflibercept (n=~108). The primary endpoint is mean change in BCVA at three months.

For THR-687, Oxurion has completed enrollment for the first part of the Phase II clinical trial (n=303, NCT05063734), known as INTEGRAL. Part A of the trial will assess two dose levels of multiple THR-687 injections, results of which will be used to determine the appropriate dose for Part B, which will compare THR-687 and aflibercept. Oxurion says it expects topline Part B data in the second half of 2023.

NEW: UBX1325 (Unity Biotechnology)

Unity describes UBX1325 as the first senolytic therapy in retina—a potent, small-molecule inhibitor of B-cell lymphoma-extra-large (Bcl-xL), which is itself a member of the B-cell chronic lymphocytic leukemia/lymphoma (Bcl-2) family of apoptosis-regulating proteins. The company reported positive results from the Phase I safety trial (n=21, NCT04537884) in DME or nAMD refractory to anti-VEGF treatment.[12] Unity says it expects to report this year 24-week data from the nAMD cohort of the Phase I trial, along with 12- and 24-week data from the Phase IIa trial in DME (n=62, NCT04857996), and 16-week safety and efficacy data from the Phase II trial in nAMD (n=46) already in the field. That trial includes an aflibercept control arm.

Vabysmo (Genentech/Roche)

The FDA approved Vabysmo (faricimab) for nAMD and DME. Faricimab is a bispecific antibody that binds to and neutralizes both angiopoietin-2 (Ang-2) and VEGF-A.

In DME, readouts of the parallel Phase III trials, YOSEMITE (n=940, NCT03622580) and RHINE (n= 951, NCT03622593), found that faricimab showed noninferiority to aflibercept.[13]

Average one-year BCVA gains with faricimab were 10.7 and 11.8 letters in YOSEMITE and RHINE with q8-week treatment and 11.6 and 10.8 letters with a personalized treatment interval (PTI) regimen, and 10.9 and 10.3 letters with aflibercept q8-weeks. At one year, more than half of the faricimab PTI arm were on q16-week dosing and more than 70 percent were on q12-week or more dosing. The ongoing Phase III Rhone-X study (n=1,800, NCT04432831) is investigating the long-term effect of faricimab in DME, with completion expected in 2023.

TENAYA (n=671, NCT03823287) and LUCERNE (n=658, NCT03823300) are Phase III trials evaluating faricimab in nAMD over 112 weeks, again with aflibercept as the comparator. Average BCVA gains at week 48 with faricimab up to q16-week treatment were 5.8 and 6.6 letters in TENAYA and LUCERNE and, 5.1 and 6.6 letters with q8-week aflibercept. At week 48, around 45 percent of the faricimab patients were on q16-week dosing. Around 80 percent were getting treatments every 12 weeks or longer.[14]

Valeda Light Delivery System (LumiThera)

Valeda uses PBM to target damaged photoreceptors. Final topline data from the ELECTROLIGHT pilot study in intermediate dry AMD (n=15, 23 eyes, NCT04522999) reported that treated patients aver-

aged a 1.28 ± 0.98-letter improvement in BCVA after six months.

Researchers also reported results of a trial using the PBM device in patients with DME (n=19; 30 eyes), which showed a 90 to 70 percent reduction of intraretinal fluid (p=0.031) among other outcomes.[15] LumiThera also completed enrollment in the LIGHTSITE III trial (n=96, NCT04065490) in dry AMD. Subjects are receiving three PBM treatments a week for three weeks for a total of nine sessions. The device has been approved in Europe.

Xiflam (InflammX)

This is an oral small-molecule therapy that targets the Connexin43 protein and blocks the formation of hemichannels. InflammX reports it's in Phase IIb trials for DME and GA, but no trials are listed in ClinicalTrials.gov.

Xipere (Clearside Biomedical)

Formerly known as CLS-TA, Xipere is a proprietary triamcinolone acetonide suspension formulated for suprachoroidal delivery. The Phase II TYBEE trial in DME (n=71, NCT03126786), comparing Xipere plus aflibercept with aflibercept plus sham suprachoroidal injection, showed that neither group achieved clinically meaningful improvement of ≥15 letters at 24 weeks: an average of +11.4 letters in the Xipere group and +13.8 in the sham group.

As for secondary outcomes, the treatment had statistically significant improvement in CST—a reduction of -212.1 (13.83) vs. -178.6 (13.61) µm. The treatment group also had a higher rate of serious adverse events (16.67 vs. 11.43 percent) but lower rates of other adverse events (8.33 vs. 11.43 percent). In May Clearside resubmitted its NDA for the indication of uveitis-associated macular edema.

Zimura (avacincaptad pegol, IVERIC bio)

IVERIC Bio reported completing enrollment in the Phase III GATHER2 trial in GA (n=448, NCT04435366), the second pivotal trial of the C5 inhibitor, with topline data to come later in the year. GATHER2 is evaluating the 2-mg dose over 24 months. Results from the Phase III GATHER1 trial in GA (n=400, NCT04435366), reported in 2020, 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.[16] RS

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Why not vitrectomy for vitreous opacities?

Why pars plana vitrectomy has come of age for vitreous opacities in selected patients.

Jaya B. Kumar, MD

Matthew A. Cunningham, MD

By Jaya B. Kumar, MD, and Matthew A. Cunningham, MD

Take-home Points

- With improved safety profiles for small-gauge vitrectomy and excellent patient outcomes, it's time to accept and expand the scope of vitreoretinal surgery to include pars plana vitrectomy for vitreous opacities.
- When assessing a patient with symptomatic VOs, pay particular attention to the lenticular status, presence of a Weiss ring, absence of vitreous cell and peripheral retinal findings.
- During the clinical evaluation, make sure to rule out mimickers such as ocular amyloidosis, lymphoma and uveitic conditions, such as birdshot chorioretinopathy.
- Make sure to review the risks of PPV with patients. These risks include retinal tears, hypotony, vitreous hemorrhage, macular edema and retinal detachment.
- By ensuring our patients have been symptomatic for more than six months, are pseudophakic and have had a Weiss ring present on exam, we've had no significant adverse events associated with PPV for symptomatic VO.

While vitreous opacities in some patients can be a mere nuisance, in others they can be visually significant and interfere with daily activities. The traditional teaching has been to simply educate patients that vitreous floaters are a benign condition with no long-term sequelae and observe them.

However, we've all had patients whose symptoms significantly impair their quality of life. As vitreoretinal surgeons, we need to be prepared to discuss treatment options with symptomatic patients. In this article, we review various exam and imaging tools that can help with the assessment of VO and educating patients about their clinical findings.

Exam findings of consequence

While examining a patient at the slit lamp, there are several findings to pay particular attention to. They include lenticular status, presence of a Weiss ring, absence of vitreous cells and peripheral retinal findings such as retinal tears or lattice degeneration.

If a patient hasn't had cataract surgery, the vitreous just posterior to the lens can't be completely removed during the operation, which could lead to incomplete resolution of the patient's symptoms. Inducing a posterior vitreous detachment, if a Weiss ring isn't present on exam, can lead to an increased risk of iatrogenic breaks during surgery.

Conversely, if no Weiss ring is present on exam and the hyaloid isn't separated during surgery, patients may become symptomatic in the future when the PVD naturally occurs.

Finally, it's critical to rule out mimickers

Bios

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Dr. Kumar disclosed being a consultant for Alimera Sciences.

