

# Avastin as monotherapy for retinopathy of prematurity

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In this issue of the *Journal of AAPOS*, Law and colleagues<sup>1</sup> reviewed the records of 7 infants treated with intravitreal bevacizumab (Avastin) together with laser photocoagulation for retinopathy of prematurity (ROP). They suggest that treatment with bevacizumab may be beneficial in these patients. Although they used a combined treatment, I believe there is a role for monotherapy with Avastin for ROP. Here, I will detail my current recommendations regarding Avastin therapy, which rest on the basis of my own clinical experience in prescribing this medication, and place the results of Law and colleagues<sup>1</sup> in the context of that experience.

The use of Avastin in the treatment of ROP is still investigational: all aspects of its risks and benefits have not been established.<sup>2</sup> However, because of the increased understanding of the 2 phases of the pathogenesis of ROP, when considering Avastin therapy, it is clear that the timing of the administration of antivascular endothelial growth factor therapy is of utmost importance. It is essential to know the postmenstrual age and thus the likely proportion of angiogenic versus fibrotic growth factors present.

The use of Avastin for ROP stage 4b or 5 must be considered rescue or desperation therapy and should always be used in combination with vitrectomy. When the membranes are significant enough to cause extensive detachment, their contraction with further worsening of the ROP should be anticipated after the administration of Avastin. The primary benefits of Avastin in this setting are to make vitrectomy easier by making iris dilation better, clearing the media, decreasing hemorrhage, and so forth.

In contrast, the use of Avastin for early ROP stage 3+, that is, for ET-ROP (no significant membrane formation), is in my experience usually successful as monotherapy. Especially for zone 1 and posterior zone 2 cases, the benefits of monotherapy are many. Compared to laser therapy, Avastin (1) is basically a less-destructive process and a more specific therapy on the basis of pathogenesis; (2) prevents the inevitable loss of visual field and reduces the occurrence of high myopia; (3) has a more immediate effect; (4) avoids anterior ischemia and iris/lens complica-

tions; (5) is valuable when retinal visualization is decreased as the result of hemorrhage and/or poor iris dilation; (6) is easily administered without requiring general anesthesia; and (7) reduces the requirements of time, technical skill, and expense for treatment. Thus, if screening allows detection at the time of ET-ROP, Avastin monotherapy may prove to be ideal for the treatment of conventional and aggressive posterior (AP) ROP.

Avastin as monotherapy for ROP stage 3+ patients with some degree of membrane formation will be adequate treatment with few exceptions: (1) Avastin administration can precipitate acute contraction with devastating results when, in AP-ROP cases, multiple clock hours of membrane formation are present, especially nasally and very close to the disk; (2) recurrences with significant tractional components (both from the ridge/extraretinal fibrovascular proliferative complex and from the advancing edge of the inner retinal vascularization) may occur with adverse outcomes when screening does not allow the administration of Avastin before the formation of confluent extraretinal fibrovascular proliferative. These recurrences, preferably identified in their early stages, require additional treatment, and Avastin monotherapy can then be used (Mintz-Hittner H. Poster #90, 2nd World ROP Congress, New Delhi, India, November 21-23, 2009).

The most difficult clinical decisions are the selection of treatment for advanced ROP stage 3+ (conventional or AP-ROP) with some degree of membrane formation and for ROP stage 4a with a greater degree of membrane formation. Postmenstrual age and degree of membrane formation are the most important factors to be considered. Often it is difficult to determine whether to combine Avastin with surgical intervention in the acute phase of ROP, and if combination therapy is indicated, the timing of the surgical intervention (acutely or later) is important and often critical. Considerable clinical judgment and close follow-up are required if Avastin monotherapy is to be used for advanced ROP stage 3+ or for ROP stage 4a. As in stage 3+ with some degree of membrane formation, early Avastin monotherapy may be successful in preventing the progression of acute ROP but may need to be followed at a later time point by laser therapy to assure the long-term stability of the retina and to ablate the remaining hypoxic avascular retina. However, a large percentage of ROP stage 4a patients treated by Avastin administration will require vitrectomy surgery or many retinal detachments will be precipitated because of membrane contraction.

In the article by Law and colleagues,<sup>1</sup> although postmenstrual age is not considered, Avastin is used only as an adjunct to laser and vitrectomy surgeries. In the cases that were stage 3+ (conventional or AP-ROP) and had been untreated previously, it is possible that Avastin monotherapy could have

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been successfully used without any laser therapy. Also, in the stage 3+ cases in which laser therapy had already been used, Avastin could have been used alone, without adding more laser therapy, with the possibility of increasing the loss of visual field or the severity of myopia. However, in the cases that were already stage 4a, the clinical judgment that vitrectomy surgery was indicated is likely correct because Avastin monotherapy is less likely to have been successful.

While still in its infancy, Avastin use has to date been unaccompanied by ocular or systemic complications. The knowledge that histopathology on an extremely immature infant demonstrated no interruption of differentiation of the retina or other evidence of ocular damage is reassuring.<sup>3</sup> However, it remains important to be vigilant in the continued search for systemic complications,<sup>2</sup> to use necessary clinical testing to identify any systemic complication in its early stages, and to establish a national

(international) registry of Avastin patients that can be followed long term so that late complications will be identified. It is essential to establish that risks of Avastin are minimal while researchers continue to gather evidence-based data on the use of Avastin in the vulnerable preterm infant.

#### References

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### An Eye on the Arts - The Arts on the Eye

#### Optical Hypertension

“Your optic nerve is small and slightly cupped,” my drawling ophthalmologist observed, having for minutes submitted that nerve, or, rather, both those nerves to baths of light—to flashing, wheeling scrutiny in which my retinas’ red veins would, mirrored, loom and fade. “And it appears, as yet, undamaged. But your pressure reads too high. Glaucoma will be the eventful result if you go untreated. What you have now we call optical hypertension.” Wow! I liked the swanky sound, the hint of jazz, the rainbow edginess: malaise of high-class orbs, screwed to taut bliss by what raw sight absorbs.

—John Updike