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New Ideas in Therapy

Experts discuss novel approaches that may enhance results in a variety of retinal diseases and conditions.

Also Inside

Online Video

INDICATION

IZERVAY™ (avacincaptad pegol intravitreal solution) is indicated for the treatment of geographic atrophy (GA) secondary to age-related macular degeneration (AMD)

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

IZERVAY is contraindicated in patients with ocular or periocular infections and in patients with active intraocular inflammation.

WARNINGS AND PRECAUTIONS

Endophthalmitis and Retinal Detachments

- Intravitreal injections, including those with IZERVAY, may be associated with endophthalmitis and retinal detachments. Proper aseptic injection technique must always be used when administering IZERVAY in order to minimize the risk of endophthalmitis. Patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment without delay and should be managed appropriately.

Neovascular AMD

- In clinical trials, use of IZERVAY was associated with increased rates of neovascular (wet) AMD or choroidal neovascularization (7% when administered monthly and 4% in the sham group) by Month 12. Patients receiving IZERVAY should be monitored for signs of neovascular AMD.

Increase in Intraocular Pressure

- Transient increases in intraocular pressure (IOP) may occur after any intravitreal injection, including with IZERVAY. Perfusion of the optic nerve head should be monitored following the injection and managed appropriately.

ADVERSE REACTIONS

Most common adverse reactions (incidence ≥5%) reported in patients receiving IZERVAY were conjunctival hemorrhage, increased IOP, blurred vision, and neovascular age-related macular degeneration.

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

astellas

IZERVAY™ (avacincaptad pegol intravitreal solution)
Rx only

Brief Summary: This information is not comprehensive. Visit IZERVAYecp.com to obtain the FDA-approved product labeling or call 609-474-6755.

1 INDICATIONS AND USAGE
IZERVAY is indicated for the treatment of geographic atrophy (GA) secondary to age-related macular degeneration (AMD).

2 DOSAGE AND ADMINISTRATION
2.1 General Dosing Information
IZERVAY must be administered by a qualified physician.

2.2 Recommended Dosage
The recommended dose for IZERVAY is 2 mg (0.1 mL of 20 mg/mL solution) administered by intravitreal injection to each affected eye once monthly (approximately every 28 ± 7 days) for up to 12 months.

2.4 Injection Procedure
Only 0.1 mL (2 mg) should be administered to deliver a single dose. Any excess volume should be disposed.

Prior to the intravitreal injection, patients should be monitored for elevated intraocular pressure (IOP) using tonometry. If necessary, ocular hypotensive medication can be given to lower the IOP.

The intravitreal injection procedure must be carried out under controlled aseptic conditions, which includes the use of surgical hand disinfection, sterile gloves, a sterile drape, and a sterile eyelid speculum (or equivalent). Adequate anesthesia and a broad-spectrum topical microbicide should be given prior to the injection.

Inject slowly until the rubber stopper reaches the end of the syringe to deliver the volume of 0.1 mL. Confirm delivery of the full dose by checking that the rubber stopper has reached the end of the syringe barrel.

Immediately following the intravitreal injection, patients should be monitored for elevation in intraocular pressure (IOP). Appropriate monitoring may consist of a check for perfusion of the optic nerve head or tonometry.

Following intravitreal injection, patients should be instructed to report any symptoms suggestive of endophthalmitis (e.g., eye pain, redness of the eye, photophobia, blurring of vision) without delay.

Each vial and syringe should only be used for the treatment of a single eye. If the contralateral eye requires treatment, a new vial and syringe should be used and the sterile field, syringe, gloves, drapes, eyelid speculum, filter needle, and injection needle should be changed before IZERVAY is administered to the other eye. Repeat the same procedure steps as above.

Any unused medicinal product or waste material should be disposed of in accordance with local regulations.

3 DOSAGE FORMS AND STRENGTHS
Intravitreal solution: 20 mg/mL clear to slightly opalescent, colorless to slightly yellow solution in a single-dose vial.

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

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

5 WARNINGS AND PRECAUTIONS
5.1 Endophthalmitis and Retinal Detachments
Intravitreal injections may be associated with endophthalmitis and retinal detachments. Proper aseptic injection techniques must always be used when administering IZERVAY in order to minimize the risk of endophthalmitis. Patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment without delay, to permit prompt and appropriate management.

5.2 Neovascular AMD
In clinical trials, use of IZERVAY was associated with increased rates of neovascular (wet) AMD or choroidal neovascularization (7% when administered monthly and 4% in the sham group) by Month 12. Patients receiving IZERVAY should be monitored for signs of neovascular AMD.

5.3 Increase in Intraocular Pressure
Transient increases in intraocular pressure (IOP) have been observed after an intravitreal injection, including with IZERVAY. Perfusion of the optic nerve head should be monitored following the injection and managed as needed.

6 ADVERSE REACTIONS
The following potentially serious adverse reactions are described elsewhere in the labeling:

- Ocular and periocular infections
- Active intraocular inflammation
- Endophthalmitis and retinal detachments
- Neovascular AMD
- Increase in intraocular pressure

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 the clinical trials of another drug and may not reflect the rates observed in practice.

The safety of avacincaptad pegol was evaluated in 733 patients with AMD in two sham-controlled studies (GATHER1 and GATHER2). Of these patients, 292 were treated with intravitreal IZERVAY 2 mg (0.1 mL of 20 mg/mL solution). Three hundred thirty-two (332) patients were assigned to sham.

Adverse reactions reported in ≥2% of patients who received treatment with IZERVAY pooled across GATHER1 and GATHER2, are listed below in Table 1.

Table 1: Common Ocular Adverse Reactions (≥2%) and greater than Sham in Study Eye

Adverse Drug Reactions	IZERVAY N=292	Sham N=332
Conjunctival hemorrhage	13%	9%
Increased IOP	9%	1%
Choroidal neovascularization	7%	4%
Blurred Vision*	8%	5%
Eye pain	4%	3%
Vitreous floaters	2%	<1%
Blepharitis	2%	<1%

* Blurred vision includes visual impairment, vision blurred, visual acuity reduced, visual acuity reduced transiently.

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
Risk Summary
There are no adequate and well-controlled studies of IZERVAY administration in pregnant women. The use of IZERVAY may be considered following an assessment of the risks and benefits.

Administration of avacincaptad pegol to pregnant rats and rabbits throughout the period of organogenesis resulted in no evidence of adverse effects to the fetus or pregnant female at intravenous (IV) doses 5.1 times and 3.2 times the human exposure (based on AUC) at the maximum recommended human dose (MRHD) of 2 mg once monthly, respectively.

In the U.S. general population, the estimated background risks of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15%-20%, respectively.

Animal Data
An embryo fetal developmental toxicity study was conducted with pregnant rats. Pregnant rats received daily intravenous (IV) injections of avacincaptad pegol from day 6 to day 17 of gestation at 0.1, 0.4, 1.2 mg/kg/day. No maternal or embryofetal adverse effects were observed at any dose evaluated. An increase in the incidence of a non-adverse skeletal variation, described as short thoracolumbar (ossification site without distal cartilage) supernumerary ribs, was observed at all doses evaluated. The clinical relevance of this finding is unknown. Plasma exposures at the high dose were 5.1 times the MRHD, based on Area Under the Curve (AUC).

An embryo fetal developmental toxicity study was conducted with pregnant rabbits. Pregnant rabbits received daily IV injections of avacincaptad pegol from day 7 to day 19 of gestation at 0.12, 0.4, 1.2 mg/kg/day. No maternal or embryofetal adverse effects were observed at any dose evaluated. Plasma exposure in pregnant rabbits at the highest dose of 1.2 mg/kg/day was 3.2 times the human exposure at the MRHD, based on AUC.

8.2 Lactation
There is no information regarding the presence of avacincaptad pegol in human milk, the effects of the drug on the breastfed infant or on milk production.

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

8.4 Pediatric Use
Safety and effectiveness of IZERVAY in pediatric patients have not been established.

8.5 Geriatric Use
Of the total number of patients who received IZERVAY in the two clinical trials, 90% (263/292) were ≥65 years and 61% (178/292) were ≥75 years of age. No significant differences in efficacy or safety of avacincaptad pegol were seen with increasing age in these studies. No dose adjustment is required in patients 65 years and above.

17 PATIENT COUNSELING INFORMATION
Advise patients that following IZERVAY administration, patients are at risk of developing neovascular AMD, endophthalmitis, elevated intraocular pressure and retinal detachments. If the eye becomes red, sensitive to light, painful, or if a patient develops a change in vision, instruct the patient to seek immediate care from an ophthalmologist.

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

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Jobson Medical Information

EDITORIAL

By Jason Hsu, MD

Little steps

"The journey of a thousand miles begins with a single step." Lao Tzu vibrantly reminds us of how the little advances we make may eventually look like a giant leap forward when viewed through a much wider-angle lens.

In retina, we have witnessed this pattern firsthand. Think about the presentation by Phil Rosenfeld, MD, PhD, on his experience injecting bevacizumab off-label for the first time, setting off a wave of its use around the world before ranibizumab was even approved by the Food and Drug Administration—a legacy which continues nearly two decades later.

Another iconic event was the discovery that macular holes could be treated with surgery by Neil Kelley, MD, and Robert Wendel, MD. I remember stories of how no one initially believed that vitrectomy and gas tamponade alone could really close the hole in nearly 60 percent of cases. Incrementally, various modifications have been made, including internal limiting membrane peeling and inverted flaps among many other tweaks that have increased closure rates to more than 90 percent.

So going back to the little steps that make a difference, I am struck by how one of the most common complaints I hear nowadays revolves around patient discomfort after intravitreal injections. The most likely culprit is povidone-iodine. Enter aqueous chlorhexidine gluconate (CHG). Several large studies have demonstrated its efficacy in preventing endophthalmitis.[1] (Note: It's critical to distinguish aqueous CHG from alcohol-based as the latter may not be as effective in preventing endophthalmitis.)

Sunir Garg, MD, has been on the vanguard of studying this antiseptic. He demonstrated significantly less corneal epitheliopathy and pain after injections when aqueous CHG was used compared to povidone-iodine.[2] Anecdotally, colleagues from practices that have converted to aqueous CHG describe night and day differences in patient discomfort and call back rates.

So why isn't everyone jumping on the bandwagon and switching to aqueous CHG? There's inertia. We retina specialists tend to be conservative. It also takes time and effort to change processes. Fear of the unknown is another issue, particularly when it comes to medicolegal concerns.

Finally, many worry about cost. Using a compounding pharmacy for CHG can be prohibitively expensive compared to povidone-iodine. Large bottles of aqueous CHG can be cost-effective but have a beyond-use date of 24 hours once opened.

Recently, Dr. Garg published a study looking at the stability and sterility of aqueous CHG 0.05% (Irrisept, Irrimax Corp.) aliquoted into 1 mL syringes and showed that it remained stable for at least 30 days.[3]

Armed with this knowledge, now may be the time to make the move to aqueous CHG, which may improve both patient satisfaction and even adherence. While this is a little step, it has the potential for a huge impact in the lives of our patients (and us!).

