Intravitreal Bevacizumab Therapy for the Treatment of ROP

Although intravitreal bevacizumab has become an increasingly popular therapy for ROP over the past 5 years, more must be learned about its long-term safety and effectiveness.

BY R.V. PAUL CHAN, MD, MSc, FACS

Retinopathy of prematurity (ROP) is a vasoproliferative disease of the developing retina that is a significant cause of pediatric morbidity and blindness throughout the world.[1] The CRYO-ROP (Cryotherapy for Retinopathy of Prematurity) and ETROP (Early Treatment for Retinopathy of Prematurity) studies provided information regarding the natural history of ROP and validated treatment criteria for the disease.[2-3] With advances in neonatal care, however, increasingly younger and lower birth-weight infants are able to survive. This presents a major challenge to all physicians treating premature infants. For the ophthalmologist, caring for micropremature babies may mean having to manage more aggressive forms of ROP, such as aggressive posterior ROP (AP-ROP), which historically have worse functional and anatomic outcomes.[4,5]

Although management by ETROP criteria has led to improved outcomes for treatment-requiring posterior (zone I) ROP, the failure rate continues to be significant for aggressive disease. There are still children whose disease progresses despite treatment, and application of conventional laser for treatment-requiring ROP in zone I or posterior zone II involves destruction of a large area of avascular retina with a potentially higher risk of complications and morbidity for the child.

AP-ROP, specifically, is extremely difficult to manage. AP-ROP may progress rapidly to retinal detachment if not recognized and treated early. In 1 series reporting outcomes of patients with zone I ROP, 17 of 48 eyes with anterior zone I ROP and 9 of 9 eyes with posterior zone 1 ROP had unfavorable outcomes after laser photocoagulation. This demonstrates that it is still not uncommon for AP-ROP to progress despite timely and appropriate treatment with laser.[6,7]

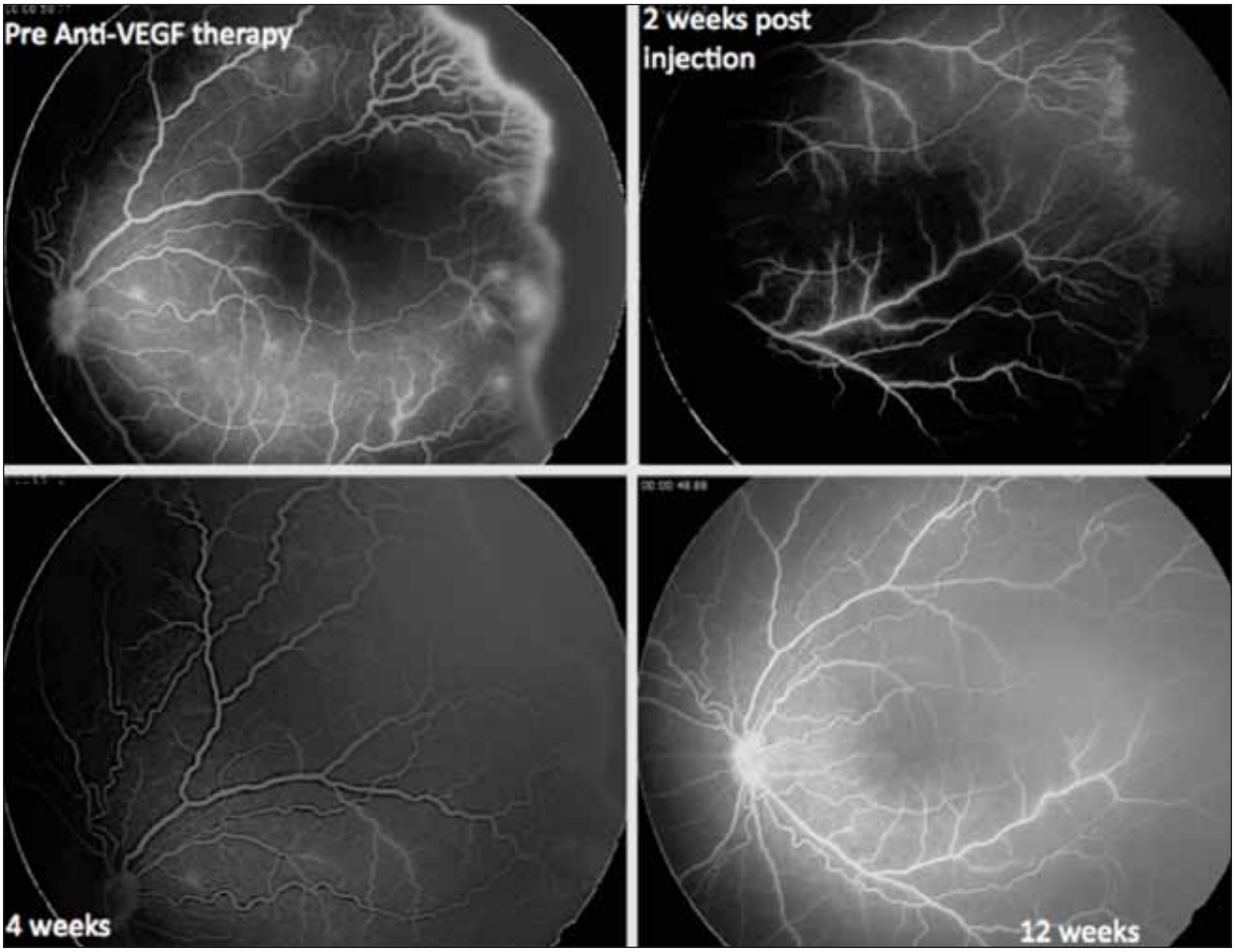
Pharmacotherapy for ROP may help to improve outcomes in some of these difficult cases. Over the past 5 years, the use of intravitreal bevacizumab (Avastin, Genentech) has become more popular for the management of ROP.

