Retinopathy of prematurity (ROP) is a leading cause of blindness in children, despite advances in understanding and management of the disease. The use of peripheral laser photoablation and early lens-sparing vitrectomy as standard therapy for ROP has led to a high rate of anatomic success and preserved visual function. In areas of the world where access to laser technology and appropriate expertise is not available, however, a safe and efficacious pharmacologic approach to the treatment of ROP might be a welcome option.

The recent publication of results of the BEAT-ROP study has focused attention on the use anti-VEGF therapy for ROP. Comparing intravitreal monotherapy of bevacizumab (Avastin, Genentech) with conventional laser therapy in infants with stage 3+ ROP, the BEAT-ROP investigators found no difference between laser and anti-VEGF treatment for zone 2 disease, but a statistically significant benefit of anti-VEGF therapy for zone 1 disease.

The study results, while encouraging, raise a number of concerns. First, the population of the study was 67% Hispanic. The study population may not be a good representation of the ethnic makeup of the United States or much of the world. Also, it is common knowledge that ROP in Hispanic infants is more difficult to treat, although it is manageable by standard techniques. Second, failure rate for laser treatment of zone 1 disease in the study was 42%, vs 6% for bevacizumab. This is higher than the laser failure rates reported in some other ROP studies. Drenser at al., for example, reported a series in which 31% of eyes received a second laser treatment, and the final failure rate was 18%. If the failure rate in BEAT-ROP was lower, approaching 30%, the difference between laser and drug would not have been statistically significant (Figure 1). This may not be a fair criticism, as the population in the Drenser et al study was not pre-
dominantly Hispanic, and it did not have a finite cutoff time for when second laser treatment could be done.

SAFETY OF ANTI-VEGF IN ROP

The BEAT-ROP study was not powered to assess safety. However, among the 150 infants randomized there were 7 deaths: 5 in the bevacizumab group and 2 in the laser group. The difference was not statistically significant, but this finding certainly merits some concern. In an editorial accompanying the study, Reynolds stated that, despite the lack of evidence, it seems reasonable to assume that intravitreal bevacizumab is safe. But neonatology has seen other examples in which therapies have been adopted because of short-term benefits before

Insurer Perspective on Bevacizumab for ROP

BY ARTHUR W. ALLEN JR, MD

Bevacizumab (Avastin, Genentech) is a VEGF inhibitor with U.S. regulatory approval for use in certain types of cancers. It is widely used off-label by ophthalmologists for treatment of a number of retinal vascular diseases. VEGF levels have been shown to be elevated in retinopathy of prematurity (ROP), and there are reports of successful use of bevacizumab in treatment of ROP.

It is hoped that this pharmacologic agent will provide a therapeutic alternative for ROP and possibly improve outcomes over the gold standard treatment, laser photocoagulation. However, the unknown risks and possible complications of this invasive treatment are of concern to insurers.

Risk is introduced when a new treatment is used in lieu of a treatment considered to be the standard of care. This is especially so when the risk-benefit ratio of a new therapy will not be known for many years, as in the treatment of premature infants. Proper informed consent, outlining the known risks of intravitreal injection and the off-label nature of the treatment, is therefore important.

Injections into the small eyes of premature infants raise a number of concerns, including the risks of lens damage, retinal perforation, and hemorrhage, as well as the need to prep the eye against infection. None of these risks, except the possibility of lens damage, are present with laser treatment. In the event of a claim, plaintiffs can point out that such a complication would not have occurred if the standard of care had been followed. In addition, proper dosage and timing for ROP treatment are not established, and the long-term consequences of systemic absorption of bevacizumab are not yet known.

Standard follow-up protocols for laser may not be appropriate for intravitreal injection. For example, retinal detachments may be seen later in bevacizumab-treated eyes than in laser-treated eyes. Therefore, the follow-up period may need to be extended, which may be a risk if the parents are not compliant with the follow-up schedule. An undiagnosed retinal detachment poses a risk for litigation.

