GEL AND GENES: NOVEL WAYS TO INTERVENE!


Dressed as Gregor Clegane (aka The Mountain) from *Game of Thrones*, Robert Avery, MD, reported on novel therapies that may reduce the burden of intravitreal injections.

BY DAVID XU, MD; AND LUV G. PATEL, MD

The Vit-Buckle Society (VBS) held an exciting *Game of Thrones*-themed online conference with many interesting talks (Figure). To start, Royce Chen, MD, shared his personal reflections on managing patients with COVID-19 in New York City. We also heard an excellent presentation by James Vander, MD, on navigating the COVID-19 world from a practice management standpoint. This article summarizes surgical talks by Rajeev Muni, MD; Ninel Gregori, MD; Gaurav Shah, MD; Caroline Baumal, MD; and Robert Avery, MD.

RAJEEV MUNI, MD - PNEUMATIC RETINOPEXY

Dr. Muni's talk expanded on the movement from traditionally held criteria for pneumatic retinopexy (PnR) to the newly defined criteria described in the Pneumatic Retinopexy Versus Vitrectomy for the Management of Primary Rhegmatogenous Retinal Detachment Outcomes Randomized Trial (PIVOT). PIVOT broadened the indications for PnR to include extensive lattice; any number, location, and size of breaks within attached retina; and breaks in attached retina that are in more than one quadrant or present inferiorly. In his practice, Dr. Muni performs the procedure in the following steps:

1. Laser retinopexy of lattice or breaks in attached retina
2. Subconjunctival anesthesia
3. Anterior chamber paracentesis
4. SF_6 gas injection
5. Use of the steamroller technique to gradually express subretinal fluid from the retinal break followed by positioning to the break
6. Staged laser retinopexy or cryopexy prior to anterior chamber paracentesis

He introduced the terms *low-* and *high-integrity retinal reattachment* (LIRA and HIRA) in the context of PnR versus pars plana vitrectomy (PPV). His studies have found that, compared with PPV, PnR favors high-integrity retinal reattachment with less retinal displacement, which is detected using fundus autofluorescence imaging. The PIVOT has also demonstrated that patients undergoing PnR have less frequent and less severe vertical metamorphopsia.

NINEL GREGORI, MD - GENE THERAPY SURGERY

Dr. Gregori shared surgical pearls for subretinal gene therapy. This technique has been used for the subretinal delivery of voretigene neparvovec-rzyl (Luxturna, Spark Therapeutics) as well as in clinical trials for choroideremia, X-linked retinitis pigmentosa, achromatopsia, and other conditions. Adeno-associated viral vectors are largely impermeable to the retina, so a subretinal injection via a retinotomy and successful creation of a bleb are important for treatment efficacy. Ideally, the viral vector is delivered to the intended retinal loci with minimal reflux into the vitreous space.

One tip from Dr. Gregori for performing the novel procedure addressed how to efficiently lift the posterior hyaloid membrane—which can be anomalous in patients with retinal dystrophy—while using triamcinolone acetonide staining and a backflush or a Finesse Flex Loop (Alcon). She also described her technique for loading the injection syringe without air bubbles, creating a balanced salt solution before the bleb is created, and using a pedal-controlled MicroDose injector (MedOne Surgical). The tip of the cannula can be beveled by the surgeon. Dr. Gregori discussed the avoidance of complications such as inadvertent suprachoroidal injection or reflux and macular hole formation, and she

advocated the use of microscope-integrated OCT to guide the surgeon and monitor progression of the bleb and foveal configuration during injection.

GAURAV SHAH, MD; AND CAROLINE BAUMAL, MD - INTERNAL LIMITING MEMBRANE PEELING DURING RETINAL DETACHMENT REPAIR

The conference included an interesting and vigorous debate between Drs. Shah and Baumal on the benefits of internal limiting membrane (ILM) peeling for routine rhegmatogenous retinal detachment repair. Dr. Shah took the pro position and cited clinical and pathophysiologic evidence: Patients who received ILM peeling have lower rates of postoperative epiretinal membrane formation and may have better visual acuity.

Dr. Baumal countered by stating that performing an ILM peel on a detached retina can be technically challenging, which increases the risk and complexity of surgery. Moreover, she stated, it can be argued that peeling the macula is separate from the primary aim of rhegmatogenous retinal detachment repair and is often unnecessary for surgical success.