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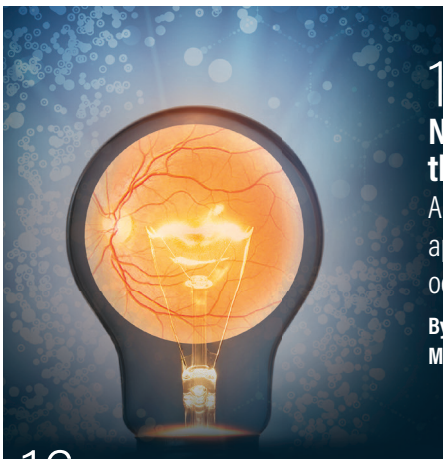
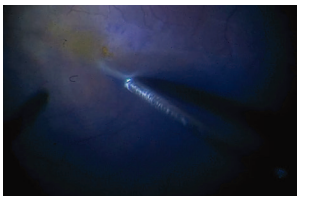
FEATURES



DEPARTMENTS

Online Video



More than meets the macula

When it's not so easy to differentiate pentosan polysulfate toxicity from age-related macular degeneration.

By Samuel Kushner-Lenhoff, MD, Nathan Agi, MD, and Lisa Olmos de Koo, MD, MBA

Samuel Kushner-Lenhoff, MD

Nathan Agi, MD

Lisa Olmos de Koo, MD, MBA

A community comprehensive ophthalmologist referred a 70-year-old woman to our clinic for a chief complaint of bilateral progressive worsening blurry vision. She reported that, although her vision had not been clear for years, it had significantly worsened over the past year in the left eye more so than in the right.

Her reading was most affected, and she reported visual distortion and missing letters. Her medical history was notable for hypothyroidism and interstitial cystitis, which previously required long term treatment with pentosan polysulfate (PPS, Elmiron, Janssen Pharmaceuticals). Notably, her urologist discontinued her PPS more than 18 months before the latest onset of symptoms. Her ocular history was noteworthy for dry age-related macular degeneration and cataract surgery in both eyes.

Pentosan polysulfate exposure

This patient suffered from years of severe interstitial cystitis complicated by Hunner lesions. Her condition was initially managed with PPS, but eventually controlled with intravesical heparin, lidocaine and buffer, as well as triamcinolone (Kenalog) injections and fulguration of the lesions. Her urologist started PPS for symptomatic management in 2011, which continued until 2021. Dosing ranged from ~100 mg to ~700 mg daily. Her estimated consumption was 200 mg daily from 2011 until 2016, and 300 mg twice daily until 2021, when she discontinued the medication due to visual symptoms. In total, this is an estimated consumption of about 1 kg over the full course of treatment.

Examination

Examination showed uncorrected vision of 20/25 in the right eye and 20/40 in the left and no improvement with pinhole. Pupils were symmetric and no afferent pupillary defect was noted. Intraocular pressures were normal. Slit lamp examination was normal except for posterior chamber lenses in both eyes and a posterior vitreous detachment in the left. Dilated examination revealed peripheral reticular changes in the periphery of both eyes. The macula was notable for patches of atrophy with surrounding drusen in both eyes. (*Figure 1A, B*).

Work-up

Fundus autofluorescence demonstrated dense peripapillary and central hypoautofluorescence surrounded by drusen and normal vessels (*Figure 1 C, D*). The periphery was notable for reticular changes with speckled hyper- and hypoautofluorescence. Optical coherence tomography showed an abnormal foveal contour and large areas of outer retinal atrophy adjacent to drusen deposits. No associated intraretinal or subretinal fluid was present (*Figure 2, page 10*).

Diagnosis and management

Given both the appearance of her fundus autofluorescence images, which are classic for PPS maculopathy, and significant cumulative exposure to PPS, we advised the patient to continue abstinence from PPS. We gave additional consideration to AMD as the diagnosis due to the substantial amount of drusen seen on exam.

We also reviewed the possibility that her PPS-associated maculopathy exacerbated her possible preexisting AMD. In the setting of her likely toxic maculopathy, we didn't recommend newly approved injectable medications such as pegcetacoplan (Syfovre, Apellis Pharmaceuticals) and avacincaptad pegol (Izervay, Astellas Pharma). We continued the patient on AREDS2 vitamin supplements and home Amsler grid monitoring, and scheduled her for surveillance imaging.

BIOS

Dr. Fortenbach is an assistant professor of ophthalmology at the University of Washington, Seattle, where **Dr. Olmos de Koo** is a professor of ophthalmology and director of the retina fellowship program, **Dr. Kushner-Lenhoff** is an ophthalmology resident and **Dr. Agi** is a retina fellow.

DISCLOSURES: The authors have no relevant relationships to disclose.

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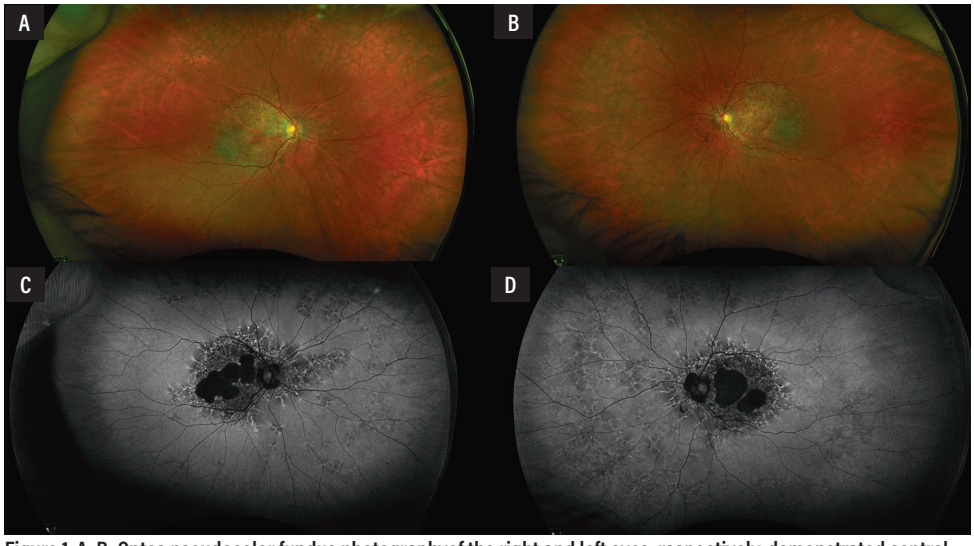


Figure 1. A, B: Optos pseudocolor fundus photographyof the right and left eyes, respectively, demonstrated central geographic atrophy in both eyes as well as peripheral reticular changes. C,D: Fundus autofluorescence in the right and left eyes showed peripapillary and macular dense hypoautofluorescence surrounded by speckled hypo- and hyperautofluorescence, which was similarly seen in the retinal periphery.

Potentially distinguishing signs

PPS was first prescribed for interstitial cystitis under the trade name Elmiron in the 1980s. The Food and Drug Administration approved it in 1996 and it remains the only approved oral medication for interstitial cystitis.[1] Its usage reflects the high disease burden; it has been estimated that 3 to 6 percent of American women over age 18 years meet criteria for interstitial cystitis.[2]

The first case of PPS-associated pigmentary maculopathy was described in 2018 by Nieraj Jain, MD, of Emory Eye Center.[3] This condition was most clearly defined by its distinctive pattern of hypo- and hyperautofluorescence within the posterior pole that may extend to the retinal periphery.

A key finding is the presence of a peripapillary halo of hypoautofluorescence, which isn't commonly seen in hereditary maculopathies or AMD.[4] This finding can clearly be seen in our patient.

OCT imaging generally demonstrates isolated thickening of or disruption in the interdigitation and ellipsoid zones. These areas of thickening are associated with hyperreflectance on near infrared imaging. In severe cases, loss of the retinal pigment epithelium and outer retina may be seen.[5]

Careful attention to these unique features may aid in distinguishing PPS-associated maculopathy from AMD. Unfortunately, the data suggest that PPS pigmentary maculopathy is underdiagnosed and is most likely mistaken as AMD or a pattern dystrophy.[4,6]

Higher dosage, higher risk

The risk and time of onset for PPS-associated pigmentary maculopathy remain areas of active research. What's clear is that higher total drug dosage and duration is associated with an increased risk of developing ocular symptoms.

Cross-sectional studies of patients on PPS suggest that maculopathy prevalence is 12.7 percent in those who have taken 500 to 999 g of PPS, but rises to 41.7 percent of those who have taken more than 1.5 kg.[7] The lowest amount of exposure was reported in a 44-year-old patient treated with 435 g of PPS over 36 months and who manifested symptoms 32 months after stopping treatment.[8]

Typically, once PPS maculopathy is diagnosed, it progresses symptomatically, as imaging will show in the months after the treatment stops.[9] Although visual acuity is generally preserved until late in the disease progression, surveys suggest that the impact on activities of daily living, such as reading in dim conditions, is more pronounced than that which the Snellen chart can measure.[10] Specifically, patients experience prolonged dark adaptation and difficulty seeing in low-luminance settings.

(Continued on page 10)

A novel approach to MH-RD in an infant

Tenon's capsule and amniotic membrane grafts to manage a rare bilateral macular hole-related retinal detachment.

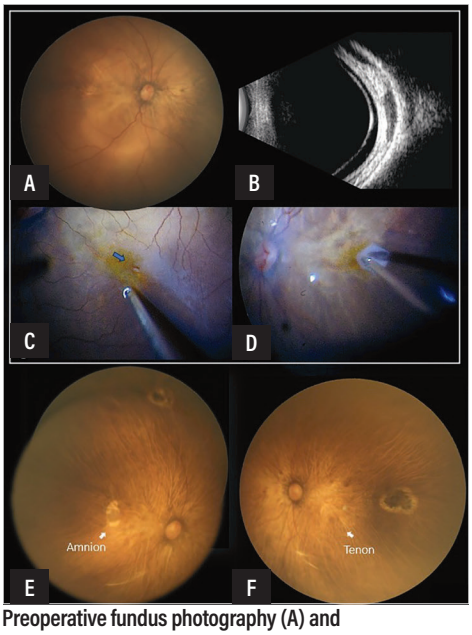
By Ece Ozdemir Zeydanli, MD, and Sengul Ozdek, MD

Ece Ozdemir Zeydanli, MD

Sengul Ozdek, MD

Retinal detachment in infants presents significant diagnostic and surgical challenges, especially when the underlying cause is elusive. Pediatric RD can result from various congenital or acquired factors.[1,2] The distinct anatomical features of pediatric eyes, the tendency for late diagnosis, and frequent bilateral involvement make these cases more complex than adult detachments, requiring specialized approaches from diagnosis to management.[1]

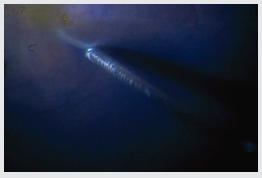
Here, we discuss a case of a 3-month-old infant referred for bilateral RD with shallow elevation and no visible retinal breaks, initially leading to a misdiagnosis of exudative RD of unknown cause. Knobloch syndrome should be considered in babies or young children with high myopia, shallow RD and no apparent breaks, especially when there's parental consanguinity and occipital skin defect or encephalocele.



Preoperative fundus photography (A) and ultrasonography (B) show a shallow retinal detachment with high myopia and chorioretinal atrophy in the right eye. C) An occult macular hole became visible when the vitreous was gently pulled with a vitrector to lift its flap. D) The macular hole was sealed with an amniotic membrane graft. One-year postoperative images show attached retina with well-sealed amniotic membrane (E) and Tenon grafts (F) in right and left eyes, respectively.

