Bevacizumab for ROP: Low Doses Prove Effective

INTRAVITREAL BEVACIZUMAB CAN be an effective treatment for retinopathy of prematurity (ROP) even at very low doses, a team of British clinical researchers has reported.

In a retrospective case series,[1] the group reported that ROP regressed completely in nearly 80% of the eyes after a single injection of bevacizumab (Avastin). The dosage—0.16 mg in 0.025 mL—was approximately one-fourth the amount that has been used in these infants for several years (0.625 mg in 0.025 mL), said Roxane J. Hillier, FRCOpth, at the Royal Victoria Infirmary in Newcastle upon Tyne, U.K.

Addressing systemic concerns. "The introduction of anti-VEGF agents to treat ROP has completely transformed our management of these babies with severe retinopathy," Dr. Hillier said. "But it's imperative that we make sure that the dose we're using is as low as possible, because there are concerns about the impact these drugs might have on the babies' systemic development," particularly their neurological and respiratory systems, she said.

In an Academy *Ophthalmic Technology Assessment* published earlier this year,[2] the authors concluded that there is level II and III evidence that intravitreal anti-VEGF therapy is at least as effective as laser photocoagulation for resolving ROP. But they noted lingering concerns about potential effects on organ development. "After intravitreal injection, bevacizumab can be detected in serum within 1 day, and serum VEGF levels are suppressed for at least 8 to 12 weeks," the *OTA* report said.

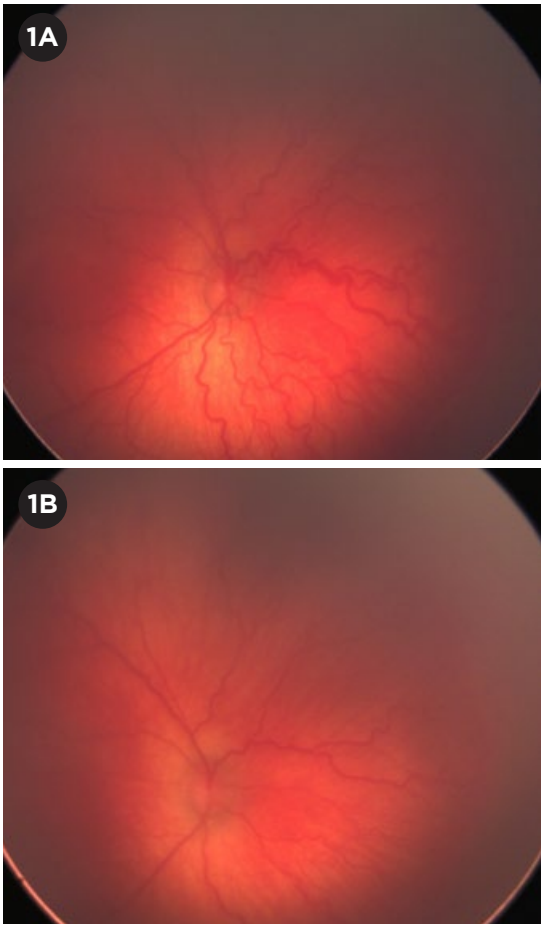
Study results. In Dr. Hillier's case series, there were 15 infants (29 eyes) with severe and posterior ROP. Primary success with intravitreal bevacizumab alone was seen in 23 of 29 eyes (79.3%). The other 6 eyes required retreatment, either with another injection or with laser photocoagulation.

Improvement in retinopathy and in plus disease began in all cases within 48 hours after the injection, Dr. Hillier and her colleagues reported. "This response was notably less brisk when compared with higher dose intravitreal bevacizumab. Nonetheless, in our experience, early signs of resolution may be expected within 48 hours, even at this very low dose," they wrote.

"What dose should we be using? We still don't know the answer," Dr. Hillier said. "But I think this paper brings us a step closer to understanding that the traditional dose that we've been using for the last few years is probably vastly in excess of what is needed."