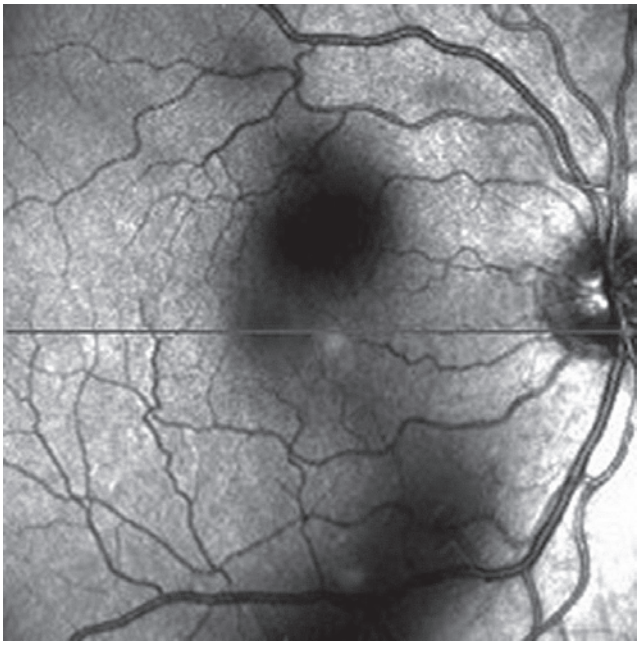
Dr. Cunningham disclosed acting as a consultant for Alimera, Allergan/AbbVie and Novartis.

such as ocular amyloidosis, lymphoma and uveitic conditions such as birdshot chorioretinopathy.

Role of multimodal imaging

Multimodal imaging is a helpful tool for the clinical assessment of VOs. Several imaging tests can aid in our evaluation of the vitreous and help to educate the patient about how their symptoms correlate with their anatomical findings.

The first test is scanning laser ophthalmoscopy imaging on optical coherence tomography to assess the shadowing of the vitreous (*Figure*). On the main OCT image, the hyaloid face separation from (or adherence to) the retina can be visualized.



Scanning laser ophthalmoscopy demonstrates vision-disturbing vitreous opacities. (*Source: Huang L, et al. Vitreous floaters and vision: Current concepts and management paradigms. In Sebag J, ed. Vitreous – in Health & Disease. New York, NY; Springer; 2014:771-788. Used with permission*)

Widefield fundus photography and autofluorescence can help to educate the patient about the anatomy of the vitreous and retina, and to highlight any peripheral pathology. Although it's not used routinely in our clinical practice, ultrasound can also be helpful to quantify vitreous opacities and correlate them with disease severity.[1]

Current treatment options for VO

Typically, when facing a patient with symptomatic VO, the management options include observation, YAG-laser vitreolysis and pars plana vitrectomy. YAG-laser vitreolysis has gained popularity for addressing visually significant floaters, because it's a relatively fast and non-invasive procedure.

The first report of YAG laser vitreolysis for floaters was published in 1993.[2] However, various reports since then have questioned the safety of YAG laser vitreolysis, with sequelae that range from refractory glaucoma to posterior capsule rupture and rapid cataract progression after the procedure.[3-6]

Because of the potential complications associated with YAG laser vitreolysis, the American Society of Retina Specialists Research and Safety in Therapeutics (ReST) committee recommended further investigation.[7]

In addition to the potential safety issues, another downside of YAG vitreolysis is that the VOs don't actually go away. The laser may displace the large floater from the central vision, but patients often have persistent symptoms. Vitrectomy surgery is the only procedure that eliminates the opacities.

PPV safety profile improves

PPV for visually significant floaters was initially reported more than 20 years ago.[8] In the past 20 years, however, the safety

PPV for visually significant floaters was initially reported more than 20 years ago. Since then the safety profile of small-gauge vitrectomy has improved dramatically.

profile of small-gauge vitrectomy has improved dramatically. Many studies have shown reduced complications with 23- and 25-gauge PPV compared to 20-gauge vitrectomy, including fewer cases of vitreous incarceration at the sclerotomy site, fewer iatrogenic breaks, and less dialysis at the vitreous base.[9-14]

Moreover, smaller probes allow for more precise and controlled surgical movements, resulting in safer removal of the vitreous and less traction on the retina. From a patient comfort perspective, the transconjunctival sutureless approach leads to less discomfort and ocular inflammation.

Despite the improved safety profile, vitreoretinal surgeons still remain hesitant to perform vitrectomies for VO. A 2015 survey assessing the management of symptomatic floaters found that only 25 percent of vitreoretinal surgeons would perform vitrectomy to address symptomatic floaters.[15] So the question is: Should we be more open to considering PPV for symptomatic VO?

Smaller probes allow for more precise and controlled movements, resulting in safer vitreous removal and less traction on the retina. From a patient comfort perspective, the transconjunctival sutureless approach leads to less discomfort.

A qualified yes for PPV

The short answer is yes—in the correct patient. The majority of patients who present with an acute PVD describe bothersome floaters or photopsias. Symptoms in most patients will improve with time, typically in three to six months, and will be tolerable. However, a small percentage of patients may have significant VOs that impair their quality of life and ability to work. In these symptomatic patients with specific exam criteria, it's not unreasonable to discuss PPV for VO.

A detailed discussion with these patients about expectations and the risks and benefits of PPV is essential. An important intraoperative complication to discuss is the potential for intraoperative retinal breaks. In most series, the reported rates of intraoperative or iatrogenic breaks are less than 5 percent.[16] Other important potential postoperative complications to include in the discussion with the patient include hypotony, vitreous hemorrhage (7 to 9 percent), macular edema (10 percent) and retinal detachment (0 to 17 percent).[16]

Criteria for PPV for VO

So, what are the specific criteria that we consider when signing a patient up for PPV for VO?

Our group evaluated the safety profile and surgical outcomes of PPV for VO in our retina-only private practice over a four-year period. A total of 104 eyes of 81 patients underwent either 23- or 25-gauge vitrectomy. All patients were required to be pseudophakic, symptomatic for more than six months, and have a Weiss ring present on exam.

Mean preoperative VA of 0.16 ±0.17 logMar units (~20/29 SE) improved to 0.12 ± 0.15 logMar units (~20/26 SE, Wilcoxon test, p=0.0083) at the last known follow-up after PPV. There were no cases of retinal tears or retinal detachments in our series. One patient developed a vitreous hemorrhage that spontaneously resolved.

We've had excellent surgical outcomes and believe the key was patient selection that met the three aforementioned criteria. Subjectively, patients were overall satisfied with the surgical outcome. Although we didn't perform a preoperative or postoperative VFQ-25 survey for our patients, 43 percent of them elected to have surgery in the fellow eye.[17]

For the patient without PVD

In our discussion with a patient who hasn't yet had cataract surgery or doesn't yet have a PVD, we find it important to counsel them about the safety of performing PPV for floaters in the ideal setting. For example, in patients without a PVD, the risk of an intraoperative retinal tear increases by a factor of almost five. The risk of retinal tears reported with induction of a PVD for PPV, whether for floaters, macular hole or epiretinal membrane, is

approximately 5 percent compared with 1 percent without induction of a PVD.[16-20] We find it important to tell patients about these risks.

In phakic patients, the surgeon isn't able to clear some of the most visually disturbing floaters located just posterior to the lens. Therefore, the patient's symptoms could persist after surgery.

Despite having cutting-edge technology and imaging platforms to enhance visualization of the vitreoretinal interface, we still lack objective data to quantify VO. Current objective data is limited to visual acuity alone, and most retina surgeons are reluctant to operate on an eye with a visual acuity of 20/20.

We need better, readily available metrics that evaluate contrast sensitivity and even quality of life measures. Some have proposed a VO severity grading scale that could provide additional objective data to retina surgeons and also serve as a helpful VO monitoring tool for referring doctors.

Bottom line

Vitreoretinal surgery has traditionally been viewed as anatomically repairing defects in the retina of symptomatic patients. With improved safety profiles of small-gauge vitrectomy and excellent patient outcomes, it's time to accept and expand the scope of vitreoretinal surgery to include PPV for VO.

Cataract surgery is routinely performed on patients with objectively "good vision," because subjectively functional vision loss can affect their quality of life. Patients with VO may similarly have a functional loss of vision with difficulty driving, reading or working. We really don't think twice about a symptomatic patient undergoing a cataract evaluation. Similarly, we shouldn't have to think twice about discussing surgery as an option for a patient with visually significant floaters that are impacting their functionality.

We must stress that although PPV for VO is generally a safe and effective procedure, complications may still occur, as they may with any surgical intervention. For that reason, we advise careful consideration of patient selection and a detailed informed consent process. RS

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We really don't think twice about a symptomatic patient having a cataract evaluation. Similarly, we shouldn't have to think twice about discussing surgery as an option for a patient with visually significant floaters that impact their functionality.

