ADVANCED DRY AMD
EMERGING TREATMENTS

Investigational pipeline provides promise for an unmet need

DIABETIC EYE DISEASE
Showcasing faricimab, the FDA-approved triple threat

UVEITIS
Utilizing ultra-widefield imaging for diagnosis & treatment

DIAGNOSTICS & IMAGING
Monitoring fellow eyes for nAMD

SURGICAL RETINA
Adapting techniques during the pandemic

GENE THERAPY
Improving microperimetry in X-linked RP
YUTIQ is designed to deliver a sustained release of flucinolone for up to 36 months for patients with chronic non-infectious uveitis affecting the posterior segment of the eye.

- **Proven to reduce uveitis recurrence at 6 and 12 months**: At 6 months, 18% for YUTIQ and 79% for sham for Study 1 and 22% for YUTIQ and 54% for sham for Study 2 ($P<.01$). At 12 months, 28% for YUTIQ and 86% for sham for Study 1 and 33% for YUTIQ and 60% for sham for Study 2.

- **Extended median time to first recurrence of uveitis**: At 12 months, NE$^1$ for YUTIQ/92 days for sham in Study 1; NE for YUTIQ/187 days for sham in Study 2.

- **Mean intraocular pressure (IOP) increase was comparable to sham**: Study was not sized to detect statistically significant differences in mean IOP.

For more information, visit YUTIQ.com.

**INDICATIONS AND USAGE**

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

**IMPORTANT SAFETY INFORMATION**

**CONTRAINDICATIONS**

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

**Hypersensitivity:** YUTIQ is contraindicated in patients with known hypersensitivity to any components of this product.

**WARNINGS AND PRECAUTIONS**

**Intravitreal Injection-related Effects:** Intravitreal injections, including those with YUTIQ, have been associated with endophthalmitis, eye inflammation, increased or decreased intraocular pressure, and choroidal or retinal detachments. Hypotony has been observed within 24 hours of injection and has resolved within 2 weeks. Patients should be monitored following the intravitreal injection.

**Steroid-related Effects:** Use of corticosteroids including YUTIQ may produce posterior subcapsular cataracts, increased intraocular pressure and glaucoma. Use of corticosteroids may enhance the establishment of secondary ocular infections due to bacteria, fungi, or viruses. Corticosteroids are not recommended to be used in patients with a history of ocular herpes simplex because of the potential for reactivation of the viral infection.

**Risk of Implant Migration:** Patients in whom the posterior capsule of the lens is absent or has a tear are at risk of implant migration into the anterior chamber.

**ADVERSE REACTIONS**

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

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

YUTIQ® (flucinolone acetonide intravitreal implant) 0.18 mg, for intravitreal injection
Initial U.S. Approval: 1983

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

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

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

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

<table>
<thead>
<tr>
<th>ADVERSE REACTIONS</th>
<th>YUTIQ (N=226 Eyes) n (%)</th>
<th>Sham Injection (N=94 Eyes) n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ocular</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cataract1</td>
<td>63/113 (56%)</td>
<td>13/56 (23%)</td>
</tr>
<tr>
<td>Visual Acuity Reduced</td>
<td>33 (15%)</td>
<td>11 (12%)</td>
</tr>
<tr>
<td>Macular Edema</td>
<td>25 (11%)</td>
<td>33 (35%)</td>
</tr>
<tr>
<td>Uveitis</td>
<td>22 (10%)</td>
<td>33 (35%)</td>
</tr>
<tr>
<td>Conjunctival Hemorrhage</td>
<td>17 (8%)</td>
<td>5 (5%)</td>
</tr>
<tr>
<td>Eye Pain</td>
<td>17 (8%)</td>
<td>12 (13%)</td>
</tr>
<tr>
<td>Hyoptony Of Eye</td>
<td>16 (7%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Anterior Chamber Inflammation</td>
<td>12 (5%)</td>
<td>6 (6%)</td>
</tr>
<tr>
<td>Dry Eye</td>
<td>10 (4%)</td>
<td>3 (3%)</td>
</tr>
<tr>
<td>Vitreous Opacities</td>
<td>9 (4%)</td>
<td>8 (9%)</td>
</tr>
<tr>
<td>Conjunctivitis</td>
<td>9 (4%)</td>
<td>5 (5%)</td>
</tr>
<tr>
<td>Posterior Capsule Opacification</td>
<td>8 (4%)</td>
<td>3 (3%)</td>
</tr>
<tr>
<td>Ocular Hypemia</td>
<td>8 (4%)</td>
<td>7 (7%)</td>
</tr>
<tr>
<td>Vitreous Haze</td>
<td>7 (3%)</td>
<td>4 (4%)</td>
</tr>
<tr>
<td>Foreign Body Sensation In Eyes</td>
<td>7 (3%)</td>
<td>2 (2%)</td>
</tr>
<tr>
<td>Vitrits</td>
<td>6 (3%)</td>
<td>8 (9%)</td>
</tr>
<tr>
<td>Vitreous Floaters</td>
<td>6 (3%)</td>
<td>5 (5%)</td>
</tr>
<tr>
<td>Eye Pruritus</td>
<td>6 (3%)</td>
<td>5 (5%)</td>
</tr>
<tr>
<td>Conjuctival Hyperemia</td>
<td>5 (2%)</td>
<td>2 (2%)</td>
</tr>
<tr>
<td>Ocular Discomfort</td>
<td>5 (2%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Macular Fibrosis</td>
<td>5 (2%)</td>
<td>2 (2%)</td>
</tr>
<tr>
<td>Glaucoma</td>
<td>4 (2%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Photopias</td>
<td>4 (2%)</td>
<td>2 (2%)</td>
</tr>
</tbody>
</table>

1. Includes cataract, cataract subcapsular and lenticular opacities in study eyes that were phakic at baseline. 113 of the 226 YUTIQ study eyes were phakic at baseline; 56 of 94 sham-controlled study eyes were phakic at baseline.

Table 2: Summary of Elevated IOP Related Adverse Reactions

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

8. USE IN SPECIFIC POPULATIONS. 8.1 Pregnancy. Risk Summary. Adequate and well-controlled studies with YUTIQ have not been conducted in pregnant women to inform drug associated risk. Animal reproduction studies have not been conducted with YUTIQ. It is not known whether YUTIQ can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Corticosteroids have been shown to be teratogenic in laboratory animals when administered systemically at relatively low dosage levels. YUTIQ should be given to a pregnant woman only if the potential benefit justifies the potential risk to the fetus. All pregnancies have a risk of birth defect, loss, or other adverse outcomes. In the United States general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively. 8.2 Lactation. Risk Summary. Systemically administered corticosteroids are present in human milk and can suppress growth, interfere with endogenous corticosteroid production. Clinical or nonclinical lactation studies have not been conducted with YUTIQ. It is not known whether intravitreal treatment with YUTIQ could result in sufficient systemic absorption to produce detectable quantities of flucinolone acetonide in human milk, or affect breastfed infants or milk production. The developmental and health benefits of breastfeeding should be considered, along with the mother’s clinical need for YUTIQ and any potential adverse effects on the breastfed child from YUTIQ.