VEGF is crucial for fetal growth and development in the third trimester, and the systemic effects of anti-VEGF injection in premature infants are not well understood. If the use of bevacizumab results in long-term systemic problems, this could result in significant liability in future years. The statute of limitations for premature infants extends a few years beyond their majority.

For high-risk eyes in which laser would cause severe field loss or result in a poor prognosis, detailed informed consent is crucial if bevacizumab therapy for ROP is elected. In general, caution is recommended if intravitreal bevacizumab is used instead of the established standard of laser photocoagulation, until the indications, dosage, timing, and complications of this new treatment modality are established.

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longer-term studies showed negative results.

Does bevacizumab enter the systemic circulation? The BEAT-ROP investigators said the bevacizumab molecule, a full antibody, is too large to “penetrate the intact retina or escape the eye except in very small amounts.” Although experimental pharmacokinetic results vary, at least 1 group has reported that intravitreal bevacizumab injection resulted in high plasma concentration in rabbits, and that the drug reached the fellow eye through the systemic circulation. A review of the safety, pharmacokinetics, and dosage of bevacizumab in ROP treatment concluded that intravitreal bevacizumab enters the general circulation, suppresses plasma VEGF levels, and remains in the blood for more than 8 weeks in primates. These authors cautioned that possible adverse effects on VEGF-dependent development must be considered.

The half-life of bevacizumab is similar to that of its smaller anti-VEGF relative, ranibizumab (Lucentis, Genetech), but the peak plasma concentrations of the 2 drugs are different. The level is higher with bevacizumab, and the drug stays in the systemic circulation longer than ranibizumab. In another clinical study, with administration of half the adult dose (ie, 0.625 mg: the dose used in the BEAT-ROP study), dramatic reduction was seen in the concentration of VEGF in plasma over 8 weeks. Dosing of bevacizumab for this indication has been empirical, and no studies have explored the lowest effective dose of anti-VEGF agents for ROP. It should be noted that, in BEAT-ROP, half the adult dose was administered in bodies that were 1/50 the size of an adult, with a volume of vitreous that is far smaller than that of an adult. A much lower dose of bevacizumab would be capable of equalizing the VEGF in the vitreous of these small infants (personal communication, John Sears).

VEGF plays important roles in development during the third trimester, when the fetus is experiencing an intense period of growth and maturation. VEGF is essential for normal angiogenesis in the growing infant, and it plays a role in many organ systems, including the central nervous system, lungs, bones, and cardiac and kidney development. All of these could potentially be affected by VEGF suppression.

FUTURE STUDIES

With so many comorbidities in preterm infants, it may not be possible to assess the real risks and benefits of anti-VEGF therapy for ROP. It seems, however, that a trial to define the lowest dose and safest anti-VEGF drug is called for.

A multicenter cooperative study to assess 2 doses of bevacizumab anti-VEGF treatment for ROP (BLOCK-ROP; http://clinicaltrials.gov/ct2/show/NCT01232777) has been called off before it was opened for participant recruitment. We believe that the safety questions that were to be addressed by BLOCK-ROP should be answered by a planned European labeling study.

CONCLUSIONS

Does anti-VEGF therapy have value for ROP? Certainly when there is no laser available, or when no doctor is available who knows how to administer appropriate laser treatment, a pharmacologic therapy could be of value. If laser and a doctor to administer it are available (and the population is less Hispanic than the BEAT-ROP population), laser is unquestionably safer for the infant.

Laser is an established, safe, effective therapy with a predictable course and a finite follow-up period of approximately 10 weeks after the infant’s due date. Anti-VEGF treatment is initially an easy treatment, but it creates an indefinite course, in which the patient may have to be followed for 6 months or more. This puts additional burdens on the parents and raises risks regarding compliance with the follow-up schedule. (See Insurer Perspective on Bevacizumab for ROP.)

It is likely that anti-VEGF therapy will have some role in ROP management in the future, but until convincing safety data are available, the right drug and the right dose are still in question. Laser is still the gold standard primary therapy for ROP in most populations.

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