

PEDIATRICS

Research Brings New Hope for Babies With Retinopathy of Prematurity

BY MIRIAM KARMEL, CONTRIBUTING WRITER

Burn or freeze? Laser or cryotherapy? The standard treatments for retinopathy of prematurity are so harsh that they're typically reserved for babies with a high risk of going blind.

ROP is a nemesis of infants who are delivered very prematurely (typically before 31 weeks of gestation) and who consequently have a very low birth weight (1,250 g or less). Some 14,000 to 16,000 premature infants born in the United States each year suffer with some degree of ROP. The incidence may be on the rise as more and more small, prematurely born infants continue to survive, said Franco M. Recchia, MD, associate professor of ophthalmology and chief of the retina division at Vanderbilt University in Nashville. Of special concern, he said, is an increase in the incidence of a subset of the disease—aggressive posterior ROP (AP-ROP).

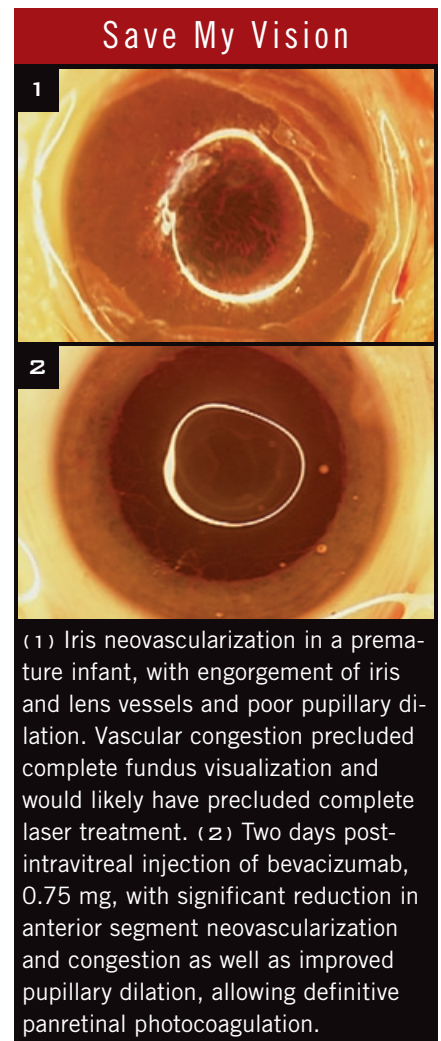
Desperately seeking better Tx.

Is there a better way to treat ROP? Researchers believe there is, as they follow a number of paths involving vascular endothelial growth factor (VEGF), either directly or upstream from the VEGF molecule. Their hope is to discover a pharmacological approach to ROP. The search for a medical therapy has been inspired by the idea of inhibiting VEGF and VEGF-like proteins that are linked to the growth of abnormal blood vessels, said Paul J. Rychwalski, MD, an associate

professor of ophthalmology at Cleveland Clinic. The oncology literature had earlier sparked interest in using the anti-VEGF drug bevacizumab (Avastin) to treat neovascular macular degeneration.

Homing in on VEGF makes sense, in terms of the current understanding of the etiology of ROP, said Michael Karin, PhD, professor of pharmacology and pathology at the University of California, San Diego. Dr. Karin's ROP work is also taking him upstream from VEGF, and he said that while VEGF performs essential functions, too much of it can lead to the growth of abnormal vessels. He explained that preterm infants receive supplemental oxygen as an essential treatment to ensure their lungs and other organs continue to develop ex utero. The trouble begins when the infants are returned to a more normal oxygen environment. "In response to stress, in this case, hypoxia, the body makes more VEGF because it thinks it isn't getting enough oxygen. So it wants to increase production of blood vessels," Dr. Karin said (See "Nurturing the Unfinished Retina.")

