

News in Review

COMMENTARY AND PERSPECTIVE

GENETICS

Potential Gene Therapy for RP

SCIENTISTS HAVE DEVELOPED A GENE therapy for the most common form of autosomal-dominant retinitis pigmentosa (RP) caused by mutations in the rhodopsin (*RHO*) gene—and successfully demonstrated that it can prevent retinal degeneration in a canine model, an approach that someday could be harnessed to halt the disease in humans.

The researchers designed an adeno-associated viral vector to knock down the expression of existing *RHO* (both normal and mutant genes) and replace them with a normal copy of human *RHO*.¹ Retinal imaging and electroretinography showed that this approach kept the rod photoreceptors healthy and prevented retinal degeneration for at least 8 months of follow-up.

A dual-purpose approach. This strategy differs in key ways from the gene augmentation approach that led to a commercially available gene therapy (Luxturna) for Leber congenital amaurosis (LCA). Because LCA is autosomal recessive, that viral vector was engineered solely to transduce the retinal pigment epithelium with a single copy of the *RPE65* gene to produce the missing protein.

In autosomal-dominant RP, rod photoreceptor cells express rhodopsin proteins from both normal and mutant *RHO*. “The mutant protein produced in the rods either interferes negatively with the wild-type protein that comes

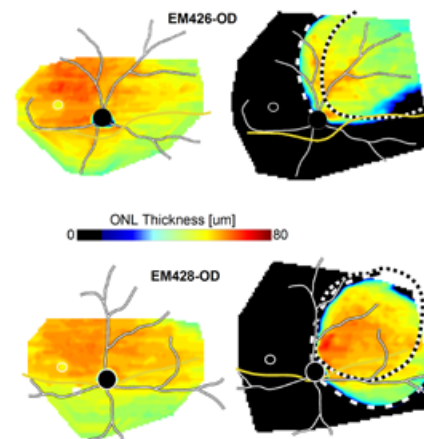
from the normal allele, or it has on its own a toxic gain of function, meaning that this protein may be toxic to the cell and kill it over time,” said William A. Beltran, DVM, PhD, at the University of Pennsylvania in Philadelphia.

The scientists concluded that their treatment would have to not only prevent the mutant gene already there from producing abnormal, toxic rhodopsin but also provide sufficient normal rhodopsin protein for the rods to survive and function normally. But in order to do this, the therapy also would need to work against the more than 150 gene mutations known to cause autosomal-dominant RP. “The challenge was to develop a treatment that can address any mutation,” Dr. Beltran said.

Their solution was a dual-purpose viral vector: One part was targeted at “knocking down” all endogenous rhodopsin mRNAs, both mutant and normal, through a technique known as RNA interference. The second part consisted of normal human *RHO* that was modified to avoid degradation by the knockdown component.

“The rods would not be able to function, or survive over the long term, if you didn’t bring back a normal wild-type copy of *RHO*. The vector also delivers a gene that has been modified at some very specific sites so that it still produces the same amino acid sequence as the rhodopsin protein, but it is not knocked down at the RNA level,” said coauthor Alfred S. Lewin, PhD, at the University of Florida in Gainesville.

What’s next. The researchers will study whether the viral vector can



NOVEL STRATEGY. Topographical maps of outer nuclear layer thickness show how the combined *RHO* knockdown and replacement therapy protected against severe retinal degeneration in a naturally occurring canine model of autosomal-dominant RP (right panels).

successfully treat areas where the retina is already degenerating. “We’re going to be looking at whether we can intervene at stages that are clinically relevant—and target areas where there are still rod photoreceptor cells left that can be rescued,” Dr. Beltran said. “If we’re able to show that, that will expand the potential candidates for gene therapy.”

—Linda Roach

1 Cideciyan AV et al. *Proc Natl Acad Sci U S A*. 2018;115(36):E8547-E8556.

Relevant financial disclosures—Dr. Beltran: Foundation Fighting Blindness: S; NIH/NEI: S; Research to Prevent Blindness: S; The Shalor Richardson Professorship Endowment: S; University of Pennsylvania: P. Dr. Lewin: NEI: S; University of Florida: P.

Bleeding Risk and NOACs

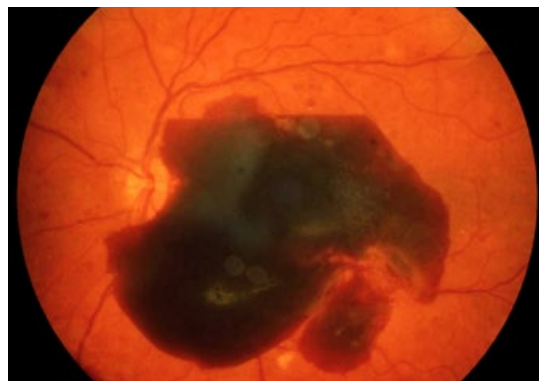
A REVIEW OF OUTCOMES IN MORE than 100,000 patients suggests that one of the novel oral anticoagulant medications (NOACs) on the market might be less likely than warfarin to cause ocular hemorrhages.