Figure 1: Mean IOP During the Studies

Figure 2: Mean IOP During the Studies

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

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<tbody>
<tr>
<td>Ocular</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vitreous Hemorrhage</td>
<td>4 (2%)</td>
<td>0</td>
</tr>
<tr>
<td>Iridocyclitis</td>
<td>3 (1%)</td>
<td>7 (7%)</td>
</tr>
<tr>
<td>Eye Inflammation</td>
<td>3 (1%)</td>
<td>2 (2%)</td>
</tr>
<tr>
<td>Choroiditis</td>
<td>3 (1%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Eye Irritation</td>
<td>3 (1%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Visual Field Defect</td>
<td>3 (1%)</td>
<td>0</td>
</tr>
<tr>
<td>Lacertation Increased</td>
<td>3 (1%)</td>
<td>0</td>
</tr>
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8.4 Pediatric Use. Safety and effectiveness of YUTIQ in pediatric patients have not been established. 8.5 Geriatric Use. No overall differences in safety or effectiveness have been observed between elderly and younger patients.

Manufactured by:
EyePoint Pharmaceuticals US, Inc., 480 Pleasant Street, Watertown, MA 02472 USA Patented.
Researchers are playing Ahab – and finding success

For AMD researchers, treatment for dry age-related macular degeneration (AMD) and geographic atrophy has been their white whale. While many innovative drugs and delivery systems exist for wet AMD, dry AMD has remained resistant to treatment.

However, David S. Boyer, MD, offers hope in his report on emerging therapies for dry AMD (page 7). Many potential treatments are showing promise in clinical trials, and it will be a race to see which candidate achieves its end points first.

On page 10, Chirag Jhaveri, MD, discusses how the now FDA-approved port delivery system will be revolutionary for ophthalmologists and retina specialists. He shares suggestions for surgeons eager to learn how to implement the implant.

We would be remiss not to mention the recent FDA approval of faricimab. Charles Wykoff, MD, PhD, walks through how the drug uniquely blocks both the VEGF and angiopoietin-2 pathways (page 14).

In uveitis, ultra-widefield imaging is a critical step in diagnosis and management, says Quan Dong Nguyen, MD, FARVO, FASRS (page 16). Posterior segment imaging can inform treatment decisions, and the most efficient and effective way to capture it is with ultra-widefield imaging, he says.

Decreased treatment burden doesn’t have to mean decreased monitoring. Anat Loewenstein, MD, MHA, suggests that consistent monitoring of nAMD progression may be the key to adapting treatment schedules (page 18). By employing at-home imaging, ophthalmologists can monitor untreated fellow eyes and treatment efficacy while patients extend their time between office visits.

Rounding out our issue is Jorge Monasterio Bel, MD, who offers tips for adjusting very large macular hole repair during the COVID-19 pandemic (page 21). He recommends adapting the internal limiting membrane flap technique.

Thank you for reading this edition of Modern Retina™.

Mike Hennessy Jr,
President and CEO of MJH Life Sciences®,
the parent company of Modern Retina™.
When golden years are not so golden
Dry AMD steals central vision for many retirees

“A considerable body of evidence points to dysfunction of the complement system and inflammation.”

After four or five decades of toil in an office or factory or driving a bus, many of our fellow citizens look forward to enjoying retirement. The freedom to read a good novel, spend a few hours trying to coax a little white golf ball into a small hole, go sightseeing or play with grandchildren are all luxuries that many of us cannot afford during busy working years. So it strikes me as particularly unfair when our senior citizen friends, family members and patients who have worked hard and paid their taxes for their whole lives lose their central vision to macular degeneration and are denied the quality of life they might have had. Their golden years are not so golden.

Although the best minds in American universities have spent decades investigating the pathogenesis of dry AMD (a substantial proportion of the National Eye Institute’s budget is devoted to supporting work in this area) and a plethora of startups and large pharmaceutical companies have spent billions in pursuit of an effective therapy, the cause(s) of this atrophic condition and the corresponding preventions or cures remain elusive. As discussed in our lead article, a considerable body of evidence points to dysfunction of the complement system and inflammation and it is no exaggeration to say the world eagerly awaits the results of clinical trials designed to explore this pathway as a therapeutic avenue. A Lasker Award and perhaps a Nobel Prize await those who finally solve this puzzle.

Until that time, what can we offer those afflicted with dry AMD? Nutritional supplements may slow progression. Many do find referral to a low vision rehabilitation specialist helpful as they learn techniques for successfully carrying out the activities of daily living and maintaining their ability to live independently. Magnifiers and telescopes help many, and devices like the so-called intraocular telescope implanted at the time of cataract surgery can help some. I personally am rooting for self-driving automobile technology to improve to the point where our elderly with AMD are able to get out and about — shopping, dining, visiting friends and family — and avoid the social isolation that so commonly leads to loneliness and depression. This may not be Elon Musk’s main motivation, but I think it would be a major benefit. •

Peter J. McDonnell, MD
is director of the Wilmer Eye Institute, Johns Hopkins University School of Medicine, Baltimore, and chief medical editor of Ophthalmology Times®.

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7 cover story

7 AMD
Treatments emerge for advanced dry AMD
By David S. Boyer, MD
PDS: A new era in treatment of wet AMD
By Lynda Charters

14 diabetic eye disease
Reshaping retina treatment with faricimab
By Lynda Charters; Reviewed by Charles Wykoff, MD, PhD

16 uveitis
Ultra-widefield imaging: A critical step in uveitis diagnosis and management
By Quan Dong Nguyen, MD, MSc, FARVO, FASRS

18 diagnostics & imaging
Monitoring patients for neovascular
AMD in the office and at home
By Anat Loewenstein, MD, MHA

21 surgical retina
Adapting the inverted internal limiting membrane flap technique in very large macular hole surgery
By Jorge Monasterio Bel, MD

23 gene therapy
AGTC-501 gene therapy offers vision gains for X-linked RP
By Lynda Charters; Reviewed by Robert A. Sisk, MD, FACS

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FOLLOW US:
Treatments emerge for advanced dry AMD

Investigational pipeline provides promise for meeting an unmet need

By David S. Boyer, MD

After 10 to 15 years of great advances in treatment for patients with exudative age-related macular degeneration (eAMD), many companies are moving to the forefront with research targeting the development of treatment for dry AMD.

