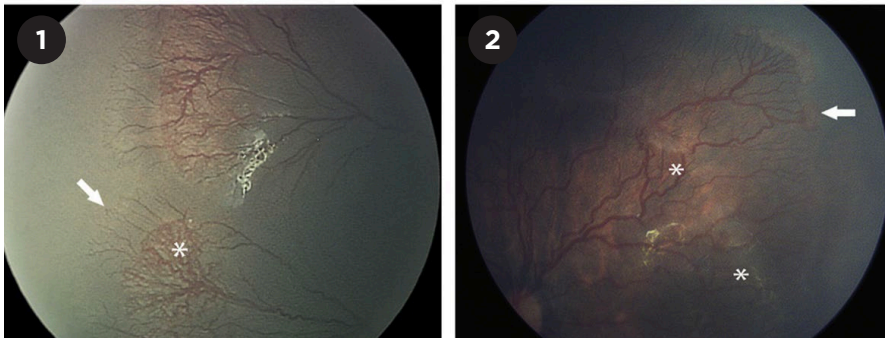
A New Field Guide to ROP: ICROP-3

Treating premature infants for retinopathy of prematurity (ROP) is "among the most dramatic of interventions, because you're taking babies who could be completely blind and potentially giving them vision for a lifetime," said Gil Binenbaum, MD, at the Children's Hospital of Philadelphia.

Today, treatment is likely to start with anti-VEGF injections. And this evolution in treatment patterns has driven the need for a more nuanced field guide to the disease. Called ICROP-3 (International Classification of Retinopathy of Prematurity, Third Edition), this expert consensus, published last year, replaces the 2005 edition and addresses phenomena seen with increased use of anti-VEGF drugs.[1]



REACTIVATION. *(1) This image shows reactivation of disease in an eye at 67 weeks' postmenstrual age (PMA). The infant had received anti-VEGF injection at 33 weeks' and 52 weeks' PMA. Reactivated stage 3 disease (asterisk) is present posteriorly to the leading edge of vascularization (arrow). (2) Reactivated stage 3 ROP at the leading edge (arrow) at 50 weeks' PMA, after anti-VEGF injection at 36 weeks' PMA. Vascularization into the peripheral avascular retina has occurred between the original ridge (asterisks) and anterior reactivation.*

Key Changes in ICROP-3

A key point with ICROP-3 is that the changes involve the language used to describe the disease, Dr. Binenbaum said. "We're not telling people how to treat."

Description of reactivation. "The most important addition is a description of disease reactivation," said David K. Wallace, MD, MPH, at Indiana University in Indianapolis. "Anti-VEGF agents have created new situations where disease regressed and then reactivated in ways we'd never seen before." These include the growth of new blood vessels where the previous ridge of ROP occurred and tufts of neovascular tissue in the posterior retina, he said.

"Reactivation after anti-VEGF treatment includes vascular dilation, tortuosity, and extraretinal neovascularization," said Mary Elizabeth Hartnett, MD, at the University of Utah in Salt Lake City. "We want to allow physiologic vascularization after anti-VEGF treatment but not to allow pathologic extraretinal neovascularization." Like Drs. Binenbaum and Wallace, Dr. Hartnett is a coauthor of ICROP-3.

Clarification of regression. ICROP-3 clarifies that regression is not the disease process in reverse. "Regression simply means the disease is going away, spontaneously or in response to treatment," said Dr. Binenbaum. Dr. Hartnett added, "With anti-VEGF treatment, we see that regression can occur very quickly, with reduced dilation of the veins and less tortuosity of the arterials and veins."

Definition of persistent avascular retina. Introduced into the lexicon by ICROP-3, persistent avascular retina (PAR) means that blood vessels failed to grow to the front of the eye. "We believe there may be a higher risk of PAR after anti-VEGF than after spontaneous regression," said Dr. Binenbaum.