View the Video

Watch as Dr. Zeydanli and Dr. Ozdek repair a macular hole-related retinal detachment in an infant with Knobloch syndrome. Go to https://bit.ly/VideoPearl-43 or scan the QR code.



Although rare, vitreoretinal interface abnormalities, including early-onset macular hole-related RD, are characteristic of Knobloch syndrome,[3,4] prompting genetic testing.

In surgery for pediatric MH-RD due to Knobloch syndrome, innovative sealing materials such as amniotic membrane grafts and autologous Tenon's capsule grafts are helpful for successful repair, particularly in young patients when internal limiting membrane peeling isn't possible.

Hidden culprits in pediatric RDs

In this case, ocular examination revealed bilateral RD, with a highly myopic fundus and severe chorioretinal atrophy. Retinoscopy revealed myopic fundus reflex. Fluorescein angiography showed no signs of inflammation, and the absence of breaks shifted our suspicion toward an occult MH.

During vitrectomy, we discovered very small MHs, which were obscured by an operculum attached to the thickened and very tightly attached posterior hyaloid, confirming the diagnosis of Knobloch syndrome. The patient later underwent genetic testing and was found to have *COL18A1* mutations.

Surgery in this case presented challenges

BIOS

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Dr. Ozdek is a professor of ophthalmology at Gazi University in Ankara.

DISCLOSURES: The authors have no relevant disclosures.

because of an unusually strong posterior vitreous adhesion, a hallmark of Knobloch syndrome.[5] In these cases, complete vitreous removal is often not possible without risking retinal breaks. However, careful dissection of the hyaloid over the macula and posterior staphyloma is critical. Bimanual techniques, assisted by perfluorocarbon liquid and repeated triamcinolone staining, are essential.

ILM peeling is generally not possible in very young pediatric patients because the ILM has not yet developed.[5] To repair the MHs effectively, sealing materials are invaluable. We used an amniotic membrane graft for the right eye, while we used an autologous Tenon's capsule graft as a seal in the left eye. One year after silicone oil removal, both retinas remained attached, and the infant was able to fixate and follow objects (*Figure, page 9*).

Tips and tricks for graft placement

The method for introducing grafts into the vitreous cavity depends on their size. Smaller grafts can be introduced through a valved trocar, while larger grafts may require the transient removal of the trocar to allow direct entry through the sclerotomy. Once inside the vitreous cavity, the amniotic membrane graft is gently manipulated under fluid or PFCL and transplanted through the MH or retinal break into the subretinal space, with the graft edges positioned under the edges of the defective area as much as possible, and with the chorion side facing the RPE.

In cases where the initial repair is at risk of failure, particularly in high-risk myopia, as in our case, a second layer of amniotic graft can be placed epiretinally (multilayer grafting). The orientation of the amniotic membrane graft is determined primarily by assessing the adhesiveness of the tissue using retinal forceps.[6] However, for a Tenon's capsule graft, orientation isn't critical. RS

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More than meets the macula

(Continued from page 8)

Bottom line and screening recommendations

Experts in PPS-associated pigmentary maculopathy suggest a comprehensive exam within six months after a patient starts PPS to establish a baseline, with repeat screening at three to five years with annual screening thereafter.[1]

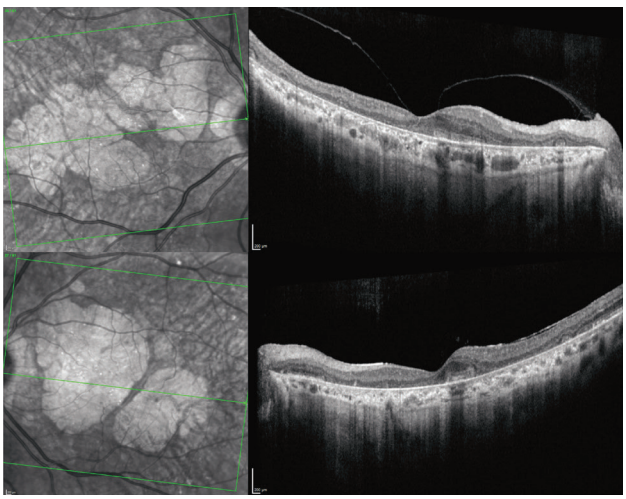

Figure 2. Optical coherence tomography of the right (top) and left eyes show geographic atrophy and dense drusenoid deposits.

Immediate cessation when indicated is strongly recommended because this disease currently has no treatment, is irreversible, and is progressive in nature. It's important to discuss the risks of maculopathy with patients on PPS and to work with our urology colleagues to promptly identify those patients with maculopathy to limit potential vision loss. RS

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Novel advances and emerging therapies for RVO

A review of the data on various approaches for treating retinal vein occlusion.

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Take-home points

- In macular edema secondary to retinal vein occlusion, new research suggests that prolonged exposure to residual intraretinal fluid and increased fluctuation in central subfield thickness are correlated to poorer visual outcomes.
- Faricimab is a novel bispecific anti-VEGF and anti-angiopoietin-2 antibody which has been found to demonstrate a high degree of efficacy, treatment durability and safety for patients with macular edema secondary to RVO.
- Eylea 8 mg is a novel anti-VEGF agent which is currently being investigated in a Phase III randomized trial in patients with RVO.
- Some potential future therapies for RVO include the port delivery system with ranibizumab, gene therapies to deliver the anti-VEGF gene and sustained-release steroid implants.

Macular edema secondary to retinal vein occlusion is a common cause of vision loss in this patient population. While traditional anti-vascular endothelial growth factor therapies have revolutionized the care of patients with RVO, treatment responses are variable, and extended durability of treatment is often needed. As treatment paradigms for this condition continue to evolve, here we aim to summarize promising therapeutic advances in patients with RVO.

Faricimab

Faricimab is a novel bispecific anti-VEGF and anti-angiopoietin-2 antibody which has already been approved by the FDA for macular edema secondary to RVO and is in clinical use. To support approval of faricimab in this setting, the Phase III BALATON and COMINO trials randomized patients 1:1 to faricimab-svoa 6 mg or aflibercept 2 mg every four weeks for 24 weeks for patients with macular edema secondary to RVO.[1] BALATON (n=553) included patients with branch RVO, while COMINO (n=729) considered patients with central or hemiretinal RVO. When considering the primary endpoint of best-corrected visual acuity change from baseline to week 24, faricimab-svoa was noninferior to aflibercept, both in BALATON (adjusted mean change: +16.9 ETDRS letters (95% confidence interval [CI]: 15.7-18.1) vs +17.5 letters (95%CI: 16.3-18.6) and COMINO (+16.9 letters [95%CI: 15.4-18.3] vs +17.3 letters [95%CI: 15.9-18.8]). There were comparable adjusted reductions in mean central subfield thickness (CST) between faricimab and aflibercept by week 24 in both trials. When absence of macular leakage on intravenous fluorescein angiography was considered, there was a greater proportion of patients achieving this endpoint with faricimab 6 mg compared to aflibercept 2 mg in both BALATON (33.6 percent vs 21 percent) and COMINO (44.4 percent vs 30

Bios

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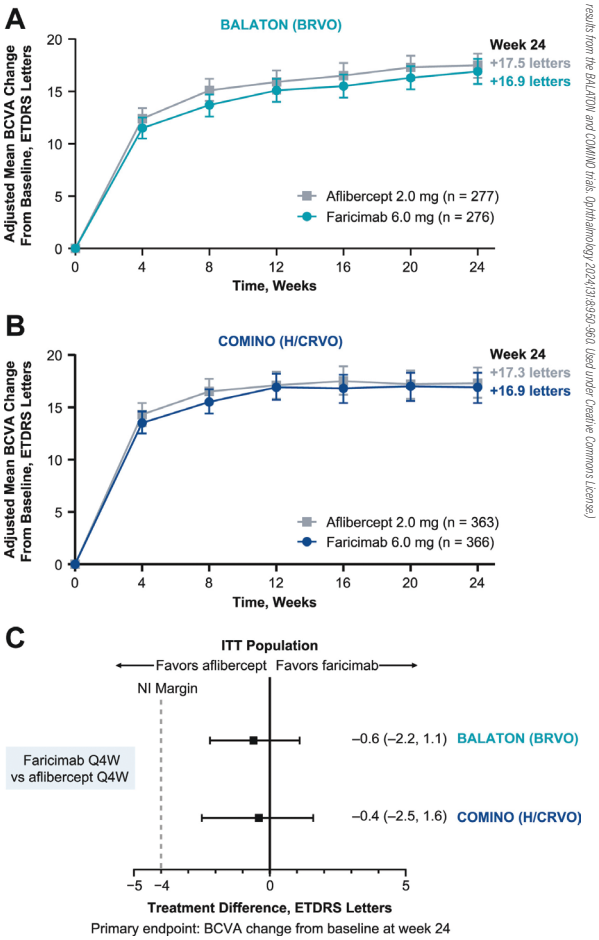
percent). The ocular adverse events were also comparable between faricimab and aflibercept. Based on these results, the FDA approved Vabysmo (faricimab-svoa) for the treatment of retinal vein occlusion in October 2023.[2] Unpublished data from Roche have recently noted updates on the efficacy and safety of faricimab for RVO up to 72 weeks, whereby participants received faricimab in a personalized treat-and-extend dosing regimen based on patients' response to treatment starting at week 24.[3] Some eyes receiving faricimab were able to extend treatment up to every four months, and vision gains and drying of retinal fluid were maintained up to week 72.

Aflibercept

High-dose aflibercept has been FDA-approved for neovascular age-related macular degeneration and diabetic macular edema, however not for RVO. Approvals for neovascular AMD and DME were based on 48-week data from the PULSAR and PHOTON Phase III randomized trials, respectively, where patients demonstrated clinical equivalent vision gains following either 12- or 16- week dosing regimens, compared with an eight-week dosing regimen for standard dose aflibercept, both after three initial monthly doses.[4,5] The randomized Phase III QUASAR study is currently underway to explore the efficacy and safety of aflibercept 8 mg in patients with macular edema secondary to RVO, and the study expects to enroll approximately 800 patients in 27 countries.[6]

Our understanding of the treatment of macular edema from RVO with standard of care anti-VEGF agents continues to advance. The COPERNICUS and GALILEO Phase III trials randomized patients to sham injections compared to intravitreal aflibercept 2 mg every four weeks for 24 weeks. These trials found a significantly greater BCVA improvement and reduction in central retinal thickness with patients treated with aflibercept, which led to the original approval for aflibercept 2 mg in patients with RVO.[7] More recently, the extent of exposure to residual intraretinal fluid (IRF) and fluctuation in central subfield thickness (CST) was correlated to visual outcomes in patients who received aflibercept 2 mg in these two trials.[8] Patients were stratified into one of three groups based on the number of visits with IRF, and CST fluctuations were evaluated based on quartiles or tertiles of CST standard deviation.



(Source: Tadayoni R, Paris L, Danzig C, et al. Efficacy and safety of faricimab for macular edema due to retinal vein occlusion: 24-Week results from the BALATON and COMINO trials. Ophthalmology 2024;131:950-960. Used under Creative Commons License.)