The lack of therapy to halt the progression of dry AMD, including geographic atrophy (GA), represents a significant unmet need considering its effect on vision and the number of people affected. The Beaver Dam Eye Study found that 42% of eyes with GA were legally blind, and as the prevalence of GA increases dramatically from 4.4% among persons 85 years and older to 22% after age 90 years, the burden of GA can be expected to grow with our aging population.1,2

Fortunately, the hunt for a treatment for dry AMD is beginning to turn up positive strategies: neuroprotection, reducing oxidative stress and accumulation of toxic byproducts, visual cycle modulation, and use of stem cell therapy. Suppressing inflammation, however, has garnered the greatest interest.

Multiple compounds that suppress inflammation by inhibiting the complement pathway are under investigation in clinical trials. The rationale for this approach comes from the finding of activated complement components and complement regulators in histopathological drusen specimens and research documenting a genetic link between the complement system and AMD.

Of the complement inhibitors being studied, two have completed phase 3 clinical trials with positive results: pegcetacoplan (formerly APL2-103; Apellis Pharmaceuticals) and avacincaptad pegol (Zimura; Iveric Bio).

Pegcetacoplan is a pegylated, highly selective peptide that binds C3, preventing its cleavage. Inhibition of C3 prevents events in the complement cascade needed for opsonization, inflammation, and formation of the membrane attack complex (MAC) that leads to cell death.

Pegcetacoplan was investigated as a treatment for GA secondary to AMD in 2 global phase 3 studies, OAKS (NCT03525613) and DERBY (NCT03525600). These identically designed, double-masked studies have a planned 24-month duration and randomized approximately 1250 patients 2:2:1:1 to intravitreal injections of pegcetacoplan monthly, pegcetacoplan every other month (EOM), sham monthly, or sham EOM.

The primary end point assessing change in total area of GA lesions was assessed at month 12 and was met by both regimens of pegcetacoplan in OAKS (monthly: 22% reduction vs sham, \( P = .0003 \); EOM: 16% reduction, \( P = .0052 \)) and by neither regimen in DERBY (monthly: 12% reduction, \( P = .0528 \); EOM: 11%; \( P = .0750 \)). A prespecified pooled data analysis showed statistical superiority of pegcetacoplan versus sham for both regimens (monthly: 17%, \( P = .0012 \); EOM: 14% reduction, \( P < .0001 \)) (Figure 1). In addition, whereas OAKS and DERBY entered patients with extrafoveal or subfoveal lesions, findings from prespecified subgroup analyses showed greater efficacy of pegcetacoplan among patients with extrafoveal lesions, which tend to grow faster than the subfoveal lesions. In a pooled analysis, extrafoveal GA growth was reduced 26% by pegcetacoplan monthly versus sham (\( P < .0001 \)) and 23% for the EOM regimen (\( P = .0002 \)).

Safety data for pegcetacoplan were encouraging. Adverse events were less frequent overall than in the...
Exudative AMD (eAMD) was identified in 6.4% of eyes in the monthly pegcetacoplan group, 5% of eyes treated with pegcetacoplan every other month, and 3.8% of sham eyes. This rate includes investigator-determined eAMD based on fluorescein angiography taken at month 12. This rate is much lower than that observed for pegcetacoplan in the phase 2 FILLY trial, although the latter study included follow-up to 18 months. The experience during the OAKS and DERBY studies remains to be seen.

Avacincaptad pegol was well tolerated. New onset of exudation occurred in approximately 9.3% of eyes treated with avacincaptad pegol versus 2.7% of control eyes. There were no ocular serious adverse events, cases of endophthalmitis, or inflammation in the avacincaptad groups.

The only other treatment for dry AMD that has advanced into a phase 3 trial is a commercially available oral formulation of low-dose doxycycline (Oracea; Galderma). Results are awaited from the TOGA trial (NCT01782989) investigating the rate of change in GA size in 286 patients randomized at 1:1 after a 6-month observation phase to doxycycline 40 mg or placebo once daily.

It is well known that tetracyclines at low doses have anti-inflammatory and antioxidative properties that could be relevant for treating dry AMD. Furthermore, minocycline has been shown to protect human retinal pigment epithelial cells against oxidative damage and attenuate photoreceptor degeneration in a bright light model in rats.3,4
In addition, doxycycline was shown at low levels to reduce neovascularization and lesion volume in a rat model of laser-induced choroidal neovascularization.5

**FUTURE DIRECTIONS**

Although complement inhibition appears to be a promising strategy for preventing progression of dry AMD, many unanswered questions exist regarding the efficacy and safety of this approach. For example, investigators do not know the source of complement activation, the involvement of the 3 complement pathways in AMD pathogenesis, whether an optimal site to block the complement cascade exists, and whether local treatment is an option. In addition, will complement inhibition require lifelong therapy? Are there associated long-term risks? Is there a role for combining treatments with different mechanisms of action?

Even though treatment that effectively reduces progression of GA can prevent visual loss in the long term, it remains to be seen how well intervention involving monthly or bimonthly injections will be accepted by patients who likely still have excellent vision despite their pathology.

Nevertheless, this is an exciting time for retinal specialists, as it appears practitioners are on the brink of a new era in which they will be able to offer treatment that will reduce the risk of visual loss for an important subset of patients with AMD.

**REFERENCES**


**DAVID S. BOYER, MD**

E: vitdoc@aol.com

David S. Boyer, MD, is a senior partner at Retina-Vitreous Associates Medical Group, California. Boyer is a consultant and/or investigator for Aqellis Pharmaceuticals, Ivrier Bio, and other companies developing treatments for dry age-related macular degeneration.
The port delivery system (PDS) with ranibizumab (Susvimo; Genentech) has ushered in a new treatment era for patients with wet age-related macular degeneration (AMD). In addition to efficacy, the treatment burden for patients needing monthly anti-VEGF injections is reduced dramatically.

PDS STUDIES
The phase 2 LADDER study (NCT02510794) evaluated the overall good safety and efficacy results of the PDS for treating neovascular AMD with 10-mg, 40-mg, and 100-mg concentrations. The results showed that with the highest concentration, about 80% of patients went 6 months or longer before needing a refill (median time to refill, nearly 16 months), which was accomplished in the office.

The 2-year, phase 3 ARCHWAY study (NCT03677934) compared the PDS containing 100 mg of ranibizumab with monthly ranibizumab injections in patients with recently diagnosed wet AMD. The results found that 98% of patients did not need additional treatment in the PDS group and the drug was well tolerated. The PORTAL study (NCT03683251), an open-label extension, phase 3 study, will evaluate how patients do after more than 2 years.