Peripheral lesions take DR imaging beyond ETDRS

Ultra-widefield imaging and artificial intelligence have called into question standards based on film photography.

SriniVas R. Sadda, MD

By SriniVas R. Sadda, MD

Take-home Points

- Advances in ultra-widefield imaging have allowed the retinal periphery to be imaged in a rapid and clinically practical manner.
- A substantial proportion of diabetic lesions reside in the more peripheral retina outside the seven standard Early Treatment Diabetic Retinopathy Study fields. Failure to consider these lesions may lead to an underestimation of retinopathy severity.
- Eyes with predominantly peripheral lesions may be at higher risk for progression, although this remains to be validated by large ongoing studies.
- Automated detection of diabetic lesions on ultra-widefield images may facilitate the development of a quantitative staging system for clinical use.

Bio

Dr. Sadda is director of Artificial Intelligence and Imaging Research at the Doheny Eye Institute and professor of ophthalmology at the University of California Los Angeles David Geffen School of Medicine.

DISCLOSURES: Dr. Sadda serves as a consultant to Amgen, AbbVie/Allergan, Genentech/Roche, Oxurion, Novartis, Regeneron, Iveric, 4D Molecular Therapeutics, Centervue, Heidelberg Engineering, Optos, Merck, Apellis, Astellas, Nanoscope, Gyroscope Therapeutics, Janssen and Pfizer; receives speaker fees from Carl Zeiss Meditec, Nidek, Novartis and Optos; and received research instruments from Nidek, Topcon, Heidelberg, Carl Zeiss Meditec, Optos and Centervue.

Diabetic retinopathy remains a leading cause of blindness among working-age individuals worldwide.[1] As retina specialists, a key component of our management of these patients is identification of diabetic lesions and staging of the severity of DR.

Our current approach to staging derives from the system originally proposed by the Airlie House investigators in 1968.[2] This system was based on comparing the severity and extent of specific diabetic lesions in various fields relative to standardized color photographs.

A total of seven 30-degree fields were chosen with a focus in the posterior pole to include the macula, optic nerve, and surrounding regions as these were thought to be most relevant for vision and to be involved early on in the disease process.

Limitations of ETDRS

The Airlie House system was further modified by the Diabetic Retinopathy Study and Early Treatment of Diabetic Retinopathy Study (ETDRS) investigators to develop a DR severity scale (DRSS) that paralleled the progression of the disease and predicted the risk for progression to proliferative diabetic retinopathy and vision loss.[3] The ETDRS-derived DRSS has been shown to be highly reproducible and has served as the backbone for clinical trials in DR over the last several decades.[4] Indeed, the reliability of this scale has allowed us to use steps of progression on this scale as an endpoint for regulatory approval of pharmacotherapeutic agents.[5,6]

Despite the enormous success and impact of the ETDRS-based DRSS, the system does have several important limita-

tions, in large part due to the constraints of the imaging technology available at the time the system was developed; namely, small-field color film photography. As a result, the system was ultimately qualitative and categorical rather than quantitative.

While a higher DRSS level indicated more advanced disease, the distance between steps was not necessarily linear. A qualitative system is also relatively imprecise. The ETDRS scale features multiple levels and is based on repeatability; a two-step progression was deemed to be meaningful.[7]

Desire for quantitative analyses

However, in this era of pharmacotherapeutics, where a regression of some DR lesions may be observed, a quantitative approach—that is, one based on precise number or area of lesions—may be preferred.[8]

Indeed, quantitative analyses of specific lesions, such as microaneurysms, has revealed that microaneurysm turnover may represent an additional risk factor for progression of DR.[9] Another limitation of the DRSS is that, while it has been invaluable in clinical research, it has proven difficult to fully translate to clinical practice. Comparison to standardized photographs and assessments of multiple fields is simply impractical in the context of a busy practice. Many simplifications, including the International Clinical disease severity scale for DR (ICDR),[10] have been proposed for routine clinical use, but these yield further loss of precision and still aren't consistently used by clinicians.

Perhaps the biggest limitation of the ETDRS-derived DRSS, however, is that it's based on a presumed representative sample of the retina that was easily accessible by standard fundus cameras. DR, however, can impact the entire retina. Advances in retinal imaging, in particular ultra-widefield (UWF) technology, has made photographic capture of the peripheral retina feasible. Whereas the ETDRS seven standard fields only covered about 30 percent of the total retinal surface area, modern UWF devices, especially with the use of steered images, can capture 90 percent or more of the retinal surface area.

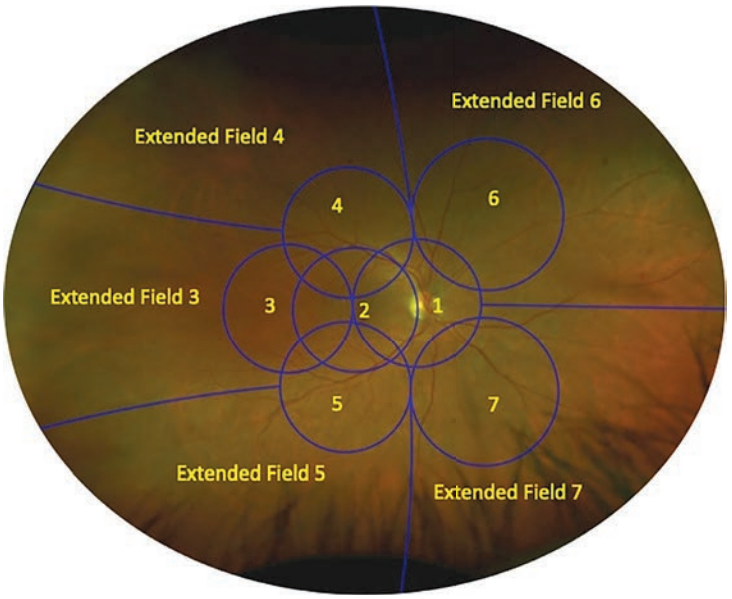

Figure 1. Ultra-widefield Optos pseudocolor image of the right eye of a patient with moderate nonproliferative diabetic retinopathy shows the seven standard Early Treatment Diabetic Retinopathy Study fields and the corresponding extended peripheral lesions. In this case, there are more extensive diabetic retinopathy lesions in extended field 6 compared to the corresponding ETDRS field 6, and thus this eye would be deemed to have predominantly peripheral lesions.

Notably, Paolo S. Silva, MD, and colleagues observed that more than 60 percent of diabetic lesions (hemorrhages, microaneurysms, intraretinal microvascular abnormalities, neovascularization) were located outside the seven ETDRS fields.[11]

Peripheral lesions and DR severity

Thus, the key question for consideration here is this: Is the assessment of these DR lesions beyond the seven standard fields of clinical importance? Dr. Silva and colleagues observed that if the peripheral lesions were considered, a

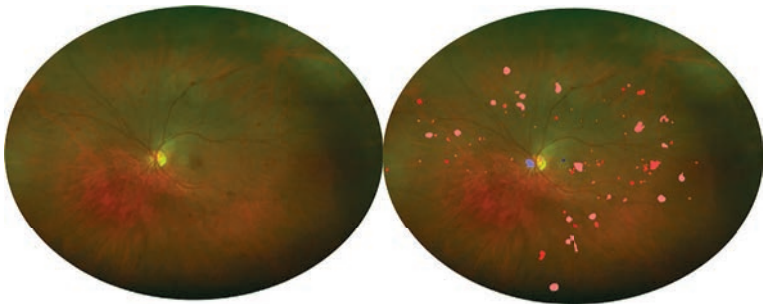

Figure 2. Left: Ultra-widefield Optos pseudocolor image of an eye with severe nonproliferative diabetic retinopathy. Right: Automated detection of DR lesions using a deep-learning algorithm. The number and distribution of lesions may be quantified.