The patients may be tiny, but the stakes are not. "There is an explosion of ROP worldwide in countries where they're just starting to save their lightest babies. If we could arm ourselves with a medical way to reduce the severity of ROP before it happens, that would be tremendous," said Dr. Rychwalski. Following are three areas of ROP research, and the first two of



Save My Vision

(1) Iris neovascularization in a premature infant, with engorgement of iris and lens vessels and poor pupillary dilation. Vascular congestion precluded complete fundus visualization and would likely have precluded complete laser treatment. (2) Two days post-intravitreal injection of bevacizumab, 0.75 mg, with significant reduction in anterior segment neovascularization and congestion as well as improved pupillary dilation, allowing definitive panretinal photocoagulation.

these involve agents already in wide clinical use for various purposes.

Reversing Angiogenesis

Building on the success of retina specialists who used bevacizumab to treat AMD, pediatric ophthalmologists are

trying the anti-VEGF drug to treat ROP, as well as studying it in two ROP trials—BLOCK-ROP and BEAT-ROP.

Dr. Recchia and colleagues recently reported on nine eyes of five infants with AP-ROP treated with bevacizumab as adjunctive therapy to laser.¹ The drug was used prior to laser in five previously untreated eyes that had severe engorgement of iris vessels and lens vessels. In an additional four eyes that already had received laser treatment, but where the disease was still progressing, bevacizumab was used to shrink the abnormal blood vessels. Complete regression was seen in all five treatment-naïve eyes, with laser or vitrectomy completed within 72 hours of injection. In the four previously treated eyes, regression was seen in two eyes; progression to retinal detachment occurred in two infants.

While no systemic complications were reported in two to 11 months of follow-up, one concern, said Dr. Recchia, is that drying up new vessels could lead to vitreoretinal traction, contraction and then tears in the retina. “We saw that in one case, and it has been reported,” he said.

Treat, and tread, carefully. The adverse event was not a small concern in an arena that has seen a number of high-profile lawsuits. Anne M. Menke, RN, PhD, risk manager for the Ophthalmic Mutual Insurance Company in San Francisco, said, “The main concerns derive from the malpractice risk of treating newborns and center on any systemic effect of Avastin on the developing neonatal brain.” Still, given bevacizumab’s safe and effective profile for various conditions in adults, its use for ROP is not surprising, she said. “Indeed, it is quite exciting.”

Bevacizumab works, said Dr. Rychwalski, who investigated its use with Carlos Alberto Abdala Caballero, MD, a vitreoretinal surgeon in Colombia, where there is a dearth of technology and physicians willing to treat ROP. “It works, but that is not sufficient,” he said. “The biggest danger is we don’t know the systemic effects.” He added that it has been used only in advanced cases. “It’s almost a rescue therapy.”

Nurturing the Unfinished Retina

The effects of VEGF and IGF-1 on ROP have been illuminated by much work in recent years, including that of Lois E. H. Smith, MD, PhD, an associate professor of ophthalmology at Harvard University. Dr. Smith and colleagues have proposed two distinct phases of ROP—vaso-obliteration followed by vaso-proliferation. Both phases are mediated by IGF-1 and VEGF, whose normal in-utero management of vascularization is derailed by premature delivery.

After premature birth, retinal vascularization is inhibited and some formed vessels disappear due to changes between the in-utero and the ex-utero environment, including hyperoxia and loss of factors from the mother such as IGF-1. As the retina matures, increasing metabolic demand and incomplete vascularization make it hypoxic, releasing vaso-formative factors, ushering in the second, vaso-proliferative phase of ROP. Just as pediatricians strive to perfect the balance of supplemental O₂ for preemies, one goal of ROP therapy may be to manage VEGF and IGF-1, essentially mimicking their in-utero behavior in each phase of ROP.

Dr. Recchia agrees. “We reserved it for the cases with a poor natural history or where the outlook with incomplete laser alone was very guarded,” he said. “We still have to be very cautious about using it because there are so many unknowns. I would reserve it only for extreme cases. Also, it’s crucial that all these decisions are made after full and detailed discussion with neonatology staff and the family.”