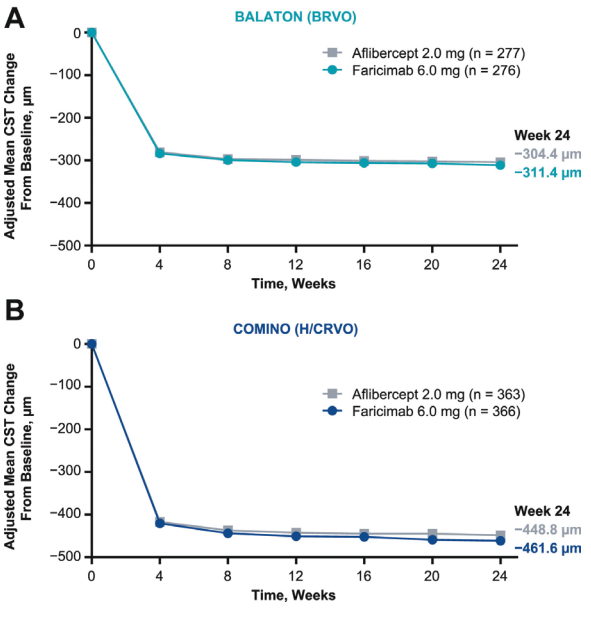
Graphs showing adjusted mean change in best-corrected visual acuity from baseline over six months in (A) BALATON and (B) COMINO and difference in adjusted mean BCVA change from baseline at the primary end point visits (C). All observed values were used regardless of the occurrence of the intercurrent events.

At week 24, eyes with the greatest number of visits with IRF had poorer BCVA gains from baseline compared to those with the least IRF exposure across a combined dataset of both trials (least-square mean difference: -5.9 letters, [95%CI: -10.0, -1.7]). Additionally, eyes with the highest fluctuation in CST had relatively worse BCVA gains from baseline compared to those with the lowest CST fluctuation (least-square mean difference: -4.6 letters, [95%CI: -9.3, 0.1]). These findings suggest that one of the unmet needs in the treatment of RVO is reducing the persistence of IRF and minimizing

CST fluctuations.

The Port Delivery System

Beyond traditional intravitreal anti-VEGF therapies, the port delivery system (PDS) with ranibizumab (Susvimo) represents a novel delivery mechanism designed for continuous delivery of ranibizumab into the vitreous to maintain constant levels of the drug over time. The PDS was evaluated in the Phase III ARCHWAY trial (n=415 patients), which randomized patients with neovascular AMD to ranibizumab PDS implantation with refill-exchanges every 24 weeks compared to monthly ranibizumab.[9] In this trial, PDS was found to be noninferior to monthly ranibizumab based on differences in adjusted mean BCVA change from baseline at two years, with approximately 95 percent of patients receiving PDS not requiring supplemental ranibizumab treatment. While cataract was the most common adverse event encountered (8.9 percent following PDS and 6 percent following monthly ranibizumab), other adverse events following PDS included conjunctival erosions (4 percent), conjunctival retractions (2.4 percent), endophthalmitis (1.6 percent) and implant dislocations (1.6 percent). While the PDS implant was FDA approved in 2021, it was voluntarily recalled by Genentech in 2022 due to an investigation related to septum dislodgement cases during the Phase III clinical trial. In July 2024, the PDS was reintroduced following component-level updates to the PDS implant and refill needle.[10] As of September 2024, the PDS is currently being evaluated in Phase III trials for DME, as well as diabetic retinopathy without DME, however there are no current trials underway for RVO.[11]



Line graphs showing adjusted mean change in central subfield thickness (CST) from baseline over six months in (A) BALATON and (B) COMINO.

(Source: Tadayoni R, Paris L, Danzig C, et al. Efficacy and safety of faricimab for macular edema due to retinal vein occlusion: 24-Week results from the BALATON and COMINO trials. Ophthalmology 2024;13(6):950-960. Used under Creative Commons License.)

Gene Therapy

Gene therapies also represent a potential promising future treatment modality in RVO. Gene therapies in this setting aim to be minimally invasive, one-time treatments whereby an adenovirus vector is used to deliver the anti-VEGF gene.[12]

Ixoberogene soroparvovec (ixo-vec) is a AAV-7m8 vector which encodes aflibercept, and is currently in a Phase II clinical trial aimed at evaluation of efficacy and safety in patients with neovascular AMD. In a Phase I, open label trial, 30 patients with neovascular AMD received an in-office ixo-vec therapy at one of four different doses, and it was found that the therapy was well tolerated with maintenance of vision and improvement of anatomical outcomes.[13]

RGX-314 is an adeno-associated virus serotype 8 vector which expresses a monoclonal antibody fragment similar to ranibizumab.[12,14] In a Phase I/IIa open-label, dose-escalation study, 42 patients with neovascular AMD who were previously treated with anti-VEGF injections received a single subretinal RGX-314 injection by a trained vitreoretinal surgeon.[14] There was one serious adverse event possibly related to RGX-314, in which a patient developed severe vision loss due to pigmentary changes in the macula; additionally, asymptomatic pigmentary changes in the inferior retinal periphery were seen in some patients who received RGX-314. Doses of 6 x 10^{10} genome copies or higher were generally associated with stable or improved BCVA and CST, with most participants needing few or no

supplemental anti-VEGF injections.

To date, ixoberogene soroparvovec and RGX-314 have been primarily tested in neovascular AMD patients, however their future application to RVO deserves consideration.

Steroid Implants

Though it hasn't been the subject of a formal drug trial, physicians have used the fluocinolone acetonide intravitreal implant (Iluvien) off-label in cases of RVO in an effort to decrease the treatment burden.

In one case report, a patient with non-ischemic CRVO was initially treated with injections of dexamethasone. However, researchers reported that these caused fluctuations in vision between 20/32 and 20/200 due to the presence of macular edema. When the FA implant was used, however, the researchers reported "sustained improvement in visual acuity from 20/200 to 20/25."[15]

The FA implant has also been used off-label in cases of ischemic CRVO and BRVO. In one case, a patient with CRVO presented with vision of 29 letters and a central retinal thickness of 664 µm.[16] After showing no response to anti-VEGF and triamcinolone injections, and just a temporary anatomical improvement after several dexamethasone implants (Ozurdex), she was implanted with the FA implant. This resulted in "significant and sustained" vision (BCVA of 38 letters) and anatomical improvement (CRT of 271 µm). The researchers reported similar improvements in a BRVO patient.[16]

Bottom Line

Significant attention and interest has been garnered for newer "second generation" treatment modalities in patients with RVO. With respect to anti-VEGF therapies, faricimab has already received FDA approval in RVO, while aflibercept 8 mg is currently undergoing a Phase III trial for this condition at sites internationally. The port delivery system of ranibizumab and gene therapies have been primarily evaluated in the setting of neovascular AMD; however, these treatments and the fluocinolone implant also carry promise for patients with RVO. Our understanding of novel treatment strategies in RVO continues to evolve, and together, these advances pave the way for improved outcomes in patients with this sight-threatening condition.

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How to recognize predictors of spontaneous macular hole closure

A review of anatomical characteristics of holes more likely to close without surgery and noninterventional management options.

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J. Fernando Arevalo, MD, PhD

By Loka Thangamathesvaran, MD, and J. Fernando Arevalo, MD, PhD

Take-home points

- Anatomic features of macular holes are important to take into consideration when evaluating which full-thickness macular holes (FTMH) will undergo spontaneous closure.
- A combination of topical steroids, carbonic anhydrase inhibitors, nonsteroidal anti-inflammatory drugs and anti-VEGF agents have been used in the management of FTMH closures.
- It's important to plan for surgery early in the treatment course to ensure no delays in the event observation or nonsurgical interventions don't work.

Full-thickness macular holes are complete defects in the neurosensory retina that are a result of multiple etiologies, including, but not limited to, vitreomacular traction, trauma, retinal detachment or uveitis. The pathophysiology of the most common etiology, VMT, includes a tractional force resulting in localized thinning of the retina that causes a progressive defect with complete loss of retinal tissue.[1]

Conventionally, the most definitive management of full-thickness macular hole (FTMH) has been pars plana vitrectomy with or without internal limiting membrane peel and tamponade with gas or silicone oil. However, these interventions present challenges, including complications such as cataract, risk of retinal detachment and the need for face-down positioning.

Although spontaneous hole closure has traditionally been observed with traumatic macular holes, with closure rates ranging from 10 to 50 percent, and reports recommending observation for up to four months to see if traumatic holes close, newer studies are finding spontaneous closures with observation and nonsurgical interventions in non-traumatic FTMH.[2]

This article will review anatomical characteristics of holes that are more likely to spontaneously close, variations in the noninterventional management options, and how to predict which holes will need surgery once these interventions are put in place.

Imaging markers of spontaneous FTMH

Our group studied imaging features associated with closure of FTMH.[3] The retrospective study included cases with an established diagnosis of FTMH, as determined by spectral-domain optical coherence tomography, that were followed without surgery and collected from retina specialists worldwide. Successful closure was defined as flattening and reattachment of the hole rim along the entire circumference of the hole.

Exclusion criteria included presence of retinal dystrophy, foveoschisis, neovascular age-related macular degeneration and history of vitreous surgery less than one year prior. SD-OCT scans were reviewed for macular parameters including apical diameter, narrowest diameter, basal diameter and height (*Figure 1*).

Bios

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Additional FTMH parameters that we evaluated include macular hole index (height/basal diameter), diameter hole index (DHI, an indicator of tangential traction defined as narrowest diameter divided by basal diameter), tractional hole index (THI, an indicator of anteroposterior traction and retinal hydration defined as height/narrowest diameter) and subretinal fluid volume.

Researchers in Spain previously evaluated these markers as potential predictors of successful outcomes in FTMH surgery. They identified a narrowest diameter for smaller macular hole and a larger tractional hole index as predictive factors for a good visual prognosis after surgery.[4]

SD-OCT parameters that characterized the vitreoretinal interface included the presence of vitreomacular traction in 12 (15.8 percent) eyes, perifoveal PVD in 42 (53.8 percent), foveal epiretinal membrane in 10 (12.8 percent), cystoid macular edema in 49 (62.8 percent) and subretinal fluid in 20 (25.6 percent).

In our study, the FTMH closed in 74 eyes of 78 patients. On multivariate analysis, initial visual acuity correlated to the height and narrowest diameter of the hole while final visual acuity correlated with the basal diameter. Time for closure of FTMH was a median of 2.8 months and correlated to the narrowest diameter and the presence of subretinal fluid. THI negatively correlated with time to closure.

Other studies of spontaneous closure

Other studies that examined characteristics of spontaneous closure found an association of faster closure rates when CME was present because the edema helps reapproximate the hole edges by a mechanism of primary intention.[5,6] This might play an important role in the management of FTMH associated with uveitis.

A study this year by Jessie Wang, MD, and colleagues, identified factors associated with decreased rates of spontaneous closure, which included increasing hole size, as every 10 µm decrease in size correlated to an increase in closure by a factor of 1.2.[7] The study also highlighted the presence of VMT related inversely to successful closure.

The study further corroborated this with the finding that patients who had undergone vitrectomy had higher closure rates due to the absence of tractional forces. Furthermore, the study found that the best-corrected visual acuity was better in patients whose holes closed with only topical drops compared to holes that required PPV. However, the holes that underwent PPV were significantly larger and had persistent VMT, which could also affect final visual acuity. However, there were no differences in BCVA between patients that underwent surgery after drops vs. surgery at the initial presentation. [7]

Agents used for FTMH closure

In our retrospective observational series, 18 eyes received the following nonsurgical interventions, with some eyes receiving multiple interventions: intravitreal anti-VEGF agents (four eyes); topical corticosteroids (13); and topical nonsteroidal anti-inflammatory drugs (seven). We didn't compare these modalities.