Neovascularization elsewhere lesions or areas of preretinal hemorrhage outside the seven standard fields would seem to be of particular concern, because they could lead to more rapid and severe vision loss.

higher severity level of DR would have been selected in about 10 percent of their cases.[11] This suggests that failure to consider peripheral DR lesions on the whole may lead to an underestimation of the DR severity level.

Neovascularization elsewhere (NVE) lesions or areas of preretinal hemorrhage (PRH) outside the seven standard fields would seem to be of particular concern, because they could lead to more rapid and severe vision loss if they're undetected and consequently not monitored or treated appropriately.

If we accept that peripheral lesions in DR could potentially be of clinical relevance, how do we actually assess them in the context of our current approach to staging DR? Dr. Silva and colleagues proposed five peripheral extended fields adjacent to ETDRS fields 3 to 7, within which the severity of DR lesions could be assessed.[12]

However, there are no reference standard photographs of lesion severity for these larger extended fields. In the absence of such references, they proposed comparing lesion severity in the peripheral extended fields with the corresponding ETDRS field (*Figure 1, page 36*). If any of the five extended fields demonstrated more DR lesions compared to its corresponding ETDRS field, they deemed the eye to contain predominantly peripheral lesions (PPL).[13] The presence of PPL is a frequent finding in eyes with DR. In a study of more than 1,400 eyes with DR, we observed that 37 percent of eyes had PPL, and more than 30 percent PPL was observed at all ETDRS DRSS levels from mild nonproliferative DR to PDR.[14]

In a subsequent, small (n=109 eyes) longitudinal study, Dr. Silva and colleagues demonstrated that DR eyes with PPL had about a four times greater risk for progression to PDR than eyes without PPL.[13] This is a striking and potentially transformative result, given that peripheral lesions weren't even considered in the ETDRS system.

Validating the value of peripheral lesions

As a result, the DRCR Retina Network initiated Protocol AA to validate whether evaluation of the retinal far periphery on UWF images improves our ability to assess DR and predict rates of DR worsening over time as compared with evaluation only of the area within the seven standard ETDRS fields.[15] Results are expected soon, and if the previous observations are confirmed, one can expect a significant evolution of our current approach to staging DR.

Protocol AA will hopefully be able to answer other important questions. Among them: Is the current method (i.e., single-field determination of PPL) for assessing the retinal periphery the best approach for staging DR? For example, should we be considering the entire periphery vs. the posterior pole (i.e., a global assessment) rather than individual fields? Also, should we be considering only the number of lesions? What about the size or surface area of lesions? We have shown that the classification of the peripheral retinopathy can change depending on the method used.[16]

Potential of AI

Perhaps an even more fundamental question is: Why should we be limited to

categorical or qualitative methods from a previous era that were necessitated by the constraints of film-based photography? In this era of digital imaging and artificial intelligence (AI), it may be possible to quantify diabetic lesions throughout the fundus including the retinal periphery.

There are currently two Food and Drug Administration-cleared AI-based technologies for automated detection of referral-warranted DR.[17,18] Both of these systems, however, were designed for standard field fundus cameras. We applied one of these systems (EyeArt) to UWF Optos pseudocolor images and observed good performance for detecting referral-warranted DR, even without optimizing the algorithms for UWF images.[19]

This bodes well for future AI-based screening using UWF images, but significantly highlights the possibility that UWF images may be combined with AI/deep learning to quantify the location, number and size of all DR lesions throughout the retina in the eyes of our diabetic patients (*Figure 2*).

Using this quantitative approach to assessing DR in the entire retina, we demonstrated a correlation between the number of DR lesions and the ETDRS DRSS.[20] If Protocol AA confirms the importance of more peripheral DR lesions, one may be able to incorporate this into a quantitative staging system by assigning a greater weight to a DR lesion based on its distance from the center of the fundus.

Bottom Line

Advances in UWF imaging have enabled the assessment of DR lesions throughout the fundus, including the retinal periphery. Preliminary studies suggest that DR eyes with predominantly peripheral lesions may be at higher risk for progression to PDR, though this requires confirmation by the pending results from Protocol AA. Combining UWF imaging with automated deep-learning tools may make it possible to quantify all DR lesions throughout the eye. This may open the door for a new quantitative and precise staging system that may transform our approach for diagnosing and monitoring our patients with diabetic retinopathy. RS

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Combining UWF imaging with deep-learning tools may make it possible to quantify all DR lesions throughout the eye and open the door for a new quantitative and precise staging system that may transform our diagnostic approach.

Retina Standouts from AAO

New insights into ILM tears, trial readouts and more

Five abstracts on gene therapy and role of central subfield thickness in diabetic macular edema, vitreous hemorrhage and retinopathy of prematurity.

By Avni P. Finn, MD, MBA

Avni P. Finn, MD, MBA

Take-home points

- Giant internal limiting membrane tears due to epiretinal membrane contracture may be more common in myopic eyes and provide a safe "handle" to initiate ERM and ILM peeling.
- A Phase III Trial evaluating faricimab for diabetic macular edema showed 72 percent of eyes in a personalized treatment arm may achieve every 12-week or greater dosing.
- A pilot study by the DRCR Retina Network on photobiomodulation (PBM) for DME showed PBM was not effective for DME in eyes with good vision.
- Six-month data for suprachoroidal injection of an adeno-associated virus vector for neovascular age-related macular degeneration reported a significant reduction in treatment burden.
- Dosing errors with the aflibercept prefilled syringe may lead to a potential 50-to-120 percent increase in dose delivered.

Bio

Dr. Finn is assistant professor of clinical ophthalmology and visual sciences at the Vanderbilt Eye Institute in Nashville, Tennessee.

DISCLOSURES: Dr. Finn disclosed relationships with Allergan/AbbVie, Genentech/Roche and Apellis Pharmaceuticals.

The annual meeting of the American Academy of Ophthalmology and the Retina Subspecialty Day affiliated with it returned to a live format in New Orleans in November, and the clinical science presented during the sessions showed that the COVID-19 pandemic, while it may have slowed some clinical trials and studies, hasn't sidetrack them completely.

Here we present five notable abstracts from the meeting: results of a retrospective review of giant internal limiting membrane tears with epiretinal membranes; updates from two Phase III trials evaluating faricimab for diabetic macular edema; a pilot study evaluating light therapy for DME; a readout of a trial of an adeno-associated virus (AAV) vector for neovascular age-related macular edema; and a report on dosing errors using the aflibercept prefilled syringe.

Mark Johnson, MD

New insights into giant ILM tears

Large ILM tears associated with ERMs often go unrecognized and are rarely discussed, Mark Johnson, MD, reported. This review of 23 eyes defined a giant ILM tear as a dehiscence large enough to result in a curved and scrolled edge of ILM.[1] Dr. Johnson and colleagues hypothesized ERM contracture contributes to the pathogenesis of these tears because they're usually located at the edge of the contracted ERM.

In this retrospective review of cases from 2016 to 2019, Dr. Johnson and his team identified ILM tears in 23 of 71 eyes with ERM. They found that radial cuts on preoperative optical coherence tomography allowed for increased detection of ILM tears and that virtually all of the ILM tears were convex with an edge pointing

toward the fovea. High myopia was more common in eyes with ILM tears.

Associated features included nerve fiber layer schisis, inner retinal dimpling in the area with absent ILM (likely due to Muller cell injury), and perivascular red lesions consistent with intraretinal cavitations or inner lamellar defects. The suspected tears were confirmed with intraoperative Brilliant Blue G (DORC) staining. Dr. Johnson stated that the ILM tear could be used as a safe handle during surgery to initiate ILM and ERM peeling.

Dr. Johnson has no relevant relationships to disclose.

Jeffrey Heier, MD

Faricimab DME Phase III readout

Faricimab, now known as Vabysmo (Genentech/Roche), is a bispecific antibody that inhibits both vascular endothelial growth factor and angiotensin 2 (Ang-2), which has the potential to increase treatment durability and efficacy. YOSEMITE and RHINE are two identical double-masked studies that enrolled almost 1,900 patients with center-involving DME and visual acuity of 20/40 or worse.[2] Patients were randomized to faricimab q8 weeks after six loading doses, faricimab personalized treatment interval (PTI) after four loading doses, or aflibercept q8 weeks after five loading doses. The primary endpoint was mean best-corrected visual acuity over weeks 48, 52 and 56.