CONSIDERATIONS IN THIS NEW TREATMENT ERA
“As we embark on this new era for the treatment of wet macular degeneration, it is important that we use all resources available to maximize our patient outcomes,” said Chirag Jhaveri, MD, from Retina Consultants of Austin, Texas, and an investigator at Austin Research Center for Retina. The PDS, approved to treat neovascular AMD, is surgically inserted via the pars plana area in the superotemporal quadrant of the eye to provide continuous slow release of the anti-VEGF drug delivered to the posterior segment.

Picking the surgical candidates is an important step. Although the procedure to insert the PDS is generally well tolerated, a preoperative evaluation is important.

Jhaveri recounted that LADDER found a high rate of vitreous hemorrhages, which was addressed and lowered substantially by adding laser cautery of the corneal bed. Surgeons should also be aware of the infection risk and
possible exposure of the device if it is not covered adequately or if the conjunctiva is not closed properly. Because the conjunctiva is thin, erosion may occur. Preoperative evaluation and meticulous care to close the conjunctiva are very important, he stated.

In addition to the conjunctival status, the tissue should have good mobility to facilitate adequate access to the subconjunctival and sub-Tenon spaces. Surgeons should look for areas of potential scleral thinning that can affect creation of the wound and avoid those areas to prevent wound dehiscence or other potential issues. He said patients who are stable on injections each month or every other month without the presence of intraretinal fluid may be good candidates for implantation of the PDS.

Surgical education and training are important for surgeons implanting the PDS, Jhaveri noted that as the device comes into more common usage, it is important to review videos before the PDS is implanted; surgical simulators are available that can provide hands-on experience. In addition, company representatives will be helpful in guiding surgeons through their first surgeries.

Jhaveri said a detailed description of the implantation and the refilling procedure are being approved. Those descriptions and any videos can be obtained by contacting Genentech representatives.

“It is important that we use all resources available to maximize our patient outcomes.”
— Chirag Jhaveri, MD

### POSITIVE IMPACT OF THE PDS

In addition to decreasing the treatment burden, the continuous exposure of the retinal tissue to ranibizumab might modify the disease process. Jhaveri said the fact that 98% of the ARCHWAY study participants did not need additional treatment before the first refill may imply that the disease is modified to the point of potential quiescence for some patients.

Another plus is the high patient satisfaction postoperatively; the implantation process is painless and patients may report slight itchiness or mild irritation 1 to 2 days later. “They notice the disease stability after implantation of the PDS. The refill process is also easy for the patients,” Jhaveri said. “It is actually more tolerable because there’s no transscleral penetration of a needle.”

The future of the PDS is bright. “The PDS has a lot of potential for wet AMD,” Jhaveri said, but cautioned that surgeons take advantage of all the resources available regarding the optimal use of the PDS. “I highly encourage surgeons to use all of the information available and the company representatives to maximize the surgical outcomes,” he said.

Studies are under way to evaluate use of the PDS in treating diabetic macular edema and diabetic retinopathy. “As better compounds are developed that may be more efficacious, such as by specific molecules, marrying the PDS platform with these new molecules may yield even better results for our patients,” Jhaveri concluded.
Biosimilars? What difference are they making?
Prof Ian Pearce
Consultant Ophthalmologist and Honorary Clinical Professor of Ophthalmology
Royal Liverpool University Hospital
Liverpool, UK

Introduction
Biologic medications have revolutionized treatment in many areas of medicine, including rheumatology,1 dermatology,2 oncology,3 gastroenterology,4 neurology,5 and management of metabolic diseases.6 However, these advances have resulted in very high-priced medications,7 and this has the potential to limit their availability and adversely affect other aspects of healthcare delivery.8 For example, in the United States in 2017, the top 10 most expensive Medicare Part B physician-administered drugs were all biologics, costing over $13 billion.9 In addition, the cost for originator biologic agents increased by 42% from 2005–2017, while that for nonbiologic medications increased by 20%.10 Global sales for the top 10 biologic medications were about $81 billion in 2019.11 It has been noted that the high cost of biologic therapies may delay treatment initiation leading to irreversible damage associated with disease progression,12,13 result in patients terminating these therapies for financial reasons,14 cause healthcare systems to limit the number of patients who can receive potentially disease-modifying biologic therapies and/or a requirement to fail on less-expensive treatments,11,15 and result in avoidable morbidity and mortality.11,13

Biosimilars
A biosimilar is a biological product that is highly similar to and has no clinically meaningful differences from an existing approved reference or innovator product (ie, the single biological product, already approved, against which a proposed biosimilar product is compared).16,17 Biosimilar medications are marketed after patent expiration and loss of exclusivity for the reference or originator product; their benefit for patients and the healthcare system is that they are generally less costly than the originator agents.16 Published estimates suggest the cost savings with biosimilars are substantial.16 It has been estimated that the use of biosimilars in Europe resulted in list-price savings of about $6 billion in 2020 (Figure 1).19 A report by the Rand Corporation indicated that the cost savings associated with the use of biosimilars in the United States will be approximately $54 billion over the period from 2017–2026.20

Have cost savings with biosimilars translated into better healthcare?
While the results summarized in the preceding section strongly support the conclusion that the advent of biosimilars has reduced the cost of therapy with biologic medications, there is limited but growing information about how these savings have translated into increased access to these treatments and better overall healthcare.

Access to medication
Results from several studies across different diseases have indicated that use of biosimilars has extended the use of these therapies to larger numbers of patients. Biosimilar tumor necrosis factor (TNF) inhibitors reached the European market in 2013 for infliximab and 2016 for etanercept.21 In the year after both biosimilars became available, the price per treatment day for all TNF inhibitor use decreased by 13% and the volume per treatment day rose by 19% (Figure 2).22 These results indicate that the lower costs of etanercept and infliximab biosimilars were associated with more patients having access to these therapies.23 The relationship between decreased cost for biosimilars and increased use extends to other therapeutic areas (Figure 3), including oncology, management of anemia, prevention of infections in patients with myelosuppression, diabetes, and assisted reproductive technology.24 Results from these and other similar studies24 support the conclusion that reducing healthcare expenditure on biologics and releasing cost savings to support wider access to these therapies can lead to more patients receiving optimal treatment for their diseases.25

Figure 1. Yearly savings from biosimilar competition (cost for post-biosimilar volume at pre-biosimilar list prices).20

Figure 2. A. Decrease in price for TNF inhibitors for 2016 vs the year before biosimilar entrance. B. Increase in use volume for TNF inhibitors for 2016 vs the year before biosimilar entrance.21

Figure 3. Change in price (C) and volume treatment days of total market (D) between year before biosimilar launch and 2017.21

EPO, erythropoietin; G-CSF, granulocyte colony-stimulating factor; HGH, human growth hormone.