Additional investigations. To clarify the issues of dosing and potential systemic risks, the Pediatric Eye Disease Investigator Group currently is conducting a prospective phase 1 multicenter trial to determine the lowest effective bevacizumab dose for treatment of type 1 ROP. This study also will collect serum levels of VEGF and bevacizumab after the injection.

Other studies in Germany and the United States are looking at the possibility that ranibizumab (Lucentis) might reduce the potential systemic risks because it has a half-life of a few



BEFORE AND AFTER. *This male twin was born at 23 weeks' gestational age. These images are of his right eye at baseline (1A) and 2 days after he received an intravitreal injection of low-dose bevacizumab (1B).*

Roxane J. Hillier, FRCOpth

hours in the circulation, compared to weeks for bevacizumab.[2]

"I think that actually there is a very good rationale potentially for using Lucentis rather than Avastin," Dr. Hillier said. "But thus far, the most robust scientific evidence for using anti-VEGF drugs in this group of babies is with Avastin." —*Linda Roach*

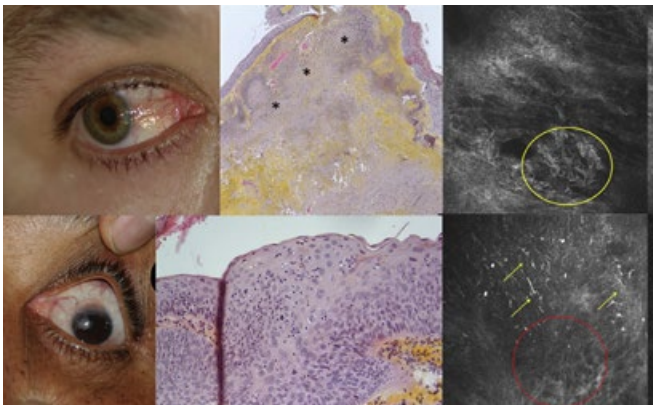
1 Hillier RJ et al. *Br J Ophthalmol.* Published online June 27, 2017.
2 VanderVeen DK et al. *Ophthalmology.* 2017; 124(5):619-633.
Relevant financial disclosures—Dr. Hillier: None.

OCULAR ONCOLOGY

Handheld Device Aids in Detecting Eyelid and Conjunctival Tumors

A HANDHELD CONFOCAL MICRO-scope originally developed for dermatologists can be used to perform noninvasive "optical biopsies" to diagnose eyelid and conjunctival malignancies, Italian and French researchers have reported.

Viewing individual cells. The group, based at the University Hospital of Saint-Étienne in Saint-Priest-en-Jarez, France, reported that a handheld reflectance confocal microscope (VivaScope 3000; Caliber Imaging & Diagnostics) enabled them to see images of individual cells in the suspicious lesions, enabling diagnosis of melanoma and squamous cell carcinomas.[1]



COMPARISON. *Clinical (left), histologic (center), and handheld reflectance confocal microscopy (right) images in patients with pinquecula (top) and squamous cell carcinoma (bottom). (Note: These images are from an earlier study.)*

Each image covers an area of 920 × 920 µm (more than double the field of view achieved by reflectance confocal microscopes that are not mobile) and up to 250 µm in depth. The horizontal optical resolution is 1.25 µm.

"The device offers you some information that is impossible to find with other devices. We observe the cells in vivo, which is amazing," said Elisa Cinotti, MD, PhD, at the University of Siena in Siena, Italy. "You can come to a diagnosis very early compared to the clinical examination, which gives you only a macroscopical view."

Procedural details. The process of using handheld in vivo confocal microscopy (IVCM) to diagnose suspicious tissues takes 5 to 10 minutes, Dr. Cinotti said. The clinician begins by topically anesthetizing the eye, then

GLAUCOMA

Look Beyond IOP to Measure Surgical Success

RESEARCHERS AT THE STEIN EYE INSTITUTE IN LOS Angeles have identified 2 risk factors significantly associated with low intraocular pressure (IOP) after trabeculectomy—the use of laser suture lysis and the individual surgeon.[1] However, patients with and without low IOP had similar rates of reoperation, vision loss, and overall surgical failure.