Outcomes better with edoxaban. A network meta-analysis of findings from 12 randomized controlled clinical trials found a statistically significant reduced risk of ocular bleeding in anticoagulated patients who took edoxaban when compared to warfarin (odds ratio: 0.59, confidence interval 0.34-0.98).¹ Traditional meta-analyses, using pooled pairwise and subgroup comparisons, also supported this conclusion (both $p = 0.02$).

The authors hypothesized that the molecular inhibition characteristics

of edoxaban and warfarin might explain the difference in bleeding outcomes. “In the case of edoxaban . . . it can be speculated that the direct inhibition of Factor Xa confers enhanced control over the coagulation cascade; in contrast, warfarin targets factors II, VII, IX, X and regulatory factors protein C, S, and Z, offering poorer pharmacodynamic precision,” they wrote.

Equivalent outcomes with other NOACs. No statistically significant reductions in risk were found with 3 other available NOACs (rivaroxaban, dabigatran, and apixaban). “There was a nonsignificant trend toward apixaban having more intraocular bleeding adverse events compared with warfarin, whereas dabigatran and rivaroxaban appeared to have similar intraocular bleeding complica-



BLEEDING. This image shows a preretinal sub-hyaloid hemorrhage.

tions profiles relative to warfarin,” the researchers wrote.

Study limitations. However, the possible ophthalmic lessons from this review study are limited because of deficiencies in the underlying data, commented M. Gilbert Grand, MD, of The Retina Institute in St. Louis.

No sham control. One difficulty is that there is no sham control, Dr.

Neuroborreliosis: Add Lyme Disease to Your Differential

OCULAR MANIFESTATIONS OF LYME DISEASE MAY

be more prevalent than commonly thought, a small prospective Swedish study suggests.

The study, conducted in western Sweden, found that the majority of patients diagnosed with neuroborreliosis (typically found in stage 2 of Lyme disease) had ophthalmic signs and symptoms.¹ The most frequent findings were blurred vision, diplopia, photophobia, redness, sixth nerve involvement, and palpebral diastasis resulting from facial palsy. Moreover, there was a positive correlation between signs and symptoms and cerebrospinal fluid (CSF) antibody titres.

Study rationale. The research team was motivated in part by evidence that “ticks are increasing in number and becoming more widespread in the northern parts of Europe,” said coauthor Marita A. Grönlund, MD, PhD, at Sahlgrenska University Hospital in Gothenburg, Sweden.

And although previous studies have documented the ocular manifestations of Lyme disease, they have been case reports and case studies, she noted. “Therefore, we and our coworkers at the [hospital’s] department of infectious diseases thought that it was of great importance to further evaluate and follow up ophthal-

mic symptoms and findings in individuals diagnosed with neuroborreliosis verified by CSF analysis.”

Study specifics. Over a 6-year period, 24 patients who had either been diagnosed with Lyme disease or were strong suspects were referred to the hospital’s department of ophthalmology. All were tested for *Borrelia burgdorferi* antibodies no later than 2 days after admission and underwent lumbar puncture no later than 3 days after admission.

Results. Neuroborreliosis was confirmed in 16 patients, while 2 patients were classified as possible cases. Diagnosis was negative in 4 patients and unknown in the remaining 2. Of the 18 patients classified as definite or possible, 14 (78%) had ophthalmic signs and symptoms. All patients improved except for 1 with fulminant papilledema; this patient still had optic disc atrophy and affected visual fields at last follow-up.

A surprise. In contrast with previous studies, the researchers found no evidence of either conjunctivitis or uveitis, Dr. Grönlund said. The reason for this remains unknown.

Take-home message. “For ophthalmologists, there might be reason to think twice about neuroborreliosis not only in subjects with facial palsy but also in those with [new-onset] diplopia and/or sixth nerve affection,” Dr. Grönlund concluded. —Jean Shaw

¹ Škiljić D et al. *Acta Ophthalmol*. Published online Aug. 26, 2018.

Relevant financial disclosures—Dr. Grönlund: None.

Grand cautioned. The researchers did not “calculate how many people get ocular bleeding because of preexisting ocular disease, without taking warfarin and the NOACs.”

No definition of hemorrhage. In addition, they did not define intraocular hemorrhage, Dr. Grand said. For instance, subconjunctival hemorrhages were included in a list of potential intraocular bleeds. “So we don’t know what type of events they were really analyzing.”

Need for clarification. The study does support the conclusion that spontaneous ocular hemorrhages occur rarely in patients undergoing anti-coagulation therapy, Dr. Grand said. However, it “does not add any data describing the risk of hemorrhage in anticoagulated patients who undergo intraocular surgery,” he said. “So this dataset, while valuable in itself, does not provide insights for ophthalmologists who must make decisions as to whether to continue or discontinue anticoagulation at the time of ophthalmic surgery.”