Other studies have used a combination of these modalities, with Dr. Wang's group using this standardized regimen:

- topical steroids prednisolone acetate 1% every six hours or difluprednate 0.05% every six to 12 hours;

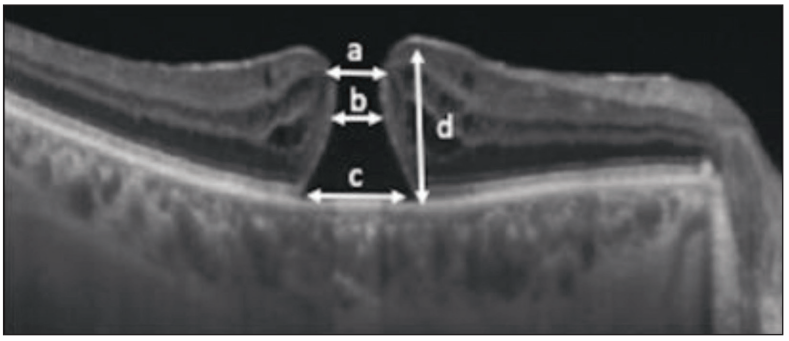

Figure 1. A diagram of full-thickness macular hole parameters: a = apical diameter; b = minimum diameter; c = basal diameter; and d = height. (*Reprinted with permission from Uwaydat SH, Mansour A, Ascaso FJ, et al. Clinical characteristics of full thickness macular holes that closed without surgery. Br J Ophthalmol. 2022;106:1463-1468.*)[3]

- NSAIDs ketorolac tromethamine 0.5% or bromfenac 0.07% every six to eight hours; and
- carbonic anhydrase inhibitors (CAIs) brinzolamide 1% or dorzolamide 2% every eight to 12 hours.[7]

In a multicenter U.S. study, participants were started on the following regimen:

- off-label topical prednisolone acetate 1% every six to eight hours or difluprednate 0.05% every eight to 12 hours;
- ketorolac-tromethamine 0.5% every six to eight hours or bromfenac 0.07% every six to 24 hours; and
- brinzolamide 1% or dorzolamide 2% every eight to 12 hours.[5]

No studies have yet compared the efficacy of these different drop regiments.

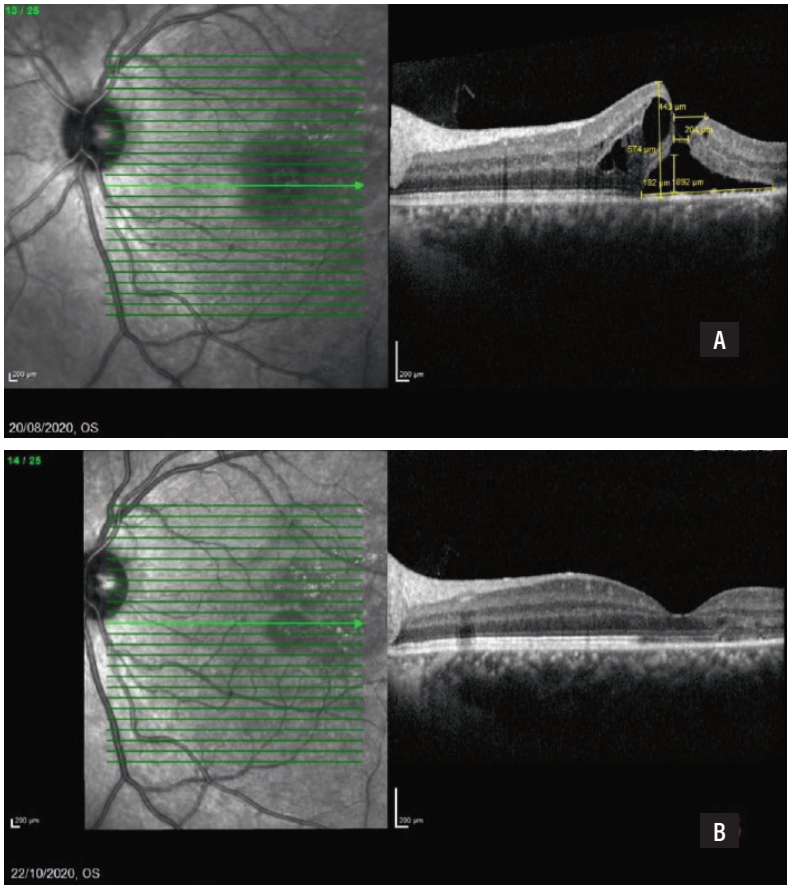

Figure 2. Spectral-domain optical coherence scans before full-thickness macular hole closure (A) and two months after closure (B). This 24-year-old White male sustained a sports injury and was started on topical NSAID. Visual acuity improved from 6/12 (20/40) to 6/6 (20/20). (*Reprinted with permission from Uwaydat SH, Mansour A, Ascaso FJ, et al. Clinical characteristics of full thickness macular holes that closed without surgery. Br J Ophthalmol. 2022;106:1463-1468.*)[3]

Dynamic predictors of FTMH closure

In our study, the mean time to closure from initial detection was 6.2 months with a mean logMAR initial (± standard deviation [SD]) visual acuity improved from 0.65 ±0.54 to 0.34 ±0.45 (Snellen equivalent 20/89 to 20/44). The initially closed FTMH reopened in seven eyes (9 percent) after a mean of 8.6 months.

Among the eyes that reopened, two closed and one stayed open after vitrectomy, and one closed on topical steroids and topical NSAIDs. Four eyes had no surgery. A total of 74 eyes had stable or improved final vision, while four eyes lost vision due to a subfoveal scar after blunt trauma (two eyes) and foveal RPE atrophy (two eyes). Three FTMH resolved after VMT resolution and three closed after a new occurrence of PVD. One FTMH closed despite the persistence of VMT.

Mean time for closure was:

- 1.6 months for eyes with trauma;
- 4.3 months for eyes without trauma but that had therapy for CME;
- 4.4 months for eyes without trauma and without therapy if the holes were <200 µm in size; and
- 24.7 months for holes >200 µm.

Figure 2 shows a case of a patient that had sustained a sports-related injury and started on topical NSAIDs, with hole closure resulting in visual acuity improvement from 20/40 to 20/20.

Dr. Wang's group noticed that when tracking the progression of FTMH size over time, the eyes that responded to drop therapy showed a rapid reduction in size. In particular, rates of macular hole narrowing and reduction in central foveal thickness acted as indicators for drop effectiveness.[7] In total 36.7 percent of patients achieved hole closure; however, final visual acuity didn't differ between eyes undergoing primary PPV vs. those taking drops before

undergoing PPV. The study didn't report on reopening of FTMH.

In the multicenter U.S. study, OCT studies showed decreased cystoid changes within two to four weeks and FTMH closure with visual acuity improvement in two to eight weeks in most eyes. The median treatment duration until initial closure was approximately 5.6 weeks. Total duration of drop treatment, including taper, ranged from 3.5 to 20 months. Two patients had FTMH recurrence at six months after an initially successful closure, and two others subsequently needed PPV for visually significant epiretinal membrane.

Anatomical markers

These studies highlight the anatomical characteristics that are important when considering which FTMH are more likely to spontaneously close. First, FTMH <200 µm, especially in the setting of trauma and without the presence of VMT, have a high likelihood of closure.[8] In addition, the absence of VMT is important because persistent tractional forces can overwhelm the RPE pump, preventing hole closure.

These studies also highlight that the use of drops can help improve the closure process without affecting the final outcomes. When comparing closure rates in patients who had FTMH closure vs. those who didn't, the participants who used drops had greater closure rates.[8,9]

Furthermore, in participants who had successful hole closure rates, there was a significant reduction in macular hole size and changes in SD-OCT markers early on in the treatment, highlighting the importance of close monitoring and quick intervention if there's no response. In particular, Dr. Wang's group recommended scheduling a tentative date for surgery even in the group that initiates drop therapy to prevent any surgical delays. Finally, it's important to review the adverse effects of these topical agents, including corneal melt, ocular surface irritation and elevated intraocular pressure.

Future studies

We need prospective, randomized, double-masked, high-powered studies in the future to improve our clinical management and to help us apply these principles into practice. First, studies that compare different noninterventional therapeutic protocols will be helpful to determine whether individual agents or specific combinations will help promote FTMH closure. This is particularly useful in patients who have contraindications to certain agents, such as topical corticosteroids (in patients with glaucoma) and topical NSAIDs (in patients with corneal surface disease).

Second, knowing how systemic conditions, such as diabetes, affect rate of hole closure can help clinical decision-making. Finally, as artificial intelligence continues to shape how we practice medicine, it will be useful to identify if OCT biomarkers can be put into an algorithm to help predict which patients can be observed and who would need surgery, and then use the dynamic response from their OCT scans to further refine clinical decision-making.

Bottom Line

Not all FTMH require surgery. Careful analysis of SD-OCT markers can help determine which FTMH might close on their own, with close vigilance to treatment response being essential in avoiding lapses in surgical intervention.

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FTMH <200 microns, especially in the setting of trauma and without VMT, have a high likelihood of closure. The absence of VMT is important because persistent tractional forces can overwhelm the RPE pump, preventing closure.

Emerging treatments for non-infectious uveitis

A look at the most interesting treatments in the pharmaceutical pipeline.


Adrienne Delaney, MD


Sumit Sharma, MD

By Adrienne Delaney, MD, and Sumit Sharma, MD

Take-home points

- Non-infectious uveitis is challenging to treat given its severity, chronicity and high recurrence rate.
- There is a need for local steroid sparing treatment options as well as more effective systemic medications with fewer side effects.
- Current treatments in the developmental pipeline include oral small molecule inhibitors like brepocitinib, systemic biologics targeting IL-17, intravitreal and topical biologics targeting IL-6 , TNF-alpha, as well as combined pharmacologic agents like dazdotuftide.

Noninfectious uveitis remains a significant challenge to treat due to its severity, chronicity and high recurrence rate. While the mainstay of initial uveitis treatment is corticosteroids, the well-known side effects of corticosteroids including systemic side effects and local side effects such as cataract and glaucoma limit their use. Various novel treatments in the pipeline for NIU include small molecule inhibitors, biologics and combination therapies.

Here, we will describe some of the emerging treatments.

Background

Uveitis describes ocular inflammation of the uveal tract, which includes the choroid, ciliary body and iris. The prevalence of uveitis in the United States is estimated to be 121 to 540 per 100,000 persons.[1]

In uveitis, immune cells such as T cells, B cells, macrophages and dendritic cells become activated and release cytokines such as TNF-α, IL-6, IL-1β and IFN-γ, which ultimately lead to intraocular inflammation.

Small Molecule Inhibitors

Brepocitinib, developed by Priovant Therapeutics, is an oral medication that selectively inhibits both Janus Kinase-1 (JAK1) and Tyrosine Kinase-2 (TYK2). JAK1 and TYK2 inhibition leads to downstream blockade of cytokines (IL-12 and IL-23), as well as modulation of Th1 and Th17 cell differentiation.[2] The dual inhibition of JAK1 and TYK2-dependent downstream pathways is theorized to provide a greater immunomodulatory effect than JAK1 inhibition alone, while avoiding adverse events related to JAK2 and JAK3 inhibition such as infection.