Both physicians made important points. It is to be hoped that debates such as this one advance specialists' understanding of surgical techniques and spur more research in the field.

DR. GREGORI SHARED SURGICAL PEARLS FOR SUBRETINAL GENE THERAPY. THIS TECHNIQUE HAS BEEN USED FOR THE SUBRETINAL DELIVERY OF VORETIGENE NEPARVOVEC-RZYL ... AS WELL AS IN CLINICAL TRIALS FOR CHOROIDEREMIA, X-LINKED RETINITIS PIGMENTOSA, ACHROMATOPSIA, AND OTHER CONDITIONS.

ROBERT AVERY, MD - REDUCING THE BURDEN OF INTRAVITREAL INJECTIONS

Dr. Avery delivered a pair of talks at this VBS meeting. In his first talk, he described tyrosine kinase inhibitors (TKIs) as an exciting novel therapeutic class for the treatment of wet age-related macular degeneration (AMD). As with the larger biological anti-VEGF agents, these small molecules were originally studied as cancer therapeutics because of their antiangiogenic effects. The major drawbacks of these molecules are their limited bioavailability and short intraocular half-life, which are overcome by intravitreal injection designed for sustained release over 3 to 6 months.

Dr. Avery's presentation was the first to report data from a phase 1 trial of a TKI. He discussed data from 12 patients with AMD-related subfoveal neovascular membrane who were divided into two dose-dependent cohorts, each receiving an implant that dissolved over 6 to 9 months. The safety profile was generally favorable. Although three patients developed pigmented keratic precipitates, no patient to date has experienced iritis, vitritis, or retinitis. One patient had vitreous opacities at 6 months that were thought to be related to a breakdown of the implant, and another patient had inert fiber and reflective material in the vitreous thought to be related to the injection procedure. Some patients showed a decrease in fluid by 2 months, suggesting possible biologic activity. The durability of therapy was as long as 4.5 months in the higher-dose cohort. Dr. Avery stated that research is ongoing to determine the durability of treatment, maximum tolerated dose, and utility of the treatment in combination with existing anti-VEGF therapies.

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Figure. VBS panelists donned *Game of Thrones* costumes during a recent virtual event.

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His second talk covered another weapon in the arsenal to reduce the burden of intravitreal injections: gene therapy. Dr. Avery presented the initial results of the OPTIC trial in wet AMD patients. This 2-year phase 1 study is assessing the safety and tolerability of a single intravitreal injection of the ADVM-022 (Adverum Biotechnologies) vector encompassing a gene expressing the aflibercept protein. Secondary outcomes include BCVA, anatomic outcomes, and patients' need for rescue injections of aflibercept (Eylea, Regeneron). Two dose-dependent cohorts of six patients each are receiving oral steroid prophylaxis for intraocular inflammation.

According to Dr. Avery, although there have been no significant adverse events, low-grade inflammation is common among the patients. Both cohorts have shown an early anatomic response, more prevalent in the higher-dose group. All six patients in the higher-dose cohort have thus far not required rescue therapy, whereas two patients in the lower-dose cohort have required rescue aflibercept injections. Two additional cohorts of this study will receive a similar dose of intravitreal vector and will use topical steroids for inflammation prophylaxis.

The second half of this presentation addressed data regarding RGX-314 (RegenxBio), an adenovirus vector delivering a gene for the ranibizumab protein. Dr. Avery explained how this vector is delivered into the subretinal space via PPV, and noted that suprachoroidal delivery systems are in development. A phase 1/2a trial is under way, with 42 patients divided into five dose cohorts. Treatment has been well tolerated thus far without significant medication-related intraocular inflammation, but Dr. Avery cautioned that two patients experienced procedure-related complications (one retinal detachment and one endophthalmitis following anterior chamber tap for protein determination). Patients enrolled in the study have so far shown a possibly dose-dependent response with respect to anatomic outcomes, visual outcomes, and injection-free follow-up. A phase 2 trial is planned, and the application of this form of therapy to additional disease processes such as diabetic retinopathy will be explored.

Most important, Dr. Avery won the coveted buckle prize for best costume! ■

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