News in Review

COMMENTARY AND PERSPECTIVE

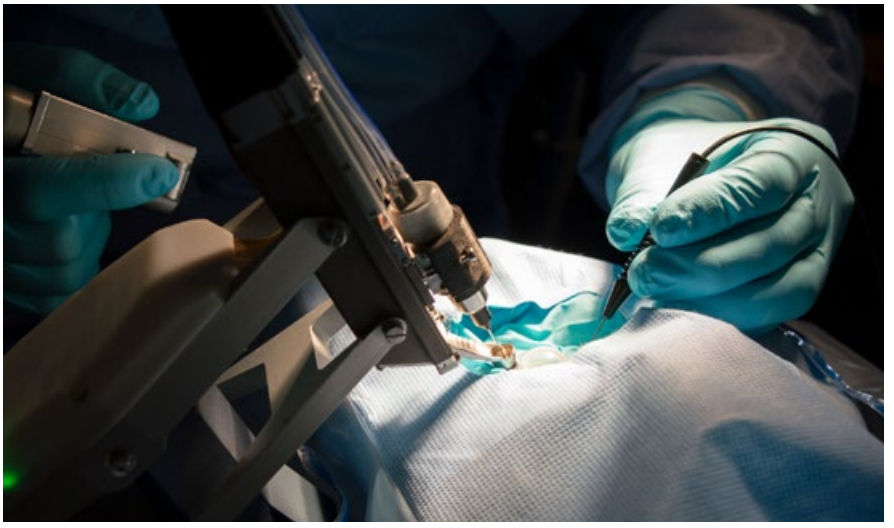
Robot Brings Greater Precision to Retinal Peeling

BRITISH VITREORETINAL SURGEONS have successfully used an ophthalmic surgical robot to perform the painstaking procedure of peeling retinal membranes, in a proof-of-principle study that they view as a step toward someday performing robot-assisted subretinal injections of therapeutic genes.[1]

Groundbreaking procedure. In response to the surgeon's manipulation of a joystick, the robot inserted a vitreoretinal pick through a 23-gauge trocar, advanced it toward the retina in 10-µm increments, and used the curved tip to lift the patient's epiretinal membrane or internal limiting membrane (ILM) in 6 patients, said Robert E. MacLaren, MD, PhD, principal investigator in the trial. There were no complications, he reported. (A second set of 6 patients served as controls.)

"We wanted to test the robot with the most delicate procedure that we currently do with our hands, and that is lifting the ILM. When we do that manually, invariably we cause a little bit of trauma to the retina. So we used retinal hemorrhages and retinal touches as a marker for the precision of the robot," Dr. MacLaren said.

Less retinal trauma. Even the steadiest surgeon's hand can move a needle tip toward the retina with precision of no better than about 100 µm, compared to 10-µm movements with the robot, said Dr. MacLaren, at the University of Oxford in the United Kingdom. Because of this, his group was not surprised to find that the robotic surgeries caused less retinal trauma than did manual membrane peeling in the control patients, he said.



A SURGICAL FIRST. *Using robotic technology, a team of surgeons performed vitreoretinal surgery inside 6 living human eyes.*

Surgical outcomes. There were 2 retinal microhemorrhages and 1 retinal touch in the robot-assisted surgeries, compared to 5 and 2, respectively, in the control group. However, it took longer to lift the membranes with the robot: a mean of 213 ± 51 seconds, versus 130 ± 118 seconds in the manual group, he said.

"You have to bear in mind that those 6 patients represented the first 6 patients when the robot was ever used in a human. And obviously I was a bit anxious doing it," Dr. MacLaren said. "The time of the sixth patient was actually quite a bit quicker than the first."

Potential applications. Looking ahead, the most exciting potential uses for the robot—developed by Preceyes BV in collaboration with Oxford researchers—are the surgical innovations that it might facilitate, Dr. MacLaren said.

Gene therapy. For instance, his group's primary objective for the near future is to take advantage of the robot's ability to hold instruments stable inside the eye, in order to perform slow, subretinal delivery of viral gene therapy vectors. The group is conducting gene therapy trials for choroideremia and X-linked retinitis pigmentosa, Dr. MacLaren said.

Novel procedures. Looking further out, Dr. MacLaren expects that the robot will "help surgeons develop operations that we currently can't do." He added, "We need to think a little bit out of the box. For example, we look at the

retina with optical coherence tomography scans and see a great level of detail, but we can't actually operate with that level of precision. The human hand is just too big and too bulky."

In contrast, Dr. MacLaren said, "With a robot you could actually advance the needle halfway into the retina and deliver treatment there. Or you could go through the retina to the junction between the retinal pigment epithelium and the photoreceptors."

Direct to the nerve. Perhaps one day the robot even could make it possible to treat the optic nerve directly, he said. "Can you imagine, if you want to inject something into the optic nerve? This would be impossible with the human hand, but a robot could do that with a very, very high degree of precision, causing minimal trauma."