A Phase II dose-ranging, randomized, double-masked trial (NEPTUNE) assessed oral brepocitinib in adults with NIU, excluding patients with anterior uveitis only.[3] Twenty-six subjects with active NIU were randomized 2:1 to brepocitinib 45 mg or 15 mg once daily. All subjects received 60 mg/day oral prednisone upon entry for two weeks and were tapered over a six-week course. Participants were evaluated for treatment failure, a composite endpoint of ocular inflammation and visual acuity, as well as

Bios

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DISCLOSURES: Dr. Sharma consults and does contracted research for Genentech/Roche, and also does research for Acelyrin.
Dr. Delaney (Jarocki) has no financial interest in any material presented.

discontinuation of the medication or initiation of rescue therapy with corticosteroids. The study's primary efficacy endpoint was the treatment failure rate at week 24, at which point patients had been off steroids for 16 weeks and only treated with brepocitinib.

At week 24, 29 percent of participants in the 45-mg group and 44 percent in the 15-mg group met treatment failure criteria, indicating lower rates of treatment failure compared to previous non-steroidal therapies for NIU such as adalimumab. Secondary endpoints, including improvements in vitreous haze grades, visual acuity and macular thickness, showed positive and dose-dependent results. Specifically, in the 45-mg group, 43 percent of those with baseline macular edema achieved resolution by week 24.

Brepocitinib demonstrates promise given its durable sustained response over 16 weeks without the use of steroids and relatively rapid action compared to studies evaluating adalimumab. The drug has been tested in more than 1,400 subjects in different inflammatory diseases, maintaining a safety profile similar to other JAK inhibitors, without additional safety signals identified. A Phase III trial for brepocitinib in NIU (CLARITY) is planned to commence in the second half of 2024.

Biologics

There are a couple of biologics being studied for NIU treatment:

• ***Anti-IL-6.*** Vamikibart, RG6179/RO7200220, developed by F. Hoffmann-La Roche, is an intravitreally delivered humanized anti–IL-6 monoclonal antibody. IL-6 plays a critical role in the differentiation of Th17 cells, which have been implicated in the pathogenesis of immune-mediated diseases.[4] Elevated levels of IL-6 have also been observed in the vitreous of patients with uveitis.[5] Tocilizumab, a systemically delivered anti-IL-6 medication has shown promising results in uveitis, so there is interest in local therapy to decrease systemic side effects.[6]

The DOVETAIL study, a Phase I trial of Vamikibart evaluated 37 participants with NIU and concurrent uveitic macular edema (UME), defined as central subfield thickness (CST) ≥325 µm on optical coherence tomography. Participants were randomized to three different doses of medication (0.25 mg, 1 mg and 2.5 mg) and monitored for changes in best-corrected visual acuity and macular thickness. Patients received three monthly intravitreal injections and were followed until week 36 (28 weeks post-treatment). BCVA improved by 9.3 ±1.6 letters and CST on OCT decreased by 161 ±28 µm at 12 weeks after three treatments, with these benefits maintained during the post-treatment observation period.[7] Therefore, preliminary results suggest a potential benefit in managing UME associated with NIU.

There are currently two identical global, randomized, double masked, Phase III trials of RO7200220 (MEERKAT and SANDCAT) in patients with all forms of NIU and concurrent UME.[8] Both trials will randomize patients into three arms: vamikibart 0.25 mg; vamikibart 1 mg; or sham control. Patients will be evaluated monthly over one year to assess the drug's safety and effectiveness. The drug will be administered four times every four weeks through week 12, followed by as-needed dosing from week 20 through 48. The primary outcome measure will be the proportion of patients with ≥15 letter BCVA improvement at week 16 from baseline.

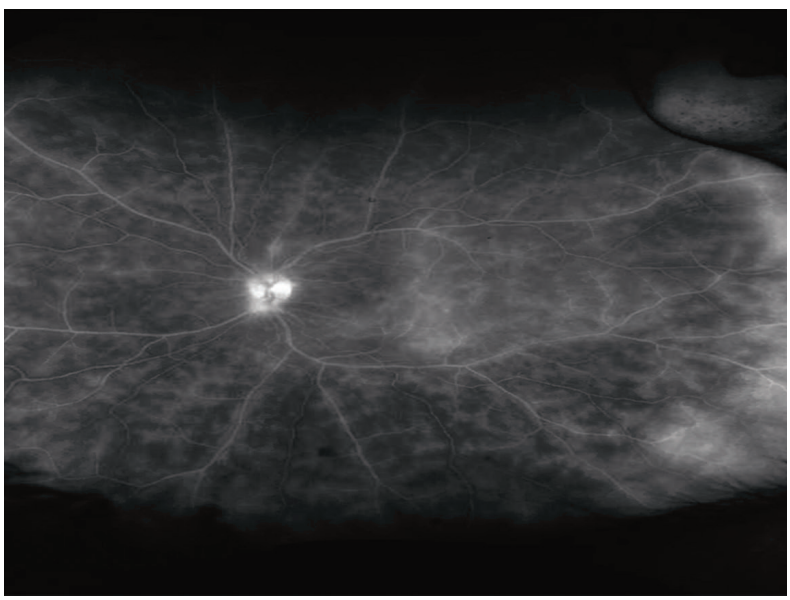
The results of these Phase III trials will be significant as they could potentially address the unmet need for effective nonsteroidal treatments. The current primary therapy for UME is steroids, which can have significant side effects such as increased intraocular pressure, cataracts and systemic health issues like hypertension and diabetes. Intravitreal anti-IL-6 if effective and safe would avoid the adverse effects of steroid treatment in patients with uveitis-associated macular edema.

• ***Anti-IL-17.*** Similar to IL-6, IL-17 is also an inflammatory cytokine that is produced by Th17 cells and recruits other inflammatory cytokines and chemokines

like TNFα. IL-17 has also been found to be upregulated in systemic diseases associated with uveitis.[9,10] There are currently multiple anti-IL-17 biologics being studied in auto-immune conditions. Secukinumab, developed by Novartis Pharmaceuticals, is a subcutaneously delivered IL-17 inhibitor that failed to meet the primary efficacy endpoints for uveitis treatment in multiple Phase III trials (SHIELD, INSURE and ENDURE). However, greater response rates with IV dosing of secukinumab suggests that patients may not have received sufficient drug with subcutaneous administration and that high-dose IV secukinumab may be necessary to deliver clinically therapeutic concentrations.[11]

This prompted the development of izokibep, a novel antibody fusion protein with an albumin binding domain to increase circulation time in the body. Izokibep (ABY-035) developed by Acelyrin is an anti-IL-17 medication whose molecular design is hypothesized to extend the drug's half-life, improve tissue penetration, and increase target site drug concentration, in comparison to other anti-IL-17 formulations.[12]

Subcutaneous izokibep is currently being evaluated in NIU in a Phase IIb/III randomized, double masked, placebo-controlled trial. All participants will receive a standardized prednisone burst starting at 60 mg/day from day one to day 14, followed by a 13-week taper. Patients are required to have active disease despite the initial two-week steroid treatment for study inclusion. At the two-week mark, participants will be randomized to placebo or izokibep 160 mg. The study will evaluate time to treatment failure and is estimated to be completed in mid-2025.



Fluorescein angiogram in a patient with intermediate uveitis showing extensive vascular leakage and capillary ferning.

Topical Anti-TNFα

While systemic anti-TNFα medications such as adalimumab have proven to be successful in NIU, serious adverse events including infections, myocardial infarctions, malignancies and hematologic reactions have been reported. There is hence a desire to develop an effective local version of this medication to avoid systemic side effects.

OCS-02 (Licaminlimab), developed by Oculis, is a new topical anti-TNFα antibody fragment. In a Phase II, multicenter, randomized, double-masked study, 43 adult patients with NIU with 2-3+ anterior chamber cell were randomized 3:1 to licaminlimab (60 mg/mL, eight drops/day for 15 days, four drops/day for seven days, then matching vehicle for seven days) or dexamethasone eye drops (eight drops/day for 15 days, tapering to one drop/day over 14 days).[13] The primary endpoint was at least a two-step decrease in AC cell grade at day 15. At day 15, 56 percent of patients treated with licaminlimab had a treatment response. Of note, by day four, 36 percent of licaminlimab-treated patients were already responders. Dexamethasone response rate by day 15 was 90 percent, however the study wasn't initially designed as a comparative study of the two treatment arms. Reassuringly, intraocular pressure wasn't increased by licaminlimab during any point in the study. Licaminlimab is the first topical biologic demonstrated to have a treatment effect on NIU. There are currently no Phase III trials planned for this medication in NIU.

Topical and Intravitreal Dazdotuftide

Dazdotuftide manufactured by Tarsier Pharma is a small synthetic molecule that combines tuftsin and phosphorycholine. Both of these anti-inflammatory molecules have separately been shown to regulate the immune system and have a strong synergistic effect by inhibiting TLR-4, NRP-1 and ACE-2.[14]

Topical dazdotuftide, TRS01, has been studied in patients with anterior NIU, in a Phase III, global randomized, double-blinded, clinical trial (TRS4Vision). Patients were randomized 2:1 to TRS01 or prednisolone drops. The primary endpoint was anterior chamber cell at week four, where 48 percent of patients treated with TRS01 achieved no anterior segment cell vs. 68 percent of patients treated with prednisolone.[15] TRS01 was inferior in proportion of patients reaching no cell at week four compared to prednisolone, the current standard of care. However, in a post-hoc analysis, two weeks after treatment had been completed, almost a third of responders treated with steroids had rebound of inflammation, while a higher rate of TRS01 responders, almost 90 percent, benefited from continued prolonged resolution of inflammation. This may indicate that individuals who initially respond to treatment with TRS01 may remain inactive for longer.

Notably, patients treated with TRS01 didn't develop IOP elevation. Overall, there was a 5.3 times higher risk for developing elevated IOP with steroid treatment compared to TRS01. The average IOP per visit remained stable for patients treated with TRS01, while it increased for those treated with steroids. A post hoc analysis found that 13 percent of responders treated with steroids experienced a clinically meaningful IOP elevation (≥10 mmHg from initial), while none of the patients treated with TRS01 experienced such elevation. Therapies that are effective and don't have an IOP effect are of critical interest in uveitis treatment.

A slow-release biodegradable intravitreal injection (TRS02) is also in development. No clinical trials have been announced for this formulation yet.

Bottom Line

In non-infectious uveitis treatment, critical unmet needs include local steroid-sparing medications and more effective systemic targeted therapeutics with better side-effect profiles. Several promising treatment options for NIU are now in various stages of development including oral small molecule inhibitors like brepocitinib, systemic therapeutics targeting IL-17 and intravitreal and topical biologics such as those targeting IL-6, TNFa antagonists, as well as combined pharmacologic agents like dazdotuftide. RS

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Department Editor ***Meera Sivalingam, MD***

Morning Glory Syndrome

Imaging is key to correctly diagnosing this optic disck anomaly.

By Theodore Bowe, MD

Theodore Bowe, MD

Introduction

A 6-month-old girl presented with esotropia since birth and concern for a retinal detachment. She was born full term and didn't have any past medical history.