"Developing low postoperative IOP does not necessarily equate with developing clinical signs of hypotony that threaten vision," said Victoria L. Tseng, MD, PhD, at Stein Eye Institute.

Study details. Dr. Tseng and her colleagues compared 64 cases of low IOP to 130 controls without low IOP. Low IOP was defined as IOP ≤ 5 mm Hg on 3 or more consecutive visits after surgery. Cases were drawn from 3,659 trabeculectomies performed by 5 surgeons between 1990 and 2013.

Assessing risk. Laser suture lysis was negatively correlated with postsurgical low IOP. Only 28.1% of low IOP cases had undergone the procedure, versus 50.8% of controls. This is not to say that the procedure was protective against hypotony, Dr. Tseng said. Rather, laser suture lysis patients had a higher mean baseline IOP and thus had farther to fall following surgery, she explained.

The second risk factor—the clinician who performed the surgery—was positively correlated with low IOP after trabeculectomy. This association is likely due to patient selection, with 1 surgeon operating on a higher proportion of patients with lower baseline IOP than the others, Dr. Tseng said. Surgical technique was probably not a factor, since the surgeons followed a similar protocol.

Bottom line. The factors associated with low IOP are likely proxies for patients requiring a lower target IOP, said Dr. Tseng. The low postoperative IOP "may have been somewhat intentional." Her advice: "The assessment of a patient's progress after surgery and the need for further procedures should be based on a full clinical assessment and not IOP alone." —*Miriam Karmel*

1 Tseng VL et al. *Ophthalmology*. Published online June 11, 2017.
Relevant financial disclosures—Dr. Tseng: None.

applies a transparent ophthalmic gel to the area being examined. With the patient supine, the physician places the 5-mm tip lightly on the lesion to be examined and moves it around on the surface as needed to optimize the image. (Recently the tip was redesigned to be removable for sterilization, she said.) The biomicroscopic images are displayed on a nearby monitor.

To test the device for ophthalmic use, a team of 3 dermatologists and 3 ophthalmologists conducted a prospective, observational study on 298 consecutive patients with eyelid margin or conjunctival lesions. Patients underwent clinical examination at the slit lamp and with IVCM. Suspected malignancies were excised from 155 eyes, and histopathology was performed to verify the original diagnoses.

Better sensitivity. The researchers found that, compared to the slit-lamp exam, the handheld confocal microscope showed higher sensitivity for malignant tumors of the eyelid margin (98% vs. 92%) and conjunctiva (100% vs. 88%).

IVCM identified all the malignant conjunctival tumors and missed only 1 cancer on the eyelid margin, a basal cell carcinoma, the authors reported. In contrast, clinical examination with the slit lamp failed to identify 5 basal cell carcinomas of the eyelid margin and 3 malignant melanomas of the conjunctiva.

"I saw some cases in which there was hyperpigmentation of the conjunctiva of a few millimeters. With IVCM, it was clear that they were melanomas. On the clinical examination, it was impossible [to reach an accurate diagnosis]," Dr. Cinotti said.

Problems with specificity. The specificity results were mixed: They were higher compared to the slit-lamp exam for the malignant eyelid margin tumors (74% vs. 46%) but lower for malignant conjunctival tumors (78% vs. 88%). Although the IVCM correctly diagnosed 100% of the cases of conjunctival malignant melanoma, it misdiagnosed 7 benign conjunctival lesions as melanoma (74% specificity for melanoma), the authors reported. As for the eyelid lesions, 5 were misdiagnosed as melanoma (64% specificity for melanoma).