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These results indicate that the lower costs of etanercept and myelosuppression, diabetes, and assisted reproductive technology.23 Results from several studies across different diseases have indicated that use of a biosimilar is a biological product that is highly similar to and has no clinically meaningful differences from its reference product.24 Biosimilars may delay treatment initiation leading to irreversible damage among stakeholders. Expansion of the specialist nursing team and improved dietitian support were specifically included in the agreement. A total of 143 patients were switched to the biosimilar and there were no adverse effects on efficacy or safety. Drug acquisition costs decreased by $40,000–$60,000 per month (Figure 5). Per the agreement, a portion of these savings was used to increase staffing and enable patient support.

Conclusions

It is well established that use of biosimilars decreases drug acquisition costs. The results summarized in this brief review show further that these savings can potentially be translated into increased access to highly effective biologic medications and the savings appropriated to earlier treatment, which has the potential to improve overall patient care. They also indicate timely use of biosimilars is cost-effective vs delaying an originator biologic until a course of conventional therapy has been carried out from the German perspective compared with early intervention with a biosimilar in patients with inflammatory bowel disease who have received a reduction of 16% in the total cost of care with early use of the biosimilar.40 A third analysis using the same design employed by Porter et al., but carried out from the Brazilian perspective, indicated a cost savings of $196,269 with early biosimilar treatment (Figure 4).25

References


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Retrospective analysis of abatacept with and without background methotrexate in biologic naive adult patients with rheumatoid arthritis and low disease Activity.

Figure 3.

Figure 4.

4. Reduction in total cost of care (50-year time horizon) associated with early initiation of treatment with an adalimumab biosimilar vs 6 months of conventional therapy followed by initiation of originator adalimumab.

Figure 5.

Number of vials of infliximab dispensed by the pharmacy and the drug acquisition costs billed to the care commissioning group.
Diabetic eye disease

Reshaping retina treatment with faricimab
The FDA-approved bispecific antibody uniquely targets two pathways

By Lynda Charters; Reviewed by Charles Wykoff, MD, PhD

The FDA’s approval of faricimab (Vabysmo; Genentech) ushers in a new era for retina treatment with the potential to have a triple effect: inhibition of the disease processes of wet age-related macular degeneration (AMD) and diabetic macular edema (DME), improvement of visual acuity, and reduction of patient treatment burden.

Faricimab, the only injectable treatment simultaneously approved by the FDA to treat both wet AMD and DME, facilitates flexible dosing regimens based on the patient’s anatomy and their visual outcomes.

“Vabysmo represents an important step forward for ophthalmology. It is the first bispecific antibody approved for the eye,” noted Charles Wykoff, MD, PhD, director of research at Retina Consultants of Texas in Houston and a faricimab phase 3 investigator. “With Vabysmo, we now have the opportunity to offer patients a medicine that could improve their vision and potentially lower the treatment burden with fewer injections over time.”

THE MECHANISM OF FARICIMAB

The drug’s beauty lies in the dual activity. “It does more than block a single cytokine,” Wykoff said. “The current VEGF agents such as bevacizumab [Avastin; Genentech], ranibizumab [Lucentis; Genentech], and aflibercept [Eyela, Regeneron Pharmaceuticals Inc.] block only the VEGF pathway. Vabysmo is unique in that in addition to blocking the same VEGF pathway, it also blocks a separate one, the angiopoietin-2 [Ang-2] pathway. With the neutralization of Ang-2, the tyrosine kinase receptor Tie-2 is activated.”

This scenario differs from the activity of the anti-VEGF therapies. When VEGF is inhibited, signaling through its receptors is decreased. The blocking of Ang-2 allows activation of a specific pathway moderated by Tie-2, resulting in a very different cellular response.

“The thought is that inhibiting both VEGF and Ang-2 is complementary and can achieve improved anatomic outcomes,” Wykoff said.

These disease pathways seem to destabilize the blood vessels, which can result in the formation of new leaky blood vessels and increased ocular inflammation.

According to Wykoff, the process of inhibiting both pathways stabilizes the blood vessels and subsequently decreases leaking and inflammation.

The reactive activity of both pathways is responsible for the increased intervals between faricimab treatments in most study patients compared with patients receiving the anti-VEGF therapies. With the individualized dosing of patients across four phase 3 trials, Wykoff pointed out that 50% of patients could go 4 months between treatments and about 75% could go 3 months or more between treatments.

FDA APPROVAL

The approval was based on results from 4 randomly assigned, multicenter, double-masked, global phase 3 studies, all of which showed consistent beneficial treatment effects in patients with wet AMD and DME.1,2 After 4 monthly loading doses of faricimab, patients recieved treatment at up to 4-month intervals, delivered comparable results to those achieved with aflibercept administered every 2 months during the first treatment year.
Patients generally tolerated faricimab well. The most frequent adverse effect was conjunctival hemorrhage, which was seen in 7% of patients. Patients treated monthly with faricimab and aflibercept did not show increased retinal toxicity.

In clinical practice, treatment with faricimab will consist of a series of 4 initial monthly injections, followed by a flexible treatment schedule based on evaluation of the patient’s anatomy and vision outcomes.

“The package insert is relatively inclusive,” Wykoff said. “When needed, patients can be treated on a monthly basis, and there certainly is the option for less frequent dosing. In most cases, physicians can use Vabysmo as required by the patients.”

**TENAYA AND LUCERNE TRIALS**

The TENAYA (NCT03823287) and LUCERNE (NCT03823300) studies included 1329 patients with wet AMD. The results showed average increases in visual acuity of +5.8 and +6.6 letters, respectively, in patients treated with 6.0-mg doses of faricimab at the 1-year evaluation compared with +5.1 and +6.6 letters in patients treated with 2.0-mg doses of aflibercept.

Wykoff noted that the results also highlighted the decreased treatment burden in patients who received faricimab: 46% in the TENAYA study and 45% in the LUCERNE study were treated every 4 months during the first year; another 34% and 33% of patients, respectively, were treated every 3 months. Those data indicated that 80% of patients did not require treatment for 3 months or more during the first year.

The visual results showed that the central subfield thickness (CST) decreased comparably, as did the size and area of the choroidal neovascularization.

“The visual benefits with Vabysmo given at up to 16-week intervals demonstrate its potential to meaningfully extend the time between treatments with sustained efficacy, thereby reducing treatment burden in patients with neovascular AMD,” according to investigators.

**YOSEMITE AND RHINE TRIALS**

In the YOSEMITE (NCT03622580) and RHINE (NCT03622580) studies that included 1891 patients with DME, the faricimab results achieved with the 6.0-mg doses were comparable with those achieved with the 2.0-mg doses of aflibercept, with average letter gains of +11.6 and +10.8 in the faricimab treat-and-extend arms, +10.7 and +11.8 letters in the 2-month arms, and +10.9 and +10.3 letters in the aflibercept arms, respectively.