Workup and Imaging

In the office, a left esotropia was noted. The right and left eyes were white and quiet with unremarkable anterior segments and clear lenses. Limited fundoscopic examination of the right eye demonstrated clear vitreous, normal optic disc and flat periphery and posterior pole with unremarkable vasculature. Fundoscopic examination of the left eye also demonstrated clear vitreous with a large, peripapillary posterior staphyloma and optic disc anomaly. There was peripheral scarring noted without evidence of a rhegmatogenous retinal detachment. At this time, the differential diagnosis included morning glory syndrome, optic nerve coloboma and peripapillary staphyloma. The patient was taken for an examination under anesthesia.

During the examination under anesthesia, the right fundus was confirmed to be normal. The left fundus was noted to have a deep set, enlarged optic disc with a glial tuft and peripapillary pigmentary changes consistent with morning glory disc anomaly (*Figure 1)*. This morning glory disc was set back into a large peripapillary cyst.

There was subretinal fibrosis and shallow, low lying temporal subretinal fluid. OCT confirmed shallow temporal subretinal fluid *(Figure 2)*.

Intraoperative B scan ultrasonography revealed a large peripapillary staphyloma with cyst *(Figure 3)*.

We diagnosed the patient with morning glory disc anomaly and arranged for outpatient neuroimaging.

Discussion

Morning glory syndrome is a sporadic congenital optic disc anomaly characterized by an enlarged, funnel-shaped optic nerve head with surrounding conical excavation filled with central glial tissue, peripapillary chorioretinal pigmentary abnormalities and straightened retinal vessels.[1]

MGS is typically diagnosed prior to the age of 2.[1] There's no gender predilection. Presenting symptoms include strabismus, which can be present in as many as 80 percent of cases, along with abnormal visual behavior.[1] There's typically significant refractive error and the visual prognosis of the affected eye is poor.[1] The pathophysiology isn't clearly understood, and it may exist on a spectrum with other congenital optic disc anomalies including optic disc

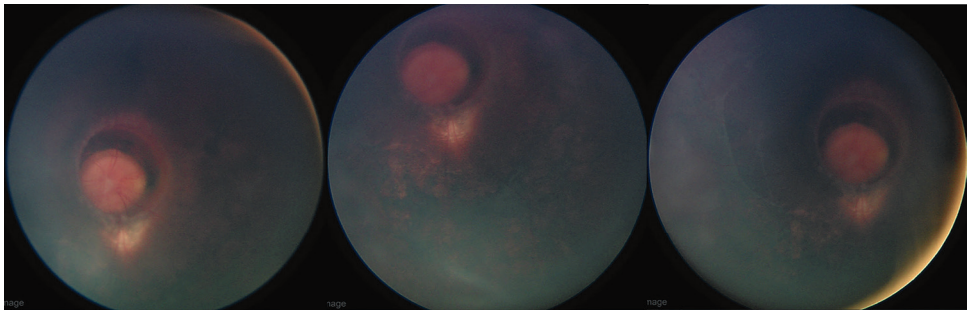

Figure 1. Color fundus photography revealed a deep set, enlarged optic nerve disc with a glial tuft within a large peripapillary staphyloma with cyst.

BIO

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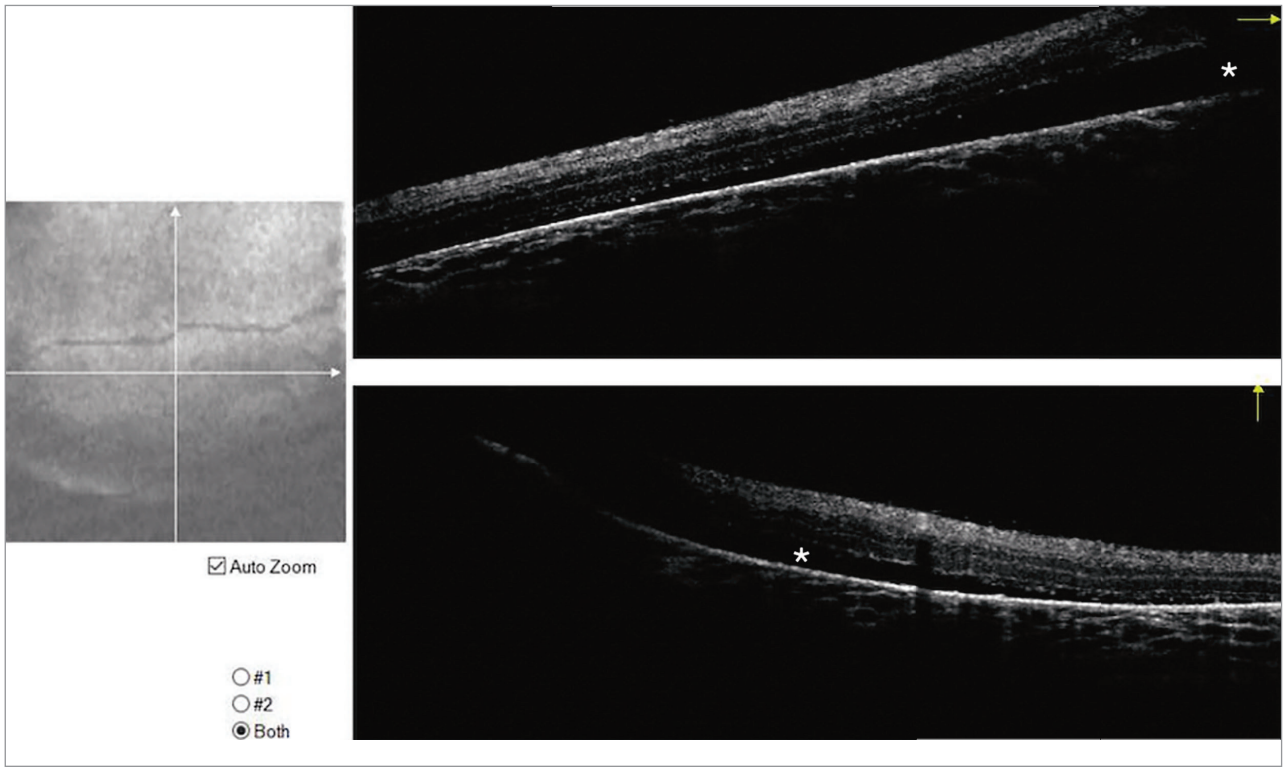

Figure 2 . Intraoperative OCT of the left eye demonstrating shallow subretinal fluid in the temporal macula.

pit, coloboma and megalopapilla. Proposed mechanisms include a primary mesenchymal abnormality, which is consistent with the contractile nature of the glial tissue.[2] The gliosis and vascular abnormalities suggest possible neuroectodermal dysgenesis.[2]

Morning glory syndrome can be confused with cavitary optic disc anomaly, which can be inherited autosomal dominantly and is typically bilateral, whereas MGS is typically unilateral and sporadic.[1] Other conditions that can mimic MGS include optic disc pit, which is a unilateral gray excavation of a portion of the optic disc. This can lead to visual impairment from subretinal fluid, intraretinal fluid, peripapillary staphyloma, glaucomatous optic neuropathy or optic nerve head coloboma.

In morning glory syndrome, visual impairment is often caused by anisometropic and strabismic amblyopia, along with associated retinal pathology. Peripheral non-perfusion can be present and can be found on fluorescein angiography. Retinal detachment can be present.

One report found that retinal detachment is found in 38 percent of cases.[4] Detachments most often involve the posterior pole, however, they can progress to involve the peripheral retina.[4] Additionally, there can be associated intraretinal fluid. The proposed mechanism of retinal detachment in MGD is vitreous traction at the nerve and macula leading to small microbreaks. Detachments are typically tractional in nature.[4]

One study supported the theory that the subretinal fluid is from a communication between cerebrospinal fluid and subretinal fluid (hypothesized to be pumped into the subretinal space via contractile motion of the glial tissue) by injecting a contrast dye intrathecally which was then found in the subretinal space on imaging.[5] Visual acui-

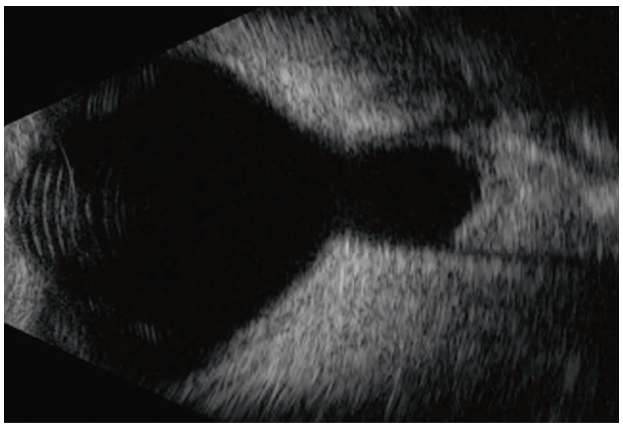

Figure 3. B scan ultrasonography of the left eye demonstrating a large peripapillary staphyloma with cyst.

ty is generally 20/200 or worse, even in patients without retinal detachments or intraretinal fluid.[6]

MGS can be associated with systemic diseases, most commonly involving the face and central nervous system.[6] Most critically, basal encephaloceles and moyamoya disease may be associated with MGS. Neuroimaging including CT and MRI should be performed to screen for these conditions. Moyamoya means "puff of smoke" in Japanese and was described in the literature in 1969.[7] The disease is named for the characteristic diffuse and tangled angiographic appearance of the collateral vessels in the brain that form secondary to narrowing of the internal carotid artery and its major intracranial branches.[7] It can result in significant neurologic morbidity due to complications such as stroke and seizure.[7]

Bottom Line

MGS is a sporadic mesenchymal optic disc abnormality that presents in infancy or early childhood, has a poor visual prognosis regardless of intervention and requires additional neuroimaging to rule out serious neurologic and vascular conditions.

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Global burden of non-infectious uveitis

Physicians must adopt a flexible and patient-centered approach in clinic.

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Uveitis presents as inflammation of the eye's uveal tissue and belongs to a spectrum of vision-threatening diseases accounting for 2.8 to 10 percent of all cases of blindness worldwide. Two-thirds of patients with non-infectious uveitis experience prolonged vision loss.[1] Complications of NIU include glaucoma, corneal deposition, cataract and macular edema.[2,3]

NIU burden impacts the daily functioning of individuals in a variety of ways, such as job insecurity and increased stress levels.[2] Affecting all age groups, the burden of NIU touches multiple facets of patients' lives from an individual, health-care system and societal perspective. Given the increase in recent literature evaluating the disease burden of NIU, we deemed that a synthesis of the global impact of NIU was warranted.

Here, we'll share some trends and findings in recent NIU literature.

Incidence and prevalence

Recent epidemiological studies have revealed that NIU incidence ranges from 3.9 to 207.8 per 100,000 person-years and the prevalence ranges from 4.5 to 704.2 per 100,000 persons.[4-7] Pediatric NIU ranges from 4.6 to 7.3 per 100,000 person-years and the prevalence ranges from 8.3 to 106 per 100,000 persons.