Both trials met the primary endpoint, showing faricimab noninferiority to aflibercept with eyes gaining 10.5 to 11.2 letters at one year. Further, Jeffrey Heier, MD, noted that more than half of eyes in the PTI arm achieved q16-week dosing and 72 percent achieved q12-week or longer dosing. Pooled data demonstrated greater reductions in central subfield thickness in the faricimab-treated group compared to aflibercept, which was maintained through week 56.

A post hoc analysis showed eyes treated with faricimab achieved this absence of DME (defined as CST <325 µm) earlier than aflibercept-treated eyes—and more faricimab eyes (90 percent) achieved this endpoint than aflibercept eyes (80 percent). Rates of ocular and nonocular adverse events were low, with no reports of retinal vasculitis or occlusive retinitis. Intraocular inflammation rates were 1.3 to 1.4 percent in the faricimab arms vs. 0.6 percent in the aflibercept arm.

Dr. Heier disclosed relationships with Regeneron Pharmaceuticals, Genentech/Roche, Novartis, Bayer and Chengdu Kanghong Biotechnology.

Judy Kim, MD

Photobiomodulation therapy for DME

Judy Kim, MD, presented results from the DRCR Retina Network pilot study evaluating photobiomodulation (PBM).[3] PBM is irradiation by light in the far-red to near-infrared light spectrum (630-900 nm). The literature has reported some beneficial effects of PBM on improved wound healing, apoptosis and oxidative stress reduction, and reduced leukostasis and expression of ICAM-1, which is involved in capillary permeability in animal models. Additionally, two small clinical studies suggested a potential benefit of PBM for DME.

This Phase II study enrolled 135 eyes with good vision (VA 20/25 or better) and center-involved DME, randomizing them to PBM (n=69) or placebo (n=66). Baseline characteristics were well balanced between the two arms. Eyes receiving PBM were treated morning and night for 90 seconds at a time with active treatment emitting light at 670 nm at a dose of 4.5 J/cm^2 with an irradiance area not greater than 50 mW/cm.^{2} Patients were seen monthly for four months, with mean CST measured at month four.

While device compliance was excellent with no reported significant treatment

The study reported that an internal limiting membrane tear could be used as a safe handle during surgery to initiate ILM and ERM peeling.

fatigue, the study found no significant difference in CST at month four between the two groups. There was an overall 13-µm gain in CST in the PBM group and 15-µm gain the placebo group. At four months, 90 percent of the PBM and 86 of the placebo group had persistent DME. There was no significant VA change or gain over time; in fact, both groups had a ≥5-letter decline over the four months. Dr. Kim said the results didn't support moving onto a Phase III trial at this dosing frequency.

Dr. Kim disclosed relationships with Genentech/Roche, Novartis and Regeneron Pharmaceuticals.


Robert Avery, MD

Two-year gene therapy results in nAMD

RGX-314 (RegenxBio) uses an AAV8 vector to deliver an anti-VEGF Fab. The procedure is being evaluated in the operating room via a subretinal route or in the clinic via a suprachoroidal route. The Phase I/IIa study enrolled 42 patients in five dose-escalation cohorts.[4]

This study is now complete with two-year follow-up. Participants had to be heavily treated with a response to anti-VEGF treatment. They received a single injection of RGX-314 via a subretinal route and overall, the treatment was well-tolerated. The most common ocular adverse event was retinal pigmentary changes, noted to be mild in 62 percent of patients, but severe in two eyes, both of which had atrophy prior to enrollment.

Thirty-six percent of eyes had postoperative inflammation, which was mild in all cases. Robert Avery, MD, noted there wasn't much treatment effect in cohorts 1 and 2. However due to dose escalation, cohorts 3 through 5 demonstrated significant and lasting results. Due to these positive results, the Phase III ATMOSPHERE trial is now enrolling. In the trial, two arms are receiving RGX-314 via a subretinal dose; monthly ranibizumab (Lucentis, Genentech/Roche) is the comparator.

Two suprachoroidal studies of RGX-314 are ongoing in patients with nAMD and nonproliferative diabetic retinopathy. Dr. Avery presented six-month data for AAVIATE, the Phase II nAMD trial, which enrolled dose-escalation cohorts compared to monthly ranibizumab. The trial so far hasn't shown any significant difference in BCVA between the two arms. Most impressive was the more-than-70 percent reduction in previous treatment burden in the RGX-314 arms, with 30 to 40 percent of patients not requiring any additional treatment. Thus far, the effect has been durable with eyes maintaining good vision over the six months. Mild IOI and episcleritis were noted, but resolved with topical treatment alone.

Dr. Avery also touched on the ALTITUDE study enrolling patients with severe NPDR and PDR. Fifteen eyes received suprachoroidal treatment with no IOI and only one case of episcleritis. A greater than two-step Diabetic Retinopathy Severity Scale improvement was seen in 33 percent of treated eyes and none in the observation arm at three months.

Dr. Avery disclosed he is a consultant to RegenxBio and Adverum.

Thirty-six percent of RGX-314-treated eyes had mild postoperative inflammation. There wasn't much treatment effect in early cohorts, but later cohorts, due to dose escalation, demonstrated significant and lasting results.


Roger Goldberg, MD

Aflibercept prefilled syringe dosing errors

The pre-filled syringe (PFS) potentially offers improved efficiency given the large number of intravitreal injections performed in the United States. Upon releasing the prefilled syringe for aflibercept, the Food and Drug Administration required Regeneron Pharmaceuticals to perform a usability study of a single injection in at least 30 patients showing accurate dosing of the labeled dose. Since the release of the PFS, transient vision loss, intraocular pressure rise and transient central retinal artery occlusion have been reported.

(Continued on page 46)

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Department Editor *David R. P. Almeida, MD, PhD*

Social media and CME

A close look at the future of lifelong learning in the Twitter era.

By David R. P. Almeida, MD, PhD, MBA

I recently attended the American Academy of Ophthalmology annual meeting in New Orleans. With COVID-19 precautions in place, live seminars have the peculiar impression that, although still the same, everything is now different. Historical approaches to continuing medical education reveal limitations and highlight the need for iterative improvements on this critical aspect of lifelong learning in medicine.

Social media and its internet- and mobile-based technologies can enhance interactivity among individuals and organizations by facilitating wide accessibility and personalization ideal for targeting specific audiences for education. While the societal implications of social media ubiquity and privacy intrusion can be left for another debate, as far as CME is concerned, evidence suggests that more youthful, technology-savvy participants prefer coordination and delivery of CME along social media lines of communication.[1]

This relationship is significant for various health-care professionals, including nurses, pharmacists, medical students, residents, fellows and practicing physicians.[1] The next generation of physicians will demand that the future of CME will have to, at least partly, exist adjacent to social media technologies.

Social media for CME awareness

Conferences, symposiums and meetings, whether virtual or live, typically dictate CME topics akin to a restaurant's à la carte menu. This provides adequate awareness to attendees of a given congress but lacks impact beyond those in the know. By contrast, social media can be deployed to increase CME awareness, and conservative measurements show this can have a modest effect on driving traffic to CME options.[2] Social media can readily engage physicians in clinical practice, whether retina specialists or radiologists, by elevating CME awareness that physicians may not traditionally be mindful of.

The not-so-distant future for CME

Ultimately, the goal of social media for CME should be for the former to facilitate the latter. Social media needs to support interactivity and allow individual learners to share ideas and questions seamlessly. Without the limitation of occupying the same location at the same time, social media can break down barriers so that learners and educators can connect and interact more easily.[3]

Critically, future CME course educators and professionals need to brand social media in a manner that can be measured and validated in terms of enhanced educational value by providing better routes for learners to provide feedback and expedite exchange between peers and colleagues.[3]

Bottom line

The practice of medicine and commitment to excellence in patient care requires the physician to continue lifelong learning. When one considers the myriad methods that can be carried out with CME, it's abundantly clear that social media can aid physicians to stay abreast of medical information and provide a bona fide manner of matriculating CME events.