Regarding the treatment burden, 53% of those in the TAE arm in the YOSEMITE study and 51% in the RHINE study were treated every 4 months during the first year; an additional 21% and 20%, respectively, were treated every 3 months. This again indicated most patients (70%) in the TAE faricimab arm required dosing after 3 months or more during the first year.

The CST decrease and resolution of intraretinal fluid that occurred throughout the first year favored faricimab versus aflibercept.

In addition to these treatment regimens, the approved regimen for DME involves 6 monthly loading doses, followed by treatment every 2 months. Patients with wet AMD and DME also can undergo monthly treatments as needed, although the study investigators pointed out that additional efficacy was not observed with monthly dosing.

“Robust vision gains and anatomical improvements with Vabysmo were achieved with adjustable dosing up to every 16 weeks, demonstrating the potential for Vabysmo to extend the durability of treatments for patients with diabetic macular edema,” Wykoff noted.

**EXTENSION STUDIES**

Extension studies are underway: AVONELLE-X (NCT04777201), the extension study of TENAYA and LUCERNE, is evaluating the long-term safety and tolerability of faricimab in wet AMD. RHONE-X (NCT0443283), the extension study of the YOSEMITE and RHINE studies, is investigating the long-term safety and tolerability of faricimab for DME.

Investigators are also considering the potential benefits of faricimab for other retinal diseases. The COMINO (NCT04740931) and BALATON (NCT04740905) trials are evaluating the efficacy and safety of the drug in patients with macular edema subsequent to retinal vein occlusion.

“The most exciting consideration is that we now have a next-generation pharmacotherapy that achieves what we know to be important in the treatment process, namely, inhibition of VEGF, that also blocks a new cytokine, Ang-2,” Wykoff concluded.

“There is a tremendous amount of preclinical data and strong clinical rational implicating Ang-2 in the pathophysiology of exudative retinal diseases, including DME and neovascular AMD. We now have a molecule that can block both pathways. There is tremendous promise that patients can achieve optimal outcomes with fewer injections over time.”

**CHARLES WYKOFF, MD, PHD**

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Wykoff is a consultant to and collaborates in research with Genentech, Regeneron Pharmaceuticals Inc., and Novartis.
Uveitis is a notoriously challenging disease to manage. Among the leading causes of vision loss worldwide, it can stem from a wide variety of infectious and noninfectious etiologies. Therefore, a multipronged assessment designed to gather as much information as possible regarding the cause and severity of the disease is critical to determine the most appropriate treatment regimen.

GO BEYOND THE REFERRAL

In our clinic, an evaluation always begins with obtaining a thorough patient history. While notes from the referring physician are important, they cannot be relied upon solely. We obtain a detailed ocular history, including symptom recurrence, duration, and severity as well as other ocular surgeries or trauma. We review the systemic history, including other illnesses or diseases as well as exposure to uveitis risk factors. Such review is critical, as diseases afflicting other organs in the body such as the kidney or lungs might preclude the use of certain types of medication. Finally, we document the patient’s treatment history, including the dosage of medication(s) and duration of therapy previously prescribed, as well as whether a certain course of therapy failed previously, or the patient experienced recurrences of disease.

SEEING “THE BIG PICTURE”

A thorough clinical examination must include both physical evaluations (ie, slit lamp, indirect ophthalmoscopy, and direct contact lens biomicroscopy) and retinal imaging, considering information garnered from both the anterior and posterior segments. Performing an anterior segment OCT may be helpful for evaluating the cornea. For the posterior segment, ultra-widefield imaging (UWF) is the most efficient and effective tool. While a typical fundus photograph captures 30 degrees of the retina and ETDRS 7 standard fields requires the compilation of 7 of these images to reach approximately 75 degrees, optomap UWF Imaging (Optos plc) captures 200 degrees (82%) in a single capture. No other imaging platform offers the ability to see this far into the periphery. The ability to do so is essential, as lesions often occur in the peripheral retina.
Uveitis and their presence would impact treatment decisions.

Utilization of wide angle imaging was demonstrated for the first time almost 10 years ago in 2 separate studies evaluating the use of UWF technology in the management of noninfectious posterior uveitis and noninfectious retinal vasculitis. The first study, a prospective, observational case series, set out to determine how often disease management decisions changed based on the additional information garnered from UWF fundus images and UWF fluorescein angiography (FA). The results showed that investigator review of UWF and UWF FA led to management changes in nearly half (48%) of the patients evaluated. In the second study, evaluation of UWF pseudo-color images led to a 14% increase in management changes, while UWF FA images led to a 51% increase.

When evaluating a UWF FA image, it is important to look at the perfusion or leakage of the vessels. The presence of retinal vascular leakage and peripheral ischemia can be important signs of significant posterior segment inflammation. These are examples of peripheral findings that would go undetected with traditional fundus photography, but that UWF is able to capture.

UWF retinal imaging also supports disease documentation. Depending on the extent of peripheral pathology identified in an initial capture, it might be prudent to reexamine after a period of time and compare the images to assess disease activity and progression before initiating treatment. Image comparison is especially beneficial when evaluating for both efficacy and safety following treatment initiation.

UNDERSTANDING POTENTIAL SYSTEMIC DISEASE FACTORS

A third critical element of uveitis evaluation is laboratory evaluations. Identifying any potential problems such as low platelet or low white blood cell count, for example, is important when considering the potential root cause of the disease and, subsequently, determining the most appropriate treatment regimen. A thorough initial investigation may also help determine the need to obtain specimen(s) to understand more, such as in the case of intraocular lymphoma, where one needs to look at the vitreous of the eye and not just the fundus.

CONCLUSION

By improving our understanding of the disease process, we may be better informed regarding our treatment and management decisions, which will hopefully lead to the best possible outcomes for our patients. This approach is particularly important in uveitis, which has a broad array of etiologies, each requiring different therapeutic approaches. In our clinics, this multifaceted approach with the addition of UWF imaging has greatly improved our ability to diagnose and manage patients with uveitis. This critical tool not only helps guide our treatment decisions, but also allows patients to be better informed should the need for intervention or procedures arise.

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Quan Dong Nguyen, MD, MSC, FARVO, FASRS

Dr. Nguyen serves on the scientific advisory boards for AlloBody, Bausch and Lomb, Regeneron, and Santen, among others. Dr. Ghoraba and Dr. Or have no relevant disclosures.
Monitoring patients for neovascular AMD in the office and at home

Remote monitoring aids in early diagnosis and effective treatment design

By Anat Loewenstein, MD, MHA

The fixed monthly dosing regimens used in pivotal trials evaluating the safety and efficacy of anti-VEGF agents for the treatment of neovascular age-related macular degeneration (nAMD) proved to be impractical in real-world settings. The growing adoption of spectral domain optical coherence tomography (SD-OCT) at the time of anti-VEGF agents’ approvals enabled anatomically driven and personalized dosing patterns in the form of as-needed and treat-and-extend (TAE) regimens. Despite our efforts, the real-world visual outcomes of anti-VEGF treatment have fallen short of those seen in pivotal trials—a trend driven primarily by undertreatment. The retina community must recognize that office-based diagnostics provide mere snapshots in time of a highly dynamic and heterogeneous disease. Moreover, anatomic end points measured on OCT, such as central retinal thickness, which were established to describe disease activity, have borne limited correlation to visual acuity (VA) outcomes. Given the significant cost of treatment and the small percentage of patients who maintain functional vision after several years of anti-VEGF therapy, our field must look for new solutions to manage our patients.

