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
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 al12 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
February 2011, Mintz-Hittner et al\textsuperscript{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\textsuperscript{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

<table>
<thead>
<tr>
<th># Eyes</th>
<th>Dosage</th>
<th>Primary Rx</th>
<th>Salvage Rx</th>
<th>Injection Location (Posterior to the Limbus)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quiroz-Mercado et al\textsuperscript{11}</td>
<td>18</td>
<td>1.25 mg</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Mintz-Hittner et al\textsuperscript{10}</td>
<td>22</td>
<td>0.625 mg</td>
<td>Yes</td>
<td>--------</td>
</tr>
<tr>
<td>Law et al\textsuperscript{26}</td>
<td>13</td>
<td>0.75 mg</td>
<td>Yes* Combination</td>
<td>--------</td>
</tr>
<tr>
<td>Wu et al\textsuperscript{16}</td>
<td>49</td>
<td>0.625 mg</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Lalwani et al\textsuperscript{12}</td>
<td>5</td>
<td>0.63 mg to 1.25 mg</td>
<td>--------</td>
<td>Yes</td>
</tr>
<tr>
<td>Kusaka et al\textsuperscript{17}</td>
<td>23</td>
<td>0.5 mg</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

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