Bio

Dr. Almeida is a vitreoretinal surgeon at Erie Retinal Surgery in Erie, Pa.

DISCLOSURE: Dr. Almeida reports no relevant financial relationships.

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Time for a financial deep dive

A review of your practice's financial metrics can help you spot problems in your billing system.

By Ellen R. Adams, MBA

Whether you're a solo practitioner or in a group practice, it's important that you periodically review your financial metrics. Financial reports will tell you more than your net revenue. When you review metrics thoughtfully, you may be able to detect problems in your billing system.

In this era of chronic staffing shortages, high staff burnout and constant adjustments due to COVID-19, a financial deep dive can help you spot sloppy claim processing, abusive billing or, worse, fraudulent claims or embezzlement.

Start with AR days

For the big-picture view, it may be easiest to start with accounts receivable (AR) days. AR days indicate how long it takes for a claim to be fully paid. For instance, let's say the only insurance you accept is Medicare and your front desk employees collect all deductibles at the time of service. Medicare would pay a clean (error-free) claim in about 14 days. In this scenario, your AR days would be about 14.

In reality, your practice accepts many insurance plans. To accurately interpret your AR days, you should first determine your payer mix. Commercial carriers usually pay a clean claim in about 30 days, but some take up to 60 days.

A typical ophthalmology practice is about half Medicare, half commercial carriers. If your practice has a larger Medicare population, you might expect a lower AR day number (around 35). A higher percentage of commercial carriers means a higher AR days number (up to 50). If your AR days is much higher, there may be a serious problem in your billing process.

What high AR days may mean

High AR days can signify inadequate staff training in your billing department, resulting in excessive claim denial and a need for reprocessing of claims. When a claim is denied, it will sit in AR until someone corrects and resubmits it. If your billing staff is submitting clean claims, high AR can indicate slow collections. This problem might be with your front desk employees or billing.

When your office collects copayments or deductibles on the date of service, your AR days will improve. Conversely, if cash is collected only after services are rendered, "the chase is on," as one astute biller put it. Your billing employees will then have to send invoices repeatedly. This often involves calling the patient to try to collect the outstanding balance.

Any time a claim is touched more than once, whether due to incorrect submission or a mishandling of patient responsible payments, your AR days will go up—and your revenue will go down.

What about low AR days?

Very low AR days are also problematic unless you offer a very high percentage of cash (usually non-covered) services, and your employees collect the full self-pay fees on the date of service. Low AR days can otherwise be an indicator that billing staff are overworked and consequently adjusting off claims that should be paid.

Billers may also know the types of claims that fail to pay and inappropriately add modifiers before they submit them. That can be a trigger for Medicare audits.

Your billing staff might also be adjusting off patient-responsible amounts—a problem that can lead to accusations of inducement. Any time you offer a service that automatically costs a patient less than the "practice down the street," the Office of Inspector General will assume the worst: that you're luring patients to your practice with free services. Slightly

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.

low AR days may indicate billers can't resolve certain categories of claims (e.g., exams billed with a modifier), and thus they adjust off the claim line item before they submit it rather than try to correct it.

Making adjustments

Once you have a handle on your AR days, you can turn to adjustments. Adjustments can be complicated. Like AR, the payer mix has significant influence on adjustments. Having a different fee schedule for each payer can be impractical, so most practices have just one.

In general, your fee schedule should be set about 10 percent higher than your highest payer for each service. If your fee schedule is too low, you'll lose revenue from higher-reimbursing payers. Set it too high and your adjustments will be nearly impossible to monitor.

The upshot of a single fee schedule is that any lower-reimbursing plans will have significant adjustments, while higher-paying plans have much lower write-offs. You should have a clear understanding of the typical adjustment rate for your practice.

If your adjustments are high, it could simply be a sign of a poorly constructed fee schedule. Or it could be a sign of claim or payment mismanagement. Overworked billing employees shouldn't be automatically adjusting off problematic claims. The root cause of any denial needs to be corrected. In a worst-case scenario, employees who feel mistreated could be adjusting off partially paid claims and payments and pocketing the balance.

Don't forget monthly gross

If you haven't been monitoring your monthly gross receipts and charges per procedure, you should add this to your financial review. Look at previous month and year reports so you can identify practice patterns. For instance, in the northern United States, gross receipts typically dip in the winter when the "snowbirds" leave for warmer climes, then bump back up in the spring.

Understand your practice revenue patterns so you can plan appropriate staffing levels. Perhaps you could increase scheduled annual diabetic and non-urgent exams during the cyclical drop in revenue, then scale back on them during busier times.

A regular review of your AR days will give you a sense of your practice's financial health. When you consistently watch your financial reports, you'll be able to identify and correct front desk or billing problems, strategize practice growth and, best of all, reward those employees who are keeping your practice financially healthy. RS

Retina standouts from AAO

(Continued from page 42)

Roger Goldberg, MD, and his team searched the FDA's adverse events reporting system and found 19,592 adverse events reported in relation to intravitreal aflibercept with 1,137 related to IOP increase, ocular hypertension or transient blindness. Since the release of PFS late in 2020, 160 of these adverse events were labeled "a device use issue" with the majority (151) reported in Europe. The European authorities released a letter citing a sevenfold increased risk of IOP elevation using the pre-filled syringe compared to the luer-lock syringe citing "incorrect preparation of the syringe."

Dr. Goldberg and his team analyzed the etiologies for the variability in the volume delivered with the PFS. The aflibercept PFS has nearly a 2-mm greater internal diameter than the ranibizumab PFS. Additionally, the dose mark thickness is three times that of the ranibizumab syringe. The thickness of the dose mark alone can account for almost a 24 µL difference in the dosage given.

In an experiment to measure dosing variability, Dr. Goldberg and his team placed the PFS plunger at three insertion levels: the proximal edge of the dose mark; the distal edge of dose mark; and the plunger cone tip at distal edge of dose mark. They tested each scenario three times and showed variability in positioning related to the dose mark thickness could lead to nearly a 50-percent increased dose, and variability in the cone tip alignment could lead to a 120-percent increase in dose delivered.

Dr. Goldberg noted that dose-setting errors with the aflibercept PFS can lead to marked increases in delivered volume due to the wide internal diameter, wide dose mark, and misalignment of the cone tip. Proper adherence to the instructions for use can minimize dose-volume errors, and industrial design of these syringes is very important, he added.

Dr. Goldberg disclosed relationships with Genentech/Roche and Regeneron Pharmaceuticals. RS

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4. Avery RA. Two-year results from the subretinal RGX-314 gene therapy Phase 1/2a study for the treatment of nAMD, and an update on suprachoroidal trials. Paper presented AAO Retina Subspecialty Day; New Orleans, LA; November 12, 2021.
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susvimo™

ranibizumab injection 100 mg/mL For Ocular Implant

SUSVIMO™ (ranibizumab injection) for intravitreal use via SUSVIMO ocular implant. This is a brief summary. Before prescribing, please refer to the full Prescribing Information.

WARNING: ENDOPHTHALMITIS

The SUSVIMO implant has been associated with a 3-fold higher rate of endophthalmitis than monthly intravitreal injections of ranibizumab. Many of these events were associated with conjunctival retractions or erosions. Appropriate conjunctiva management and early detection with surgical repair of conjunctival retractions or erosions may reduce the risk of endophthalmitis. In clinical trials, 2.0% of patients receiving a ranibizumab implant experienced at least one episode of endophthalmitis *(see Contraindications (4.1), Warnings and Precautions (5.1))*.

1 INDICATIONS AND USAGE

SUSVIMO (ranibizumab injection) is indicated for the treatment of patients with Neovascular (wet) Age-related Macular Degeneration (AMD) who have previously responded to at least two intravitreal injections of a Vascular Endothelial Growth Factor (VEGF) inhibitor medication.

4 CONTRAINDICATIONS

4.1 Ocular or Periocular Infections

SUSVIMO (ranibizumab injection) is contraindicated in patients with ocular or periocular infections.