Fortunately, there are published data from earlier research on the safety of vitreoretinal surgery in patients taking warfarin² or the NOACs,³ Dr. Grand noted.

Need for further research. This study also raises an issue worthy of further examination, Dr. Grand pointed out. “There are certain ophthalmic diseases, such as exudative age-related macular degeneration or proliferative retinopathies, in which patients bleed spontaneously whether or not they’re taking anticoagulants,” he said. “What this study does not determine, and what we need to know, is whether anticoagulation therapy in those patients increases their risk of hemorrhages.”

—Linda Roach

1 Phan K et al. *Br J Ophthalmol*. Published online June 20, 2018.

2 Dayani PN, Grand MG. *Arch Ophthalmol*. 2006; 124(11):1558-1565.

3 Grand MG, Walia HS. *Retina*. 2016;36(2):299-304.

Relevant financial disclosures—Dr. Grand: None.

RETINA

PRP Preferred for Some Patients?

IN THE IDEAL WORLD OF CONTROLLED scientific studies, the strategy of treating proliferative diabetic retinopathy (PDR) with intravitreal injections has proved effective and possibly superior to panretinal photocoagulation (PRP). Now researchers report that in the “real” world, where patients are often lost to follow-up, PRP may be the better option.¹

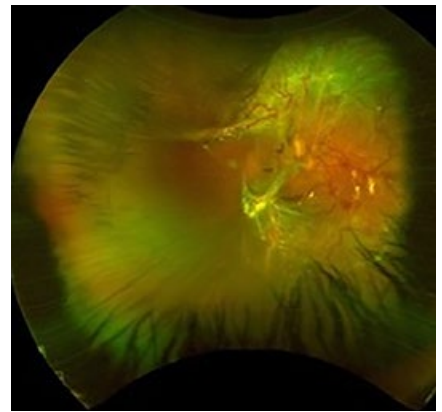
“Part of the impetus for this study was that we know PRP has long-lasting effects on stabilizing PDR, but we have little data on whether anti-VEGF therapy has any long-lasting effects once it is stopped,” said Jason Hsu, MD, at Wills Eye Hospital in Baltimore.

Now, data exist. “Our study suggests that if there is a period of loss to follow-up, patients with PDR who receive PRP may have better outcomes compared to those who received only anti-VEGF therapy,” said coauthor Anthony Obeid, MD, MPH, also at Wills Eye Hospital.

Retrospective cohort. The findings are based on medical records of 59 patients with PDR (76 eyes) who returned at various time points for follow-up treatment. All of the 59 patients had been lost to follow-up for 6 or more months immediately after receiving either intravitreal injections (20 patients; 30 eyes) or PRP (39 patients; 46 eyes).

Findings include the following:

- Visual acuity (VA) scores worsened in anti-VEGF eyes, from 20/54 at the visit before patients were lost to follow-up to 20/187 at the return visit and 20/166 at the final visit.
- In PRP eyes, VA significantly worsened from 20/53 at the visit before patients were lost to follow-up to 20/83 at the return visit. However, VA improved by the final visit to 20/58.
- There was a significantly greater incidence of neovascularization of the iris in the anti-VEGF group compared to the PRP arm at the final visit (4 vs. 0).
- A significantly greater number of



RD RISK. This eye with PDR developed an RD after being lost to follow-up.

eyes in the anti-VEGF group had tractional retinal detachment (RD) after patients returned to care. At the return visit, 5 in the anti-VEGF group experienced tractional RD, versus none in the PRP group. At the final visit, 10 anti-VEGF patients had tractional RD, versus 1 PRP patient. However, the incidence of tractional RD was lower in eyes that received a greater number of anti-VEGF injections prior to being lost to follow-up. “This may suggest that receiving a certain minimum number of injections may have lasting effects on PDR regression,” Dr. Obeid said.

Stick with PRP. The findings are particularly relevant as practice patterns are shifting toward anti-VEGF monotherapy for eyes with PDR, the authors said. They assume even greater relevance given the “strikingly high” rates of patients lost to follow-up,² said Dr. Hsu.

“Some clinicians believe that PRP may not be necessary or can be delayed while the patient is actively receiving anti-VEGF treatments,” Dr. Hsu added. “However, our study suggests that physicians may want to proceed with PRP at an earlier time point given the potential for poorer outcomes with erratic follow-up.” (For more on this topic, see pg. 23.)

—Miriam Karmel

1 Obeid A et al. *Ophthalmology*. Published online Aug. 2, 2018.

2 Obeid A et al. *Ophthalmology*. 2018;129(9): 1386-1392.

Relevant financial disclosures—Drs. Hsu and Obeid: None.