Recent studies have shown an increasing prevalence of NIU over time. A study by Kazuhiko Umazume, MD, and co-authors reported a change from 386.5 in 2012 to 439.3 per 100,000 persons in 2016.[5] Likewise, Oulu, Finland's Mira Siiskonen, MD, and colleagues reported a change from 64 in 2008 to 106 per 100,000 persons in the pediatric population.[8]

A retrospective study that evaluated the association between air pollution and NIU in Taiwan reported an incidence of 1,256.49 cases in a population of 100,000 followed over 11 years. Air pollution was significantly associated with incidental uveitis, particularly at higher total hydrocarbon, methane and nitrogen oxide levels.[9]

An evaluation of NIU attacks compared by seasons noted a higher incidence of NIU attacks in the winter than autumn, with significant association to the number of rainy days and average wind speed per month.[10]

Recent literature has shown variable epidemiological outcomes of NIU across different contexts, including adults vs. pediatrics, comorbid systemic disease, hospitalization, various subtypes of NIU, various intervention outcomes and during the COVID-19 pandemic. Among systemic diseases, the most common associations were of juvenile idiopathic arthritis, ankylosing spondylitis, spondyloarthritis, psoriatic arthritis and Behçet disease.

Studies have demonstrated the highest NIU prevalence in Asia, followed by Europe and North America, while the highest incidence was in Asia, followed by North America and Europe. Asian countries often see higher rates of BD and Vogt-Koyanagi-Harada Disease, while Western countries see higher rates of AS, PsA and SpA.

Economic burden

The economic burden of NIU relies on direct medical costs, intervention and medication costs, direct medical resource use, indirect resource use and costs, and adverse event costs. Most cost-burden studies detail direct medical costs, such as procedural, inpatient, outpatient, visitation, emergency room and investigation costs. Fewer studies reported intervention and medication costs (e.g., prescription drug and pharmacy service costs) and medical resource use (e.g., number of inpatient and outpatient visits, time for service acquisition).

Average annual health-care costs ranged from $11,166 to $54,537.[11] In 2009, the average cost of NIU management ranged from 3.1 to 8.3 times the cost of the average pri-

BIOS

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Table 1. Major takeaways on non-infectious uveitis.

Perspective of burden	Summary points
Incidence and prevalence	• Global NIU incidence ranges from 3.9-207.8 per 100,000 person-years. • Global NIU prevalence ranges from 4.5-704.2 per 100,000 persons. • There is an increasing trend of NIU in adult and pediatric populations over time. • The highest prevalence is seen in Asia, followed by Europe and North America, while the highest incidence is seen in Asia, followed by North America and Europe.
Economic burden	• Yearly health care costs per patient ranges from USD $11,166 to $54,537. • NIU patients face between 3.1 and 8.3 times the costs of the average privately insured patient. • There is a tendency to over-investigate routine workup of anterior uveitis, which may contribute to increased cost burden to the health-care system.
Quality of life impact	• QoL outcomes of NIU patients are often assessed using the Visual Function Questionnaire 25 (VFQ-25) and 36-Item Short Form Survey (SF-36). • Children with JIA-uveitis of African American descent experience a more severe disease course than non-Hispanic Caucasian children by increased ocular complications, vision loss and blindness. • Patients with anxiety or depression experience worse QoL outcomes. • QoL instruments note significantly lower scores in patients with JIA-uveitis compared to JIA without uveitis. • Adult NIU with systemic disease present with significantly lower QoL scores compared to adult NIU without systemic disease.

vately insured patient in the United States.[11]

A study of health-care utilization for NIU patients undergoing different therapies noted that monthly per-patient-per-month costs of corticosteroids, immunosuppressants and biologics were $935, $1,738 and $1,439, respectively.[12] While immunosuppressants and biologics were associated with improvements in ophthalmic symptoms, hospital admission rates and ER visits, corticosteroids were associated with increases in these measures, suggesting that corticosteroids may be an overused therapy for NIU.[12]

Economic burden is heavily associated with quality of life outcomes. Economic hardship was found to be a significant factor that contributed to poor mental health outcomes in patients with NIU.[13] Work discontinuation due to NIU burden contributes to the economic burden of individuals, with a disproportionate impact in individuals of low- and middle-income countries. Service provisions alleviate some of the burden on individual from more affluent countries.[14]

Cost-effectiveness evidence

A growing trend in economic evaluations is cost-effectiveness and cost-utility studies. NIU is often managed with systemic corticosteroids and immunosuppressants, such as adalimumab, methotrexate and mycophenolate mofetil. The cost-effectiveness of triamcinolone acetonide for suprachoroidal injection, dexamethasone implants and fluocinolone acetonide implants have also been assessed.

Recent studies have suggested that adalimumab may be a more cost-effective option than current practice guidelines for patients with active uveitis at greater risk of blindness.[15–18] A study by researchers at the University of Sheffield[19] suggested that dexamethasone is a cost-effective option compared to limited current practice for uveitis management. Likewise, the MUST Trial[20] concluded that fluocinolone acetonide implant therapy was a cost-effective option compared to systemic therapy in non-contraindicated and treatment failure contexts.

A recent study of clinical practice patterns in the context of NIU revealed that there's a tendency to over-investigate routine workup of anterior uveitis in Canada.[21] Adhering to clinical practice guidelines may result in cost savings of $600,000 per year to the Canadian health-care system.

Humanistic burden

The QoL of patients with NIU have been evaluated through a number of QoL instruments, including the Visual Function Questionnaire 25, 36-Item Short Form Survey, EuroQol 5D and Pediatric Quality of Life. QoL outcomes were often compared across age groups, comorbid systemic diseases and various treatment modalities. Fourteen QoL instruments were employed across studies evaluating the humanistic burden of NIU, with the majority using VFQ-25 followed by SF-36.

Recent studies have investigated the QoL outcomes of patients with NIU in pediatric populations, in populations with systemic disease and in populations undergoing sys-

temic medical therapies. Studies assessing QoL are most often conducted in Europe, followed by North America and Asia.

In a study comparing racial differences of QoL outcomes in patients with JIA-associated uveitis, researchers[22] noted that children with JIA-uveitis of African-American descent experience a more severe disease course than non-Hispanic Caucasian children by increased ocular complications, vision loss and blindness.

A qualitative thematic analysis in Australia[23] noted that aside from recognized challenges and difficulties faced by populations with vision impairments, NIU patients face additional challenges such as prognostic uncertainty and associated discomfort, and concern regarding inflammatory relapses.

Another thematic study on pediatric NIU populations reported that themes including "impact on school," "social factors" and "emotional reactions" are significant predictors of poor QoL outcomes.[24]

QoL outcomes were further significantly reduced in NIU patients with anxiety or depression compared to NIU patients without.[25]

Studies comparing QoL outcomes of JIA-uveitis and non-uveitic JIA note significantly lower QoL in patients with JIA-uveitis. Other studies assessing QoL outcomes of adult NIU with systemic disease vs. healthy controls report significantly lower scores among adult NIU participants with systemic disease

Bottom line

Given the significant burden of NIU from an economic, humanistic and epidemiological standpoint, it's important for ophthalmologists to have an understanding of the unique experience of this complex disease, including its subtypes and systemic comorbidities. It's also important to continue to find cost-effective therapy options, address QoL predictors and alleviate barriers of NIU patients in their pursuit to normalcy. Finally, the scarcity of evidence evaluating the burden of NIU in non-Westernized countries warrants further studies in these geographical regions. RS

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Home is where the heart is, but ...

... it can also be where shared pain and understanding are in the form of a social media community.

By Jayanth Sridhar, MD

In previous iterations of this column, we've reviewed the cautionary tales tied to today's social media boom in medicine—privacy concerns, potential medicolegal liability, battling misinformation, protecting the digital landscape from financial pressures, etc.

Social media also has a place in medicine for physicians to find another home of sorts, a place that can be a refuge from the realities of day-to-day life in the modern health-care landscape.

Burnout in medicine is a well-known major issue facing doctors today. While ophthalmology tends to be slightly more protected than other specialties, even we eye surgeons aren't immune to the pressures of an overstuffed plate of reduced reimbursements, increased documentation demands, malpractice fears and burgeoning patient loads.

Quotable

"What makes all these social media groups sustainable and good for the mind, body and soul? The key word is they are nonjudgmental."

A haven of sorts

Social media communities may not be the panacea, but they can be helpful to struggling doctors. This has been especially important as more and more physicians become employees rather than employers and interface less often in real life on a personal level, referring to one another's privately owned businesses. Moreover, as medicine becomes less financially lucrative in an increasingly expensive world, doctors can learn from colleagues how to pursue non-medical ventures.

For example, the Physician Side Gigs (PSG) Facebook group created by Nisha Mehta, MD, allows physicians to discuss their projects outside of medicine along with financial issues within the field.

Given the popularity of PSG, Dr. Mehta created a second, larger Facebook group called Physician Community, which features physicians throughout the United States networking and discussing more broad topics with the added benefit of asking anonymous questions. The Physician Moms Group (PMG) is another Facebook social network allowing female doctors to collaborate and share notes on their unique challenges in medicine.

ARF on Telegram

Because Facebook may seem dated to the new generation, young retina specialists have gravitated toward the Telegram smartphone app to join the American Retina Forum (ARF). Founded by retina specialists Mitul Mehta, MD, and Hemang Pandya, MD, ARF offers a haven for doctors to ask surgical and medical retina questions and share cases in a nonjudgmental manner.

ARF is a terrific example of social media serving not as a replacement for in-person connection but rather as a conduit for it. ARF now hosts a national conference, with the 2024 symposium having taken place in August, where physicians who collaborate every day virtually can finally meet face-to-face and share thoughts in a traditional continuing medical education meeting setting.

What makes these social media groups sustainable and good for the mind, body and soul? The key word is they're *nonjudgmental.* Continuing in this spirit, successful future social media collaboration in retina will need to be inclusive, minimally influenced—or not at all—by financial pressures, positive, and realistic, rather than whitewashing, in their depictions of being a physician in the 2020s. Give your social media group heart, and that's where you'll find a home. RS

BIO

Dr. Sridhar is an associate professor of clinical ophthalmology at Bascom Palmer Eye Institute, Miami.

DISCLOSURE: Dr. Sridhar is a consultant to Alcon, DORC, Genentech/Roche and Regeneron Pharmaceuticals.

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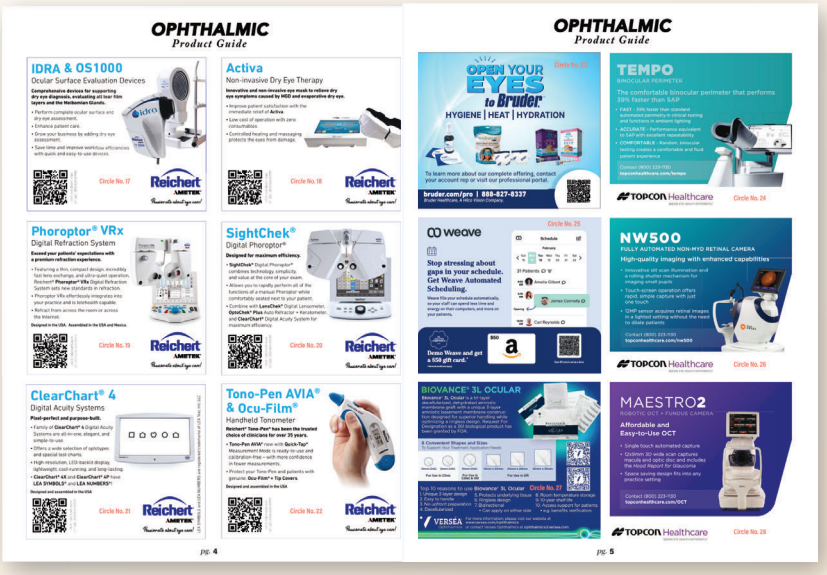

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