4.2 Active Intraocular Inflammation

SUSVIMO (ranibizumab injection) is contraindicated in patients with active intraocular inflammation.

4.3 Hypersensitivity

SUSVIMO (ranibizumab injection) is contraindicated in patients with known hypersensitivity to ranibizumab products or any of the excipients in SUSVIMO (ranibizumab injection).

5 WARNINGS AND PRECAUTIONS

The SUSVIMO implant and/or implant-related procedures have been associated with endophthalmitis, rhegmatogenous retinal detachment, implant dislocation, vitreous hemorrhage, conjunctival erosion, conjunctival retraction, and conjunctival blebs. Patients should be instructed to report any signs or symptoms that could be associated with these events without delay. In some cases, these events can present asymptomatically. The implant and the tissue overlying the implant flange should be monitored routinely following the implant insertion, and refill-exchange procedures to permit early medical or surgical intervention as necessary. Special precautions need to be taken when handling SUSVIMO components *(see How Supplied/Storage and Handling (16.3))*.

5.1 Endophthalmitis

In the active comparator period of controlled clinical trials, the ranibizumab implant has been associated with a 3-fold higher rate of endophthalmitis than monthly intravitreal injections of ranibizumab (1.7% in the SUSVIMO arm vs 0.5% in the intravitreal arm). When including extension phases of clinical trials, 2.0% (11/555) of patients receiving the ranibizumab implant experienced an episode of endophthalmitis. Reports occurred between days 5 and 853, with a median of 173 days. Many, but not all, of the cases of endophthalmitis reported a preceding or concurrent conjunctival retraction or erosion event.

Endophthalmitis should be treated promptly in an effort to reduce the risk of vision loss and maximize recovery. The SUSVIMO (ranibizumab injection) dose (refill-exchange) should be delayed until resolution of endophthalmitis *(see Dosage and Administration (2.9) and Adverse Reactions (6.1))*.

Patients should not have an active or suspected ocular or periocular infection or severe systemic infection at the time of any SUSVIMO implant or refill procedure. Appropriate intraoperative handling followed by secure closure of the conjunctiva and Tenon's capsule, and early detection and surgical repair of conjunctival erosions or retractions may reduce the risk of endophthalmitis *(see Warnings and Precautions (5.5))*.

5.2 Rhegmatogenous Retinal Detachment

Rhegmatogenous retinal detachments have occurred in clinical trials of SUSVIMO and may result in vision loss. Rhegmatogenous retinal detachments should be promptly treated with an intervention (e.g., pneumatic retinopexy, vitrectomy, or laser photocoagulation). SUSVIMO (ranibizumab injection) dose (refill-exchange) should be delayed in the presence of a retinal detachment or retinal break *(see Dosage and Administration (2.9))*.

Careful evaluation of the retinal periphery is recommended to be performed, and any suspected areas of abnormal vitreo-retinal adhesion or retinal breaks should be treated before inserting the implant in the eye.

5.3 Implant Dislocation

In clinical trials, the device has dislocated/subluxated into the vitreous cavity or has extended outside the vitreous cavity into or beyond the subconjunctival space. Device dislocation requires urgent surgical intervention. Strict adherence to the scleral incision length and appropriate targeting of the pars plana during laser ablation may reduce the risk of implant dislocation.

5.4 Vitreous Hemorrhage

Vitreous hemorrhages may result in temporary vision loss. Vitrectomy may be needed in the case of a non-clearing vitreous hemorrhage *(see Dosage and Administration (2.9))*.

In clinical trials of SUSVIMO including extension phases, vitreous hemorrhages were reported in 5.2% (23/443) of patients receiving SUSVIMO. The majority of these hemorrhages occurred within the first post-operative month following surgical implantation and the majority of vitreous hemorrhages resolved spontaneously. Patients on antithrombotic medication (e.g., oral anticoagulants, aspirin, nonsteroidal anti-inflammatory drugs) may be at increased risk of vitreous hemorrhage. Antithrombotic medications are recommended to be temporarily interrupted prior to the implant insertion procedure. The SUSVIMO (ranibizumab injection) dose (refill-exchange) should be delayed in the event of sight-threatening vitreous hemorrhage. The use of pars plana laser ablation and scleral cauterization should be performed to reduce the risk of vitreous hemorrhage.

5.5 Conjunctival Erosion or Retraction

A conjunctival erosion is a full thickness degradation or breakdown of the conjunctiva in the area of the implant flange. A conjunctival retraction is a recession or opening of the limbal and/or radial peritomy. Conjunctival erosions or retractions have been associated with an increased risk of endophthalmitis, especially if the implant becomes exposed. Surgical intervention (e.g., conjunctival/Tenon's capsule repair) is recommended to be performed in case of conjunctival erosion or retraction with or without exposure of the implant flange.

In clinical trials of SUSVIMO including extension phases, 3.6% (16/443) of patients receiving SUSVIMO reported conjunctival erosion and 1.6% (7/443) of patients receiving SUSVIMO reported conjunctival retraction in the study eye.

Appropriate intraoperative handling of conjunctiva and Tenon's capsule to preserve tissue integrity and secure closure of peritomy while ensuring placement of sutures away from implant edge may reduce the risk of conjunctival erosion or retraction. The implant and the tissue overlying the implant flange should be monitored routinely following the implant insertion.

5.6 Conjunctival Bleb

A conjunctival bleb is an encapsulated elevation of the conjunctiva above the implant flange, which may be secondary to subconjunctival thickening or fluid. Conjunctival blebs may require surgical management to avoid further complications, especially if the implant septum is no longer identifiable due to the conjunctival bleb.

In clinical trials of SUSVIMO including extension phases, 5.9% (26/443) of patients receiving SUSVIMO reported conjunctival bleb/conjunctival filtering bleb leak in the study eye. Strict adherence to the scleral incision length, appropriate intraoperative handling of conjunctiva and Tenon's capsule to preserve tissue integrity and secure closure of peritomy, and proper seating of the refill needle during refill-exchange procedures may reduce the risk of conjunctival bleb.

5.7 Postoperative Decrease in Visual Acuity

Visual acuity was decreased by 4 letters on average in the first postoperative month and 2 letters on average in the second postoperative month following initial implantation of SUSVIMO [*see Clinical studies (14)*].

5.8 Air Bubbles Causing Improper Filling of the Implant

Minimize air bubbles within the implant reservoir as they may cause slower drug release. During the initial fill procedure, if an air bubble is present, it must be no larger than 1/3 of the widest diameter of the implant. If excess air is observed after initial fill, **do not** use the implant. During the refill-exchange procedure, if excess air is present in the syringe and needle **do not** use the syringe and needle. If excess air bubbles are observed after the refill-exchange procedure, consider repeating the refill-exchange procedure.

5.9 Deflection of the Implant

Use caution when performing ophthalmic procedures that may cause deflection of the implant and subsequent injury. For example, B-scan ophthalmic ultrasound, scleral depression, or gonioscopy.

6 ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the label:

- Endophthalmitis *(see Warnings and Precautions (5.1))*
- Rhegmatogenous Retinal Detachment *(see Warnings and Precautions (5.2))*
- Implant Dislocation *(see Warnings and Precautions (5.3))*
- Vitreous Hemorrhage *(see Warnings and Precautions (5.4))*
- Conjunctival Erosion or Retraction *(see Warnings and Precautions (5.5))*
- Conjunctival Bleb *(see Warnings and Precautions (5.6))*
- Postoperative Decrease in Visual Acuity *(see Warnings and Precautions (5.7))*

6.1 Clinical Trials 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 (Table 2) reflect exposure of 248 patients with nAMD in the Archway study following the SUSVIMO initial fill and implant insertion, refill, and implant removal (if necessary) procedures up to Week 40. In this patient population the most common (≥ 10%) adverse reactions up to Week 40 were conjunctival hemorrhage (72%), conjunctival hyperemia (26%), iritis (23%), and eye pain (10%).