Dr. Hartnett added, "we need to compare the occurrence of PAR in eyes with spontaneous and treated regression; PAR may vascularize later."

Addition of posterior zone 2. ROP is mapped onto three concentric zones

BY REBECCA TAYLOR, CONTRIBUTING WRITER, INTERVIEWING **GIL BINENBAUM, MD, MARY ELIZABETH HARTNETT, MD, DAVID K. WALLACE, MD, MPH,** AND **HAWKE H. YOON, MD.**

of the eye—zone 1 (most posterior), zone 2 (middle), and zone 3 (most anterior)—and classified by the most posterior disease. ICROP-3 added a subdivision of zone 2 closest to zone 1.

"Posterior zone 2 is two [optic] disc diameters into zone 2 from zone 1," said Dr. Binenbaum. This is a critical nuance, he said, because "the more posterior the disease, the more aggressive it tends to be."

Definition of notch. A notch is an incursion of ROP from one zone into another. A notch that extends into zone 1, with most of the vascularization in zone 2, is now called "zone 1 secondary to notch," said Dr. Hartnett.

Broader definition of aggressive ROP. Aggressive ROP (A-ROP) replaces aggressive posterior ROP (AP-ROP), based on international input that this form doesn't only occur posteriorly.

"When vessels start growing in the wrong direction, first you see a white line, or stage 1 ROP; then it develops into a white wall, or stage 2," said Dr. Binenbaum. "When blood vessels grow into the vitreous with fibrovascular proliferation, that's classic stage 3."

Aggressive ROP, he said, looks different from typical stage 3 ROP. "Aggressive ROP involves lacy, flat, subtle neovascularization and skips stages 1 and 2. You may need extra magnification and will need to look closely for this flat neovascularization, because aggressive ROP progresses quickly—and if you wait for classic stage 3 to develop, it's likely too late for treatment to effectively prevent a retinal detachment."

"I appreciate ICROP-3 talking about the tempo of how things change," said Hawke H. Yoon, MD, at Lurie Children's Hospital of Chicago. "I ask my trainees all the time: 'Is this changing rapidly? Has it gone from stage 1 to stage 3 within a week?'"

New subclassifications for stage 5. Stage 4 ROP still classifies a partial retinal detachment. Stage 5 has three new subclassifications, said Dr. Hartnett: "5a is a total retinal detachment, 5b is a closed funnel where vitreous opacities may obscure the optic nerve, and 5c has anterior segment abnormalities."

Broader definition of plus disease. "ICROP-3 classifies plus disease as a spectrum of changes in the dilation and tortuosity of retinal veins or arteries," said Dr. Hartnett. It now uses all of so much we don't know about ROP; every answer raises 10 more questions."

Dr. Yoon agreed. "With a lower dose, do we increase the risk that we have to do repeat injections?" he asked. "Do we lose the benefit of the lower dose if it is given at different times—or is that better, systemically, for the child?"

A Look at Two Pivotal Studies

ROP-3 and ROP-4, both phase 3 trials, are seeking to clarify the benefits of bevacizumab for ROP.

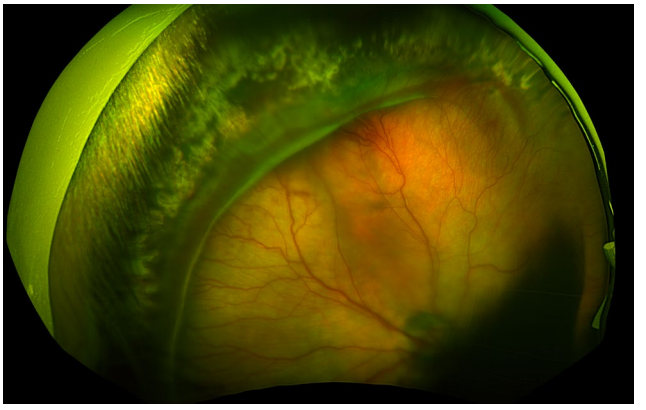
The studies are collaborations between PEDIG and DRCR.net. "It's the first time that these two networks of retina specialists and pediatric ophthalmologists have collaborated on a study together," said Dr. Wallace, who is protocol chair for both studies.