THE ROLE OF VEGF IN ROP

It is known that vascular endothelial growth factor (VEGF) is a key player in both normal vascular development and in the pathogenesis of ROP. Studies have shown that physiologic levels of VEGF are necessary to maintain and help stimulate normal vascular growth.[8]

When a baby is born very premature and is placed in a hyperoxic environment, VEGF production is downregulated, causing immature vessels to stop growing. This produces peripheral avascular retina, and the more immature the infant, the larger this avascular area is likely to be. Eventually, the avascular retina becomes ischemic and stimulates VEGF production. Sustained high levels of VEGF can promote the progression of ROP and neovascularization and can even cause vasodilatation and tortuosity of vessels, ultimately leading to plus disease. Iris vessel dilatation and rubeosis iridis may also ensue.[8]

Treatment of the peripheral avascular retina with



(Courtesy of Dr. Hugo Quiroz-Mercado and Dr. Maria Ana Martinez-Castellanos)

Figure 1. Fluorescein angiogram (FA) pre- and post-intravitreal injection of anti-VEGF therapy. FA reveals regression of neovascularization.

cryotherapy or laser therapy promotes a reduction of VEGF levels, which then induces regression of neovascularization.[9]

ANTI-VEGF THERAPY AND ROP: WHAT WE KNOW

Because we know that ROP is a VEGF-driven disease and that decreasing VEGF levels promote regression of neovascularization, intravitreal anti-VEGF agents have been utilized for treatment of this condition. The use of pegaptanib (Macugen, Eyetech) for ROP demonstrated decreased vascular activity after injection but did not prevent progression to retinal detachment.[10] When intravitreal bevacizumab became commonly used for the treatment of neovascular age-related macular degeneration (AMD) and diabetic retinopathy, some investigators felt that bevacizumab might also benefit ROP patients. Several case series have reported regression of ROP in patients treated with bevacizumab alone or in combination with conventional laser.[8-18]

Quiroz-Mercado et al[12] reported results in 18 eyes with ROP that were treated with bevacizumab for both primary and salvage therapy. Neovascularization regressed in all cases and, to date, no serious adverse events have been seen in this series with 5 years of follow-up. Of the patients included in this series, all required only one injection of bevacizumab to promote regression of disease.[12] At 5 years after injection, most patients in this cohort had some degree of myopia and all but one patient was reported to have appropriate development per the Denver Developmental Screening Test.[19]

To prospectively investigate the safety and efficacy of intravitreal bevacizumab for treatment-requiring ROP, the BEAT-ROP (Bevacizumab Eliminates the Angiogenic Threat of Retinopathy of Prematurity)[20] and BLOCK-ROP (Pan-VEGF Blockade for the Treatment of Retinopathy of Prematurity)[21] studies were initiated. In

(Courtesy of Dr. Hugo Quiroz-Mercado and Dr. Maria Ana Martinez-Castellanos)

Figure 2. Eleven months post-intravitreal injection of anti-VEGF therapy. FA reveals persistent avascular peripheral retina.

February 2011, Mintz-Hittner et al[22] presented the BEAT-ROP results, which demonstrated superiority of intravitreal bevacizumab over conventional laser for treatment-requiring ROP in zone I (zone I, stage 3 with plus disease).