Table 2 Adverse Reactions in nAMD patients occurring in ≥ 4% of patients in the SUSVIMO arm

	Week 40	
Adverse Reactions	**SUSVIMO n = 248**	**Intravitreal ranibizumab n = 167**
Conjunctival hemorrhage	72%	6%
Conjunctival hyperemia	26%	2%
Iritis[1]	23%	0.6%
Eye pain	10%	5%
Vitreous floaters	9%	2%
Conjunctival bleb/ filtering bleb leak[2]	9%	0
Foreign body sensation in eyes	7%	1%
Headache[3]	7%	2%
Hypotony of eye	6%	0
Vitreous detachment	6%	5%
Vitreous hemorrhage	5%	2%
Conjunctival edema	5%	0
Corneal disorder	4%	0
Corneal abrasion[4]	4%	0.6%
Corneal edema	4%	0

[1]Iritis includes: iritis, anterior chamber flare, and anterior chamber cell

[2]Conjunctival bleb/filtering bleb leak includes: conjunctival bleb, conjunctival filtering bleb leak, conjunctival cyst, subconjunctival cyst, and implant site cyst

[3]Headache includes: headache and procedural headache

[4]Corneal abrasion includes: corneal abrasion and vital dye staining cornea present.

6.2 Immunogenicity

As with all therapeutic proteins, there is potential for immune response in patients treated with ranibizumab including SUSVIMO. The detection of an immune response is highly dependent on the sensitivity, specificity, and drug tolerance level of the assay. Additionally, the observed incidence of antibody positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies in the study described below with the incidence of antibodies in other studies or to other products may be misleading.

In previously treated nAMD patients, anti-ranibizumab antibodies were detected in 2.1% (5 of 243) of patients prior to insertion of the SUSVIMO implant. After the SUSVIMO implant insertion and treatment, anti-ranibizumab antibodies developed in 12% (29 of 247) patients. No clinically meaningful differences in the pharmacokinetics, efficacy, or safety in patients with treatment-emergent anti-ranibizumab antibodies were observed.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no adequate and well-controlled studies of SUSVIMO (ranibizumab injection) 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 up to 41 times the human exposure (based on serum levels following the recommended clinical dose). No skeletal abnormalities were observed at serum trough levels similar to the 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))*, treatment with SUSVIMO (ranibizumab injection) may pose a risk to human embryofetal development.

All pregnancies have a background risk of birth defects, loss, and 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 is 2% – 4% and of miscarriage is 15% – 20% of clinically recognized pregnancies.

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 41 times higher than observed human C_{max} levels of SUSVIMO (ranibizumab injection) after treatment of a single eye.

No skeletal abnormalities were seen at the lower dose of 0.125 mg/eye, a dose which resulted in trough exposures similar to single eye treatment with SUSVIMO (ranibizumab injection) 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 SUSVIMO is administered to a nursing woman.

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

8.3 Females and Males of Reproductive Potential

Contraception

Females of reproductive potential should use effective contraception during treatment with SUSVIMO (ranibizumab injection) and for at least 12 months after the last dose of SUSVIMO (ranibizumab injection).

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 SUSVIMO (ranibizumab injection) may pose a risk to reproductive capacity.

8.4 Pediatric Use

The safety and efficacy of SUSVIMO (ranibizumab injection) in pediatric patients have not been established.

8.5 Geriatric Use

In the Archway study, 90% (222 of 248) of the patients randomized to treatment with SUSVIMO were ≥ 65 years old and approximately 57% (141 of 248) were ≥ 75 years old. No notable difference in treatment effect or safety was seen with increasing age.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Advise patients on the following after the implant insertion procedure:

Positioning:

- Keep head above shoulder level for the rest of the day.
- Sleep with head on 3 or more pillows during the day and the night after surgery.

How to care for the treated eye after the procedure:

- Do not remove the eye shield until they are instructed to do so by their healthcare provider. At bedtime, continue to wear the eye shield for at least 7 nights following the implant surgery.
- Administer all post-operative eye medications as directed by their healthcare provider.
- Do not push on the eye, rub the eye, or touch the area of the eye where the implant is located (underneath the eyelid in the upper and outer part of the eye) for 30 days following the implant insertion.
- Do not participate in strenuous activities until 1-month after the implant insertion or after discussion with their healthcare provider.

Magnetic Resonance (MR) Conditional information:

- The SUSVIMO implant is MR conditional. Inform their healthcare provider that they have SUSVIMO implanted in their eye and show their healthcare provider the SUSVIMO implant card should they require Magnetic resonance imaging (MRI).

Advise patients on the following after the Refill-Exchange procedure:

- Refrain from pushing on the treated eye, rubbing the eye, or touching the eye in the area of the implant (located underneath the eyelid in the upper and outer part of your eye) for 7 days following the refill-exchange procedure.
- Administer eye drops as directed by their healthcare provider.

Advise patients on the following after the implant removal procedure (if it is deemed medically necessary):

- Keep your head above shoulder level for the rest of the day.
- Sleep with your head on 3 or more pillows if lying down during the day and the night after implant removal.
- Wear an eye shield for at least 7 nights following the implant removal.
- Do not participate in strenuous activities until 14 days following the implant removal.
- Administer all post-operative anti-inflammatory and antimicrobial drops, as directed by your healthcare provider.

Advise patients on the following throughout SUSVIMO treatment:

- Do not drive or use machinery until the eye shield can be removed and visual function has recovered sufficiently *(see Adverse Reactions (6.1))*.
- The SUSVIMO implant and/or implant related procedures have been associated with conjunctival reactions (bleb, erosion, retraction), vitreous hemorrhage, endophthalmitis, rhegmatogenous retinal detachment, the dislocation of the implant, and a temporary decrease in vision.
- While the implant is in the eye, avoid rubbing the eye or touching the area as much as possible. However, if necessary to do so, make sure hands are cleaned prior to touching the eye.
- Seek immediate care from an ophthalmologist if there are sudden changes in their vision (an increase in moving spots, the appearance of "spider webs", flashing lights, or a loss in vision), increasing eye pain, progressive vision loss, sensitivity to light, redness in the white of the eye, a sudden sensation that something is in their eye, or eye discharge or watering *(see Warnings and Precautions (5))*.

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

The first and only continuous delivery treatment for nAMD[1]

Not to scale.

For more information, visit **SUSVIMO-HCP.com**

nAMD=neovascular (wet) age-related macular degeneration.

INDICATION

SUSVIMO (ranibizumab injection) is indicated for the treatment of patients with neovascular (wet) age-related macular degeneration (AMD) who have previously responded to at least 2 intravitreal injections of a vascular endothelial growth factor (VEGF) inhibitor medication.

IMPORTANT SAFETY INFORMATION

WARNING: ENDOPHTHALMITIS

The SUSVIMO implant has been associated with a 3-fold higher rate of endophthalmitis than monthly intravitreal injections of ranibizumab. In clinical trials, 2.0% of patients receiving an implant experienced at least 1 episode of endophthalmitis.

CONTRAINDICATIONS

- Ocular or periocular infections
- Active intraocular inflammation
- Hypersensitivity

WARNINGS AND PRECAUTIONS

- The SUSVIMO implant and/or implant-related procedures have been associated with endophthalmitis, rhegmatogenous retinal detachment, implant dislocation, vitreous hemorrhage, conjunctival retraction, conjunctival erosion, and conjunctival bleb. Patients should be instructed to report signs or symptoms that could be associated with these events without delay. Additional surgical and/or medical management may be required
- Vitreous hemorrhage: Temporarily discontinue antithrombotic medication prior to the implant insertion procedure to reduce the risk of vitreous hemorrhage. Vitrectomy may be needed
- Postoperative decrease in visual acuity: A decrease in visual acuity usually occurs over the first 2 postoperative months

ADVERSE REACTIONS

The most common adverse reactions were conjunctival hemorrhage (72%), conjunctival hyperemia (26%), iritis (23%), and eye pain (10%).

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.

Please see Brief Summary of full SUSVIMO Prescribing Information on adjacent page for additional Important Safety Information, including **BOXED WARNING**.

REFERENCE

1. SUSVIMO [package insert]. South San Francisco, CA: Genentech, Inc; 2021.

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susvimo™
ranibizumab injection 100 mg/mL
For Ocular Implant