Why bevacizumab? "It's the most commonly used anti-VEGF for ROP around the world and considerably less expensive than its alternatives," Dr. Wallace said. "In Europe, ophthalmologists organized the RAINBOW[1] study, which compared ranibizumab to laser, so we can add the most if we study bevacizumab."

ROP-3: bevacizumab versus laser. "We took the data from ROP-1 [a previous de-escalating dose study], did a Bayesian statistical analysis, and calculated the probability that each dose was at least 95% effective," said Dr. Wallace. "We settled on .06 mg, or about 10% of the original dose."

ROP-3 is randomizing that .06-mg dose against laser treatment with 212 infants recruited over the next few years, with infants followed out to six years, he said.

Bevacizumab often works better than laser for more aggressive ROP, although the risk is reactivation years later, said Dr. Yoon. "I feel much more comfortable [with ROP-3] than with ROP-1 and ROP-2, because the rescue protocols are very robust, and most of us are doing 'insurance' laser if needed to make sure we don't miss complications down the road."



IMAGING. *Stage 3 disease in a 5-month-old child. The flying baby technique was used to create this image.*

ROP-4: low versus lower dose of bevacizumab. ROP-4 is testing two low doses of bevacizumab—.25 and .06 mg—in 80 infants followed out to one year, said Dr. Wallace. "Short-term success is defined as improvement within five days, without any reactivation of severe disease within the first four weeks," he said.

"One of the theoretical advantages of bevacizumab is that the blood vessels grow farther into the peripheral retina, which might translate into better peripheral visual fields later," Dr. Wallace said. He added, "There's

1 Fleck BW et al., for the RAINBOW Investigator Group. *Ophthalmol Retina.* 2022;6(7):628-637.

(Note: for results from another study on low-dose bevacizumab, see page 19 in this issue.)

zone 1 to identify plus disease and includes the less severe pre-plus form.

Long-term sequelae. These are given expanded emphasis in ICROP-3 and include such sequelae as late retinal detachments; macular anomalies, including smaller foveal avascular zone; retinal vascular changes such as persistent tortuosity; and glaucoma.

Understanding VEGF in ROP

Approximately 10 years ago, 10% or fewer cases of posterior ROP were treated with anti-VEGF drugs, Dr. Binenbaum said. In contrast, "from 2015 to 2017, 75% of cases used anti-VEGF as the first-line treatment."

Normal VEGF physiology. VEGF aids the development of blood vessels in the retina, brain, kidneys, and other organs. "VEGF orders the division of endothelial cells [of the retina] so that daughter cells can migrate linearly toward the ora serrata," said Dr. Hartnett. In researching VEGF, her lab at the University of Utah found that "overactive VEGF signaling causes endothelial cells to have disordered growth [which manifests] as pathologic extraretinal neovascularization."

While normal levels of systemic VEGF aren't yet established, Dr. Hartnett added, "VEGF is a survival factor for both endothelial cells and neurons." And, as Dr. Binenbaum pointed out, "ROP is a disease of the developing retinal vasculature, and normal development of the vasculature involves the same factors as in ROP."

VEGF pathophysiology in ROP. "The severe neovascularization in ROP is driven by a VEGF storm in the eye," said Dr. Wallace, "and hypoxic avascular retina is a major driver for that."

Low oxygen levels can increase VEGF, said Dr. Hartnett. "A preemie might need high oxygen initially, which can slow normal retinal vascularization, but when weaned to ambient air, the retina can stimulate the production of VEGF, and too much VEGF activation leads to disordered vascularization."