MOVING BEYOND THE AMSLER GRID

Long-term treatment outcomes are largely predetermined by a patient’s VA at the time of nAMD diagnosis. Reliance on infrequent routine office visits and self-reported symptoms means only 36% of nAMD patients present at the time of diagnosis with at least 20/40 VA, per real-world Intelligent Research in Sight Registry data. A subgroup analysis of that data set found that eyes with 20/40 baseline vision maintain functional vision at 2 years and that eyes with presenting VA of less than 20/40 never reach 20/40 VA after 2 years of treatment (Figure 1). Early detection of conversion from intermediate AMD to nAMD requires expanding our armamentarium beyond the Amsler grid.

An artificial intelligence-enabled, at-home patient monitoring system that has proven to be effective in both randomized controlled clinical trials and in real-world settings utilizes the ForeseeHome preferential hyperacuity perimeter to detect metamorphopsic changes caused by nAMD conversion. In a recent analysis of almost 9000 real-world patients who used such a monitoring system, 81% of conversions to nAMD were caught at VA of 20/40 or better. If monitoring systems similar to the one reviewed in this study were to be widely adopted, a higher percentage of patients with 20/40 VA may present to the clinic at the time of nAMD diagnosis. In such a system, office-based eye care providers would prescribe home monitoring for patients at risk of converting to nAMD, and a dedicated remote monitoring service would support the patient in their monitoring journey, forming a new ecosystem of support for early disease detection.

Remote monitoring service providers can become important partners in these emerging decentralized care models by fronting the investment for a large fleet of securely teleconnected home-use devices, training patients on using home monitoring platforms, and tracking patient adherence. Medicare coverage for the
ForeseeHome program in the United States has allowed the Notal Vision Monitoring Center to become the first ophthalmic remote monitoring service to establish a patient engagement infrastructure of clinically trained ophthalmic professionals. It should be noted that the trained specialists at the Notal Vision Monitoring Center have replaced the nonspecialized call center staff utilized in earlier iterations of the program.

MONITORING FOR THE MODERN TREATMENT ERA

Changes in treatment options require us to rethink monitoring and diagnostic approaches to nAMD. Take the expected uptake of the port delivery system (PDS) with ranibizumab (Susvimo) as an example. The PDS aims to reduce the number of office visits for patients with nAMD who required frequent treatment. Typically, patients with unilateral nAMD would have their fellow eye monitored for conversion to nAMD each visit. However, given the reduced refill frequency of patients implanted with the PDS, fellow eyes with intermediate AMD are at increased risk of undetected conversion to nAMD. In these patients, a monitoring scheme that includes the ForeseeHome platform may help detect conversion to nAMD when VA is still above the 20/40 threshold, thereby increasing the likelihood that long-term visual function will exist in that eye following therapy.

Patients who are already undergoing anti-VEGF therapy for the treatment of nAMD may also benefit from at-home technology, particularly if they are undergoing TAE regimens that rely on anatomic end points to determine whether therapy should be administered. Home OCT systems have shown promise in early clinical trials. Successful patient self-operation of the Notal Home OCT system was reported in 93% of eyes, with VA as low as 20/320. The system uses a deep learning–based algorithm for automated, quantitative evaluation of OCT scans. Longitudinal data from studies in Israel and the United States have demonstrated high agreement with human expert grading for the presence and quantity of retinal fluid, and imaging reports have allowed detailed characterization of fluid dynamics.

Some patients receiving anti-VEGF treatment for nAMD on TAE regimens have demonstrated fluid accumulation during the interval between visits (Figure 2). Use of home OCT could alleviate real-world vision loss in these patients by providing alerts when a patient’s fluid volumes exceed a tolerable level, thus allowing proactive and personalized treatment based on anatomic findings. Specific thresholds for intraretinal and subretinal volumes will allow highly individualized fluid management.

**FIGURE 1.** Baseline visual acuity (VA) predicts long-term outcomes of anti-VEGF therapy as shown in Intelligent Research in Sight Registry data analysis by baseline VA group.
Patient adherence with self-imaging needs to be high for the goal of minimizing cumulative fluid exposure to be achieved. Heier and Holekamp recently reported findings from a feasibility study, which found that at least 1 eye was scanned 5.7 days per week among patients using a home OCT device.6

NEW MONITORING FOR A NEW AGE

The advent of long-acting drugs and slow-release systems that aim to reduce the treatment burden on patients and caregivers calls for concomitant monitoring services that can remotely monitor fluid volumes in patients with active disease and can monitor fellow eyes for conversion to wet AMD. These expected synergies between innovative treatments and diagnostics draw parallels to the early days of the anti-VEGF and SD-OCT era, during which the latter technology paved the way for practical use of the former.

Adequate insurance coverage will be needed to motivate monitoring service providers and treating physicians to implement such new patient management paradigms. The dedicated billing codes for remote OCT recently established in the United States lay a good foundation. Recurring billing opportunities with zero capital investment to a practice are expected to drive adoption of this next generation of diagnostic imaging.

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Adapting the inverted internal limiting membrane flap technique in very large macular hole surgery

In the face of the COVID-19 pandemic, the procedure required adjustments

By Jorge Monasterio Bel, MD; Reviewed by Eduardo Pérez-Salvador García, MD, PhD

Because of the COVID-19 pandemic, the drastic decrease in operating room availability caused the cancellation and postponement of a lot of surgeries. This issue has affected patients with macular holes, bringing about cases of very large, chronic, full-thickness macular holes with a long time of evolution. To achieve the closure and anatomical improvement of these macular holes, we propose the peeling of internal limiting membrane (ILM) and its transposition over the hole, followed by use of a viscoelastic adhesive as a ballast to keep the free flap in the correct position and avoid its migration and displacement from the fovea during fluid-air exchange.

**SURGICAL TECHNIQUE**

The previous staining of ILM before the peeling is recommended when performing this technique. Staining will help the correct visualization of the flap, covering the hole during flap transposition and fluid-air exchange when the risk of migration of the flap is higher.