GCSF: Regulating Angiogenesis

Dr. Rychwalski and colleagues have also been exploring a hunch that granulocyte colony-stimulating factor (GCSF), a biologic commonly used to increase leukocyte counts in neutropenic adults and children, might also have a regulatory effect on vasculogenesis and thus prevent ROP. This hunch led to a retrospective chart review of 213 infants who, for nonophthalmic reasons, received GCSF in the neonatal intensive care unit at the University of Louisville.

Fifty infants with low birth weight and a gestation of 32 weeks and under were matched to a control group that did not receive GCSF. Only 10 percent of the infants who received GCSF required laser treatment, compared with 18.6 percent of the controls.² Further, those babies in the GCSF group who required laser had an exceptionally low average birth weight and had received relatively low doses of GCSF.

Why GCSF? GCSF has been shown

to increase levels of insulin-like growth factor-1 (IGF-1), which “supports the normal, measured, calm vascularization of the retina,” Dr. Rychwalski explained. Conversely, falling levels of IGF-1 appear to set off a disorderly, aggressive vascularization of the retina. So GCSF, which is given to many premature infants, might be used to prevent ROP, particularly in infants with falling IGF-1 levels.

“We don’t know exactly the mechanism,” Dr. Rychwalski said. “It could have a direct effect on VEGF, or, more likely, upstream from VEGF to IGF-1.”

The beauty of this approach, as opposed to, say, using Avastin, is that it doesn’t destroy VEGF. “We don’t want to inhibit vascularization,” said Dr. Rychwalski. “What we’re trying to see is if there are ways to avoid the neovascularization and its complications. Are there ways to take babies who are at risk and, with pharmacotherapy, support normal vascularization of the retina?”

JNK1: Reducing Angiogenesis

Researchers at the University of California, San Diego, are looking upstream from VEGF to the protein kinase JNK1. The JNK group of protein kinases—discovered in 1993—responds to the stress of hypoxia by inducing the overproduction of VEGF. Inhibiting JNK1 could nip that overproduction in the bud.

Using a mouse model of ROP, the

UCSD team showed that mice lacking JNK1 exhibited lower levels of VEGF in the retina.³ And by injecting a JNK peptide inhibitor in the mouse retina, the researchers were able to decrease VEGF expression. But angiogenesis and normal retinal function were barely disrupted.

Novel (and safer?) mechanism. The mechanism of action is different from Avastin, said Dr. Karin. Avastin, he explained, is an antibody that recognizes the VEGF molecule, binds to it and makes it unavailable for the receptors. Essentially, it blocks the VEGF's action. JNK1 inhibitor, on the other hand, blocks the transcription of the upregulation of the VEGF gene. "So we are inhibiting the synthesis of VEGF, rather than the biological activity of VEGF," he said. "We are just reducing the excessive production of VEGF."

He called Avastin "a very good drug for blocking VEGF completely." But the effect of that total blockage is unknown. "We think it's probably going to be safer to reduce this abnormal production of VEGF—the increase associated with the hypoxic response—rather than taking VEGF completely away," Dr. Karin said. Next, he hopes to test JNK1 in monkey models. And it may allow pediatric research to return a favor to retinal medicine. "We think this type of approach would be relevant not only for ROP but also for wet AMD," he said. "Our preliminary results support this."

1 Law, J. et al. Intravitreal bevacizumab (Avastin) as adjunctive treatment for severe retinopathy of prematurity (ROP). Presented at the 2009 meeting of AAPOS, April 21, San Francisco.

2 Bhola, R. et al. Effect of granulocyte colony stimulating factor (G-CSF) on the incidence and progression of retinopathy of prematurity (ROP). Presented at the 2009 meeting of AAPOS, April 21, San Francisco.

3 Guma, M. et al. Published online, May 11, 2009, in advance of print in the *Proceedings of the National Academy of Sciences*.

Drs. Recchia and Rychwalski report no related financial interests. Dr. Karin has applied for a patent on the use of JNK1 inhibitors.

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