While it may seem counterintuitive, inhibiting an angiogenic factor can both reduce pathologic angiogenesis and facilitate normal angiogenesis.[2]

The impact of IFG-1. Insulin-like growth factor 1 (IGF-1), which usually comes from the mother until well into the third trimester, also affects VEGF and blood vessel development, said Dr. Binenbaum. "When preemies lose that source, VEGF activity is poor, and by the time the baby starts to make IGF-1, there's too much VEGF from the retina, and the vessels grow out of control," he said.

Anti-VEGF injections. Bevacizumab works by directly binding to VEGF, thus inactivating it, said Dr. Wallace. The goal of anti-VEGF injections is to find the Goldilocks mean—that is, enough drug to inhibit ROP but not too much to disrupt subsequent normal vessel development.

"Bevacizumab wears off by about six weeks, so reactivation might occur weeks, months, or reportedly years later," said Dr. Binenbaum. Conversely, he said, "lasering the retina destroys the source of the VEGF, generally [preventing] recurrence of ROP."

How bevacizumab works, and why reactivation occurs, isn't fully understood, said Dr. Yoon. "After anti-VEGF injections, we wonder if the rapid removal of VEGF—or the antibody itself—changes the physiology of the peripheral retina so that it's more prone to early or late complications." Dr. Yoon added that many clinicians do "insurance" laser after bevacizumab for PAR at around 60 weeks' postconceptual age.

Systemic concerns. Does bevacizumab have a negative effect on neurodevelopment? "We don't think so, or we wouldn't be using it," said Dr. Wallace. "There is an association between intravitreal injections of bevacizumab and a reduction in circulating VEGF levels, but we don't know if that's cause and effect."

Although some studies have found an association between bevacizumab and measures of development, Dr. Wallace noted that "smaller, sicker infants tend to get bevacizumab while bigger, healthier infants tend to get laser—and the latter tend to do better, with regard to many outcomes, regardless of how [their] ROP was treated." The studies ROP-3 and ROP-4, by equally distributing factors associated with neurodevelopmental outcomes, may shed light on this (see "A Look at Two Pivotal Studies").

Of note, a previous study from the Pediatric Eye Disease Investigator Group (PEDIG) found a disconnect between anti-VEGF dose and levels of systemic VEGF, said Dr. Hartnett. "You would expect a lower dose of anti-VEGF to have a lesser effect on reducing systemic VEGF, but we didn't find that association, which raises the question of [how much] of the circulating VEGF is from the eye." Previous studies also have found conflicting results on whether anti-VEGF agents increase neurodevelopmental delays.[2]

Overall, said Dr. Yoon, "We started using bevacizumab about 10 years ago and still don't know the long-term side effects—but most of us are comfortable taking those unknown risks over the risk of blindness."

1 Chiang MF et al. *Ophthalmology*. 2021;128(10):e51-e68.
2 Hartnett ME. *Am J Ophthalmol*. 2020;218:208-213.

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Dr. Hartnett holds an endowed chair in ophthalmology and visual sciences, is a distinguished professor, and is founder and director of pediatric retina at the University of Utah in Salt Lake City. She also is principal investigator of the university's Retinal Angiogenesis Laboratory. *Relevant financial disclosures: NEI: S; Regeneron: C,P; Wolters-Kluwer Lippincott: P.*
Dr. Wallace serves as protocol chair for the ROP-3 and ROP-4 clinical trials and was chair of PEDIG for five years. He is chair of ophthalmology at the Indiana University School of Medicine and director of the Eugene and Marilyn Glick Eye Institute in Indianapolis. *Relevant financial disclosures: NEI: S.*
Dr. Yoon is a pediatric ophthalmologist at the Ann & Robert H. Lurie Children's Hospital of Chicago, principal investigator for that site's ROP-3 and ROP-4 studies, and associate professor of ophthalmology at Northwestern University Feinberg School of Medicine in Chicago. *Relevant financial disclosures: None.*
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