When vitrectomy is combined with phacoemulsification of the lens, the anterior lens capsule can also be used as a free flap in macular hole surgery. In this case, the staining of anterior capsule with dyes, such as trypan blue, is also advisable. Once it is removed during phacoemulsification, the anterior capsule should be preserved in physiological saline solution (0.9%) until the end of the posterior vitrectomy. After peeling the ILM, position the anterior capsule over the macular hole. Using anterior lens capsule as the flap presents several advantages because we get a bigger, more rigid, more circular, and more regular-shaped flap. These features make the transposition of the flap easier than when the ILM is used. Additionally, this technique eliminates having to peel the ILM in one big piece, which decreases surgical difficulty.

After peeling the ILM, its placement over the macular hole can be challenging because the ILM usually sticks to Eckardt forceps. This problem can be solved by pulling apart the flap with the light probe. Afterward, with the forceps closed, move the ILM and position it over the hole.

**Figures 1 and 2.** These intraoperative images show how to apply viscoelastic adhesive with a silicone-sleeve cannula over the internal limiting membrane used as flap.
We suggest positioning the flap, anterior capsule, or ILM toward the temporal area of the macula because during fluid-air exchange, the flap tends to move to papilla. When the flap is in the correct position, apply a viscoelastic adhesive with a silicone-sleeve cannula (Figures 1 and 2). This will keep the free flap in place during fluid-air exchange. The fluid-air exchange should be slow, with exchange pressures lower than 40 mmHg and low vacuum. Remember to put the silicone sleeve of the extrusion cannula over the papilla and be careful not to catch and suck the flap, particularly in the end of the exchange when we take the last fluid from the posterior pole.

After the fluid-air exchange, we should check that the flap is well positioned (Figure 3), which is easily ascertainable if staining had been performed (as previously explained).

RESULTS

This adaptation of the surgery technique of the inverted ILM flap was performed in 5 consecutive patients from January to September. The patients presented with stage 4, long-term evolved, very large macular holes. All of them presented with a size greater than 850 μm, and 4 of them presented with a size greater than 1100 μm. Macular hole mean size was 1208.8 μm. ILM was used as the flap in 3 of the cases, and the anterior lens capsule was used in 2 cases. Viscoelastic adhesive and dye were used in all cases, following the technique exposed. Optical coherence tomography performed 24 hours after surgery in all cases showed the flap was well positioned. Moreover, flap macular hole closure was achieved in all cases.

We have found out that in some of these cases with so much evolution time, some parts of the ILM became fibrosed, usually at the edges of the macular hole. In these cases, we suggest, if possible, using the anterior lens capsule as flap as well as removing the ILM due to the possibility it could stimulate inflammation, which leads to bad results.

CONCLUSIONS

Viscoelastic adhesive is a good choice to hold the flap in the correct position, and it avoids the need for the “tuck technique” and its possible mechanical damage to the retinal pigment epithelium (RPE) layer and foveal choroids. Furthermore, it allows us not to keep an attached part of the ILM at the edge of the macular hole to avoid its migration, which is not always possible. It is a simple and cost-effective alternative that has showed no toxic impact on the retina, which can be left in the position.

The use of the anterior lens capsule as flap presents several advantages and could be an especially useful alternative when there is fibrosis of the ILM. We recommend the staining of the flap, regardless of the use of the anterior lens capsule or the ILM.

Both alternatives described in this article consist in autologous procedures and demonstrate the benefits of this kind of procedure. The employment of amniotic membrane as flap, when the use of the anterior lens capsule or ILM is not possible, provides another alternative.

Based on our outcomes, we suggest performing this technique in chronic, long-evolved, full-thickness and persistent macular holes larger than 650 μm.

REFERENCES


AGTC-501 gene therapy offers vision gains for X-linked RP
Higher doses achieve acceptable outcomes and microperimetry improvements

By Lynda Charters; Reviewed by Robert A. Sisk, MD, FACS

AGTC-501 (Applied Genetic Technologies Corporation), a novel gene therapy in development for the potential treatment of X-linked retinitis pigmentosa (RP), showed an acceptable safety profile and visual function improvements in the study’s higher dose groups, according to Robert A. Sisk, MD, FACS, from the Cincinnati Eye Institute in Ohio.

Sisk outlined the safety and efficacy findings of a phase 1/2 study of AGTC-501 gene therapy, a recombinant adeno-associated virus (AAV) 2 vector, for X-linked RP resulting from mutations in the RPGR gene, which accounts for 10% of RP cases.

AGTC-501 TRIAL
This study was a 12-month open-label, dose-escalation trial that included 29 male patients aged 6 years and older with the RPGR mutation. All patients were treated with 1 subretinal injection in the study eye. The first 9 patients received peripheral retinal injections as part of a safety assessment, which was the primary outcome, and the rest of the patients were treated centrally.

The safety assessment also included immunologic responses to the AAV capsid and the RPGR proteins expressed, Sisk explained. Key secondary outcomes included visual function measured by microperimetry (Macular Integrity Assessment) and retinal structure seen on optical coherence tomography (OCT).

SAFETY AND VISION RESULTS WITH AGTC-501
The safety results showed that no serious adverse events were related to the treatment. The initial surgical approach resulted in 4 peripheral retinal detachments related to dosing targeting the peripheral retina. The detachments did not occur when the central retina was targeted.

Grade 1 to 2 intraocular inflammation developed in about 20% (5/29) of patients and all were reported as resolved. About one-third of the patients had intraocular pressure elevations related to corticosteroid use and all have resolved without IOP related morbidities. The immunologic results did not suggest safety concerns.

The microperimetry sensitivity improved at month 12 in all centrally dosed patients across the central 36 points, which corresponds to the most anatomically and functionally intact areas in the patient population, he explained. Sisk also noted that the FDA has accepted a change of 7 or more decibels in 5 or more loci in the central microperimetry as clinically meaningful.

During the course of the study, the investigators observed that patients without foveal ellipsoid zone (EZ) integrity before the treatment did not have improved microperimetry. When those patients were excluded from analysis, 50% of patients were responders to treatment. Another 2 patients also had significant improvements in microperimetry compared with the untreated fellow eye.

OPTIMIZING OUTCOMES WITH AGTC-501
In addition to avoiding treatment targeting the peripheral retina, patient selection is paramount to achieve the best results. “Advanced disease with absence of baseline microperimetry or a foveal EZ line precluded meaningful microperimetry or visual benefits,” Sisk said.

Clinical trials of AGTC-501 for the potential treatment of X-link RP are continuing. The Skyline trial (NCT03316560) is an expansion of this phase 1/2 clinical trial, and the Vista trial (NCT04850118) is a phase 2/3 safety and efficacy clinical trial.

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This article is adapted from Sisk’s presentation at the American Academy of Ophthalmology 2021 annual meeting. Sisk is a consultant to AGTC.

The full article can be found online.
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