Dr. Cinotti explained that some types of tumors contain large cells that make the IVCM images difficult to interpret or ambiguous. "Our study had a large group of patients, but we still have a lot of work to do on this. It's still quite new. We need more work on the criteria for diagnosis," she said. *—Linda Roach*

1 Cinotti E et al. *JAMA Ophthalmol.* Published online June 22, 2017.

Relevant financial disclosures—Dr. Cinotti: None.

WORLD HEALTH

Unique Retinal Lesions Found in Ebola Survivors

BRITISH RESEARCHERS HAVE IDENTI-fied unique retinal scarring in survivors of Ebola virus disease (EVD), the distribution of which suggests a neurotrophic spread of the disease into the eye.[1]

A surprising find. Paul J. Steptoe, BSci, MBChB, and his team conducted a case control study in Freetown, Sierra Leone, to investigate ocular signs in EVD survivors. A total of 82 patients with ocular symptoms and 105 controls underwent ophthalmic examination, including widefield retinal imaging.

Lesion appearance. "Despite a high prevalence of background retinal disease in our study population, we discovered a novel retinal lesion in almost 15% of survivors," said Dr. Steptoe, at the University of Liverpool and Royal Liverpool Hospital in Liverpool, U.K. "And although the shape of the lesions varied, we were surprised to find a very unusual angulated appearance, often resembling a diamond or wedge shape."

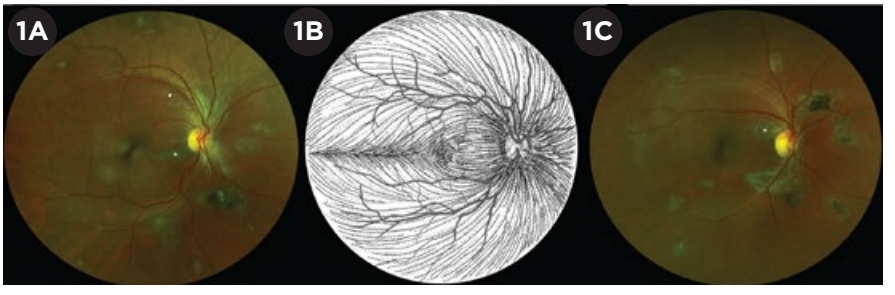
Lesion location. These lesions were located either in the fundus periphery or adjacent to the optic disc. When they were near the optic disc, their curvilinear projections from the disc margin aligned with the retinal ganglion cell axons that make up the optic nerve. "This distribution suggests a neuronal transmission of the disease to the retina in a similar fashion to West Nile virus retinitis," said Dr. Steptoe.

Is cataract surgery safe? Cataract surgery is currently denied EVD survivors for fear of viral persistence in the ocular fluid. To assess the validity of this claim, the researchers also tested the aqueous fluid in 2 survivors who had cataracts but no anterior chamber inflammation; both were negative for the Ebola virus.

"Although larger investigations are ongoing, our study provides provisional evidence that cataract surgery is indeed safe for these EVD survivors," said Dr. Steptoe. His team is currently conducting a yearlong follow-up to assess the recurrence of EVD as well as any further retinal changes in survivors. *—Mike Mott*

1 Steptoe PJ et al. *Emerg Infect* Dis. 2017;23(7): 1102-1109.

Relevant financial disclosures—Dr. Steptoe: Bayer Global Ophthalmology Awards Programme: S; Optos: S; The Dowager Countess Eleanor Peel Trust: S.



LESIONS. *Retinal images (1A, 1C) show Ebola peripapillary and peripheral lesions following the anatomic distribution of the ganglion cell axons (1B). Asterisks in the fundus photos indicate curvilinear lesions distinct from the retinal vasculature. White arrowhead indicates retinal nerve fiber wedge defect.*

Paul Steptoe, BSci, MBChB

For the financial disclosure key, see page 10. For full disclosures, including category descriptions, view this News in Review at aao.org/eyenet.