—Linda Roach

1 MacLaren RE et al. Results from the first use of a robot to operate inside a human eye. Paper presented at: ARVO 2017 Annual Meeting; May 8, 2017; Baltimore.

Relevant financial disclosures—Dr. MacLaren: NightstaRx: C,E,O,P; University of Oxford: E,P.

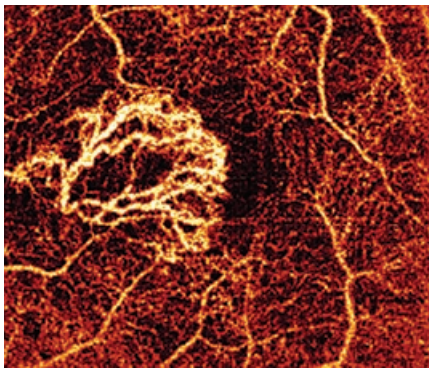
RETINA

Brolucizumab May Offer Extended VEGF Inhibition

BROLUCIZUMAB, A NOVEL DRUG that blocks vascular endothelial growth factor (VEGF)–A, has been found to be noninferior to aflibercept at preserving vision in patients with active choroidal neovascularization (CNV) secondary to age-related macular degeneration (AMD).[1] Published data from a phase 2 trial also suggest that patients treated every 8 weeks with brolucizumab might experience some advantages compared to patients injected with 2 mg of aflibercept, notably a more durable treatment effect and extended intervals between intravitreal injections.

Pharmacokinetics. Brolucizumab (also known as RTH258) is a humanized single-chain antibody fragment that inhibits all isoforms of VEGF-A with a molecular weight of 26 kDa.

"On a molar basis, 6 mg of brolucizumab equals approximately 12 times the 2.0-mg dose of aflibercept and 22 times the 0.5-mg dose of ranibizumab," the authors wrote.[1] "These attributes may confer potential advantages in the treatment of neovascular AMD. A small molecular weight and high drug concentration gradient between the vitreous and retina may support drug distribution into the retina. Assuming comparable half-life, higher molar doses of drug may be cleared more slowly from the eye, thus prolonging duration



REDUCED DOSING? *Early results indicate that brolucizumab may allow for an extended interval between intravitreal injections for CNV (shown here).*

CORNEA

Antidepressants and Ocular Pain in Dry Eye Disease

OCULAR PAIN IS A COMMON SYMPTOM IN PATIENTS with dry eye disease (DED). But what factors determine the level of pain? To their surprise, researchers at Massachusetts Eye and Ear in Boston found a relationship between ocular pain severity and the use of antidepressant medications, but not with any clinical signs of DED.[1]

Pain prevalence. For this study, 84 patients with DED underwent an ocular surface exam and answered an Ocular Surface Disease Index (OSDI) questionnaire. They were also asked to rate their ocular pain severity using a 10-point scale.

A majority (88%) of the patients reported some degree of ocular pain. However, the pain had only a moderate correlation with OSDI scores. In addition, pain severity was significantly associated with the use of antidepressant medications—but not with corneal fluorescein staining or tear break-up time. Moreover, although patients without ocular pain showed a significant correlation between OSDI scores and corneal fluorescein staining, there was no such correlation in patients with pain.

Symptoms versus signs. "It is well known that the symptoms and signs of DED do not have a strong relationship, and our study supports this," said coauthor Reza Dana MD, MSc, MPH, at Massachusetts Eye and Ear. "In pain-free patients, there was a significant correlation between symptoms and signs that was otherwise absent in those reporting pain."

These findings suggest that the discordance between DED signs and symptoms may be due to different degrees of neural involvement. As such, treatment should be tailored accordingly, Dr. Dana said. "In patients without a significant neuropathic component, tear film management is usually enough," he said.

However, Dr. Dana said, "In patients with a major neuropathic component—which may be suggested by a lack of correlation between symptoms and signs and/or possibly the presence of pain—you might also consider the use of autologous serum eye drops or systemic medications such as gabapentin and similar drugs."

—Mike Mott

1 Satitpitakul V et al. *Am J Ophthalmol.* 2017;179:198-204.

Relevant financial disclosures—Dr. Dana: None.

of action," they explained.

Study results. For this phase 2 study, researchers evaluated 89 patients, 44 of whom received injections of brolucizumab (6 mg). The remaining 45 received 2-mg injections of aflibercept.

Through 40 weeks of treatment, the brolucizumab group had more stable reductions in central subfield thickness (CSFT) and greater resolution of intra- and subretinal fluid. At week 40, fluid resolution had occurred in 61% of subjects receiving intravitreal brolucizumab, compared to 35% of the aflibercept patients.