Although the results of the BEAT-ROP study are encouraging, the long-term complications of intravitreal bevacizumab therapy for ROP have not been fully elucidated. There have been reports of local adverse events such as vitreous hemorrhage and progression to retinal detachment after anti-VEGF therapy.[23,24] Infection, rhegmatogenous retinal detachment, and cataract are also potential complications after the injection itself. However, the major concern with anti-VEGF therapy for ROP is the

TABLE 1. DOSAGES OF BEVACIZUMAB USED IN PUBLISHED CASE SERIES

	# Eyes	Dosage	Primary Rx	Salvage Rx	Injection Location (Posterior to the Limbus)
Quiroz-Mercado et al11	18	1.25 mg	Yes	Yes	1 mm
Mintz-Hittner et al10	22	0.625 mg	Yes	--------	2.5 mm
Law et al26	13	0.75 mg	Yes* Combination	--------	1 mm
Wu et al16	49	0.625 mg	Yes	Yes	Pars plicata
Lalwani et al12	5	0.63 mg to 1.25 mg	--------	Yes	Pars plicata
Kusaka et al17	23	0.5 mg	Yes	Yes	0.5 mm

potential for disruption of normal vascular development locally and systemically. Delay in normal vascularization is a concern, as areas of peripheral retinal nonperfusion may develop after intravitreal bevacizumab.[25]

NEW GOLD STANDARD?

An editorial on the results of BEAT-ROP suggested that, "intravitreal bevacizumab should become the treatment of choice for zone I retinopathy of prematurity."[26]

It is clear that intravitreal bevacizumab is effective in promoting regression of treatment-requiring ROP, and this regression is often quite dramatic, occurring within the first 24 to 48 hours after injection. Despite its effectiveness, there are still a number of questions and concerns with regard to the use of anti-VEGF therapy for ROP.

Pegaptanib, bevacizumab, and ranibizumab have all been utilized for the treatment of ROP, but which drug is best for managing this disease? All of these agents have been effective in decreasing vascular activity, and, unlike treatment for AMD, which generally requires multiple injections over an extended period of time, treatment of ROP has typically been shown to require a single injection.

Various dosages of bevacizumab have been used (Table 1), but the ideal dosage for the drug remains unclear. In early reports, investigators used 1.25 mg (0.05cc) bevacizumab, which would often increase the intraocular pressure (IOP) in neonatal eyes, requiring an anterior chamber paracentesis. Subsequently, 0.625 mg bevacizumab has been shown to be effective in controlling disease, and this now appears to be the preferred dose. However, a lower dose may yet prove equally effective and even preferred in the developing eye.

Exactly when and how often we may need to inject has been a topic of much discussion. Intravitreal bevacizumab has been used for both primary and salvage therapy and for different degrees of disease (eg, threshold disease, type 1 prethreshold disease, stage 3 alone, and stage 4a). It appears that timing is crucial for success. If used too early, intravitreal bevacizumab may promote significant delay of normal vascularization. Conversely, if used too late, when there is already significant traction on the retina, intravitreal bevacizumab may decrease neovascularization but promote progression to retinal detachment. This progression to retinal detachment, often termed "ROP crunch" can occur rather quickly, and there is evidence that, in cases in which conventional treatment failed, intravitreal bevacizumab is effective as an adjunct to laser or surgery.[27]

What if disease progresses after initial injection? Is additional anti-VEGF treatment indicated, or is conventional

laser a better choice in case of recurrence? In zone I or posterior zone II ROP requiring treatment, injecting an anti-VEGF agent can stop the disease and allow the normal vasculature to extend more anteriorly. If disease subsequently progresses and treatment is required, conventional laser could be a viable option, as there may be less avascular retina that requires ablation. Or does anti-VEGF therapy obviate the need for conventional laser for ROP? Anti-VEGF monotherapy works, but whether or not monotherapy or combination therapy with laser has better outcomes is yet to be determined.

GLOBAL CONSIDERATIONS

The use of intravitreal anti-VEGF therapy for ROP may have a significant global impact. As health care delivery improves in developing countries, the neonatal and premature population will continue to increase, resulting in the need for ophthalmologists who may not have experience with ROP to manage and treat this condition. In many developing countries, clinicians' ability to perform indirect laser photocoagulation may be inadequate, and a neonatal anesthesia service may also be lacking. In most cases, intravitreal bevacizumab can be performed without sedation or anesthesia, and the injection is easy to do at the bedside.

CONCLUSION

Over the past 5 years, we have learned a significant amount regarding the effectiveness and short-term outcomes of intravitreal anti-VEGF agents for treatment-requiring ROP. We have learned that intravitreal bevacizumab works well for zone 1 disease requiring treatment, and, although it is easy for some to loosely claim the off-label use of intravitreal bevacizumab for ROP as the new gold standard of care, we must keep in mind that there is still much to learn about this treatment modality. Its long-term safety has not been determined in a prospective trial and, given the fact that conventional laser for type 1 prethreshold ROP is a proven method of treatment, we cannot exclude laser from our treatment paradigm. ■

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