With regard to unscheduled treatments, unplanned injections numbered 6 in the brolucizumab eyes and 15 in the aflibercept group. Furthermore, when the researchers extended the treatment interval to 12 weeks, approximately 50% of the evaluable brolucizumab eyes maintained their best-corrected visual acuity (BCVA) without requiring any unscheduled injections.

Additional results. In late June, Novartis released positive results from 2 phase 3 studies of brolucizumab. According to the company, researchers evaluated 3- and 6-mg doses of the drug and found that both doses provided excellent visual acuity and reduced injection burden when compared to aflibercept. However, the results have yet to be published.

Drug delivery. Brolucizumab's small molecular size might give it another advantage in the future, said Pravin U. Dugel, MD, at Retinal Consultants of Arizona in Phoenix and the University of Southern California, in Los Angeles. Specifically, it's possible that the drug could be delivered via an ocular implant. "We don't have one yet [for anti-VEGF drugs], but I think we're all convinced that one day we will. So, because of its size, brolucizumab would seem like it could be an ideal anti-VEGF agent to be packaged in this way."

—Linda Roach

1 Dugel PU et al. *Ophthalmology*. Published online May 24, 2017.

Relevant financial disclosures—Dr. Dugel: Alcon: C; Allergan: C; Genentech: C; Novartis: C; Roche: C.

GLAUCOMA

Support Grows for Using OCT to Detect Progression

A RECENT ANALYSIS FROM THE ADvanced Imaging for Glaucoma (AIG) study strengthens the case for using optical coherence tomography (OCT) in everyday clinical practice.[1] However, the findings do not suggest that OCT will replace visual fields (VFs) at this time.

Early and late. The comparison of OCT and VF showed the usefulness of OCT structural analysis for detecting progression in both early and late stages of glaucoma, said David Huang, MD, PhD, at Casey Eye Institute in Portland, Oregon.

In early stages of glaucoma, peripapillary retinal nerve fiber layer (NFL) thickness and macular ganglion cell complex (GCC) thickness, as measured by OCT, were together more sensitive than were VF parameters in detecting progression. And in a separate finding, one Dr. Huang called "important and novel," OCT detected progression in advanced glaucoma on a par with VF. The ability of OCT to monitor advanced glaucoma was mostly due to GCC, as the AIG study confirmed findings from other studies that showed NFL to be less sensitive in advanced disease.

Multicenter analysis. The study, conducted at 5 universities, included 417 glaucoma suspect and preperimetric glaucoma eyes and 377 perimetric glaucoma eyes. Fourier-domain OCT was used to map the thickness of the NFL and GCC. OCT-based progression detection was defined as a significant negative trend for either average NFL or GCC thickness. VF progression was detected if either the visual field index (VFI) trend analysis or the Guided Progression Analysis (GPA) event analysis reached significance.

Findings. In the glaucoma suspect/preperimetric group, OCT detected progression in 38.9% of eyes, versus 18.7% using VF parameters. In early perimetric glaucoma, OCT had a significantly higher detection rate compared to VF: 49.7% versus 32%, respectively.

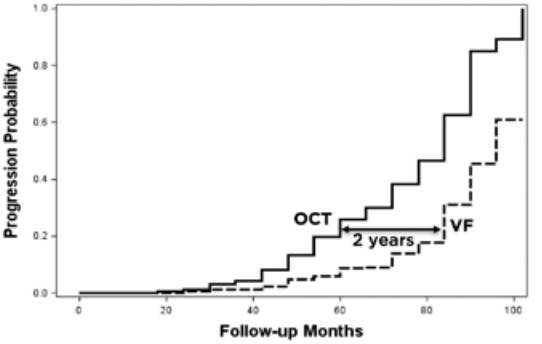
However, "In a significant percentage of eyes, progression was detected only on VF," Dr. Huang said. "This percentage is large in later stages and small in the earlier stages of glaucoma."

Clinical implications. Although OCT proved useful in monitoring progression, Dr. Huang said, "VF is needed in initial patient evaluation to establish the stage of glaucoma." He added that in advanced disease, when patients need to be closely monitored, both technologies are needed.

Looking ahead. "The evidence is strong that OCT should be an important part of progression monitoring in preperimetric glaucoma and mild perimetric glaucoma," Dr. Huang said. "Since OCT scanning is relatively quick, it could easily be performed on every visit. In early glaucoma, OCT could help catch progression sooner and measure the rate of progression more precisely." *—Miriam Karmel*

1 Dastiridou A et al. Comparison of glaucoma progression detection by optical coherence tomography and visual field. Presented at: ARVO 2017 Annual Meeting; May 8, 2017; Baltimore.

Relevant financial disclosures—Dr. Huang: Optovue: O,P,S.



TREND ANALYSIS. *Kaplan-Meier plots of glaucoma progression.*

David Huang, MD, PhD

See the financial disclosure key, page 8. **For full disclosures,** including category descriptions, view this News in Review at aao.org/eyenet.