Intravitreal bevacizumab for retinopathy of prematurity: Considerations for informed consent

Retinopathy of prematurity (ROP), a disease of abnormal blood vessel proliferation in the retina, is estimated to account for approximately 20% of cases of pediatric blindness worldwide.[1] Guidelines set by the American Academy of Pediatrics, the American Academy of Ophthalmology, and the American Association for Pediatric Ophthalmology and Strabismus outline criteria for the screening and treatment of ROP.[2,3] Laser photocoagulation and cryotherapy have long been available as treatment options; however, laser has essentially replaced cryotherapy as the standard of care.[1] Although visual and structural outcomes are significantly better with laser treatment, a proportion of treated eyes still progress to unfavourable outcomes despite treatment. Treatment with laser results in irreversible destruction of the avascular retina, leading to permanent visual field deficits. Additionally, high incidence of strabismus and refractive errors after treatment remain an issue.[4–6]

Beginning in 2007, results of a newer treatment modality involving the use of anti-vascular endothelial growth factor (VEGF) agents have been published.[7–21] In early case reports, there was extensive variability in the stage of disease treated and the use of anti-VEGF agents as first-line or salvage treatment and their use alone or in combination with other treatment modalities. A prospective randomized multicentre trial comparing laser treatment with anti-VEGF monotherapy was published in 2011 (BEAT-ROP [Bbevacizumab Eliminates the Angiogenic Threat of Retinopathy of Prematurity]).[22] Based on results of this trial, the authors concluded that intravitreal bevacizumab (IVB) offered a significant benefit over laser for the treatment of stage 3+ ROP in zone I.

Although some practitioners have expressed great enthusiasm, including endorsements that "intravitreal bevacizumab should become the treatment of choice for zone I retinopathy of prematurity,"[23] others have expressed concern about the use of IVB in a neonatal population, the risk for systemic absorption, and the unknown long-term risks that may potentially be associated with their use.[24–32] Additionally, there is controversy as to how to implement the use of IVB in ROP safely and how to conduct an informed consent process that is reflective of these safety concerns. In this editorial, we offer a framework for the consent process that may prove useful to ophthalmologists worldwide who treat ROP.

Introducing a new treatment modality: research or innovation?

The introduction of any new treatment modality in the clinical setting can be done as part of routine clinical care, research, or innovation. This raises an important issue as to whether IVB can be considered part of routine clinical care. Clearly, a solid evidence base is a vital prerequisite to adopting IVB as part of routine clinical care. Mintz-Hitner et al. provided a much-needed randomized controlled trial in this field; however, a number of other recent publications suggest that there are significant concerns regarding reactivation and treatment failure.[33–35] Although no treatment is expected to be perfectly safe and effective before being implemented, the risks and benefits of a new treatment should be at least comparable to the current gold standard. In this regard, we argue that there is insufficient data regarding long-term safety, efficacy, and visual outcomes with IVB to compare with laser. However, the results of the BEAT-ROP study are compelling enough to state that, at least in the short term, IVB results in better outcomes compared with laser and therefore should be considered part of routine clinical care in selected patients with zone I disease. The use of IVB outside the indications used by BEAT-ROP do not have a strong evidence base.

Even if IVB forms part of the treatment option, the off-label use of bevacizumab should be identified during the consent discussion. Off-label use of medicine in pediatrics, especially neonatology, is common practice. A recent literature review found that the use of off-label medications in neonatal intensive care units ranged from 55% to 80%.[36] Off-label use should be disclosed to families but cannot be considered an exclusionary criteria for the use of IVB. Indeed, if it were, the majority of medications used in pediatrics could not be used.[37]

The treatment of ROP has made significant advances based on the results of major clinical trials, including CRYO-ROP (Cryotherapy for Retinopathy of Prematurity) and ET-ROP (Early Treatment for Retinopathy of Prematurity).[38,39] The field has been advanced by the publication of small nonrandomized retrospective case series as well as the presentation of treatment successes and failures at major medical meetings. Research involves a formal protocol, whereas innovation is a variation in practice conducted on an individual basis in response to emerging data in the field.[40] Marron argues that in research, protection of participants is formalized through insitutional oversight mechanisms, whereas in innovation, it occurs 1 patient at a time and relies on the clinician's competence and integrity.[40] It is incumbent on ROP practitioners using IVB to carefully weigh the risks and benefits before offering treatment. Additionally, a rigorous informed consent process is a fundamental component in moving forward with research or innovation in an ethically responsible manner. As ethicist Norm Fost argues: "All innovative treatment involves uncertain risks and benefits. Because of this, the standards for consent should generally be high."[41] Therefore, whether use of IVB in ROP is regarded as research or innovation by the clinician or their institution, informed consent must play utmost importance.

Consent for IVB Injections: A Framework for ROP Practitioners

After the publication of BEAT-ROP in 2011, we conducted a web-based survey (SurveyMonkey.com) of pediatric ophthalmologists and vitreoretinal specialists who treat ROP in the United States and Canada.[42] The aim of the survey was to investigate what information should be incorporated in the consent process when IVB is presented as a treatment option to parents. Based on the responses, we developed a list of 9 discussion points that provide the foundation of the consent discussion. This consent framework has been used by the authors and continues to be updated with our cumulative experiences and emerging literature. We currently include the following topics related to IVB during our detailed consenting process with parents of babies with ROP requiring treatment. This information is not exhaustive and is designed to complement the standard information normally given before obtaining consent for laser treatment.

(1) Pathophysiology of ROP is explained to parents to introduce the logic and purpose of using laser or IVB and how these modalities produce their beneficial effects.
(2) The initial effect of IVB and laser on a baby are described, including the time needed for procedure, the method of anaesthesia used, and the stress of treatment on the baby.
(3) The results of ET-ROP and BEAT-ROP and the reported success for laser and IVB reported in the literature are reviewed.
(4) Local adverse events including infection, hemorrhage, retinal detachment, cataract, high intraocular pressure, and progression of disease despite treatment for both laser and IVB are described.
(5) Data suggesting systemic absorption from IVB injection, which may result in potential unintended effects on other developing tissues/organs in the body, are shared.
(6) Because of the risk for late disease reactivation, patients receiving IVB must undergo dilated fundoscopy with scleral depression for a significantly longer period than neonates who receive conventional laser treatment. This will place extra examination stress on the baby and will burden the family with frequent hospital visits after discharge from hospital. This information is particularly important in a vast country like Canada where families may have to travel long distances for access to specialized ophthalmic services for ROP.
(7) Limited data are available on long-term visual outcomes for ROP patients treated with IVB, whereas laser has a long track record. Development of macula and peripheral retina may not be normal following IVB. There is emerging evidence that long-term complication of high myopia may be less likely with IVB, although conflicting reports are found in the literature. Similarly, a decrease in chances for development of strabismus and preservation of larger visual fields with IVB compared with laser are potential benefits that remains unproven.
(8) No data are available on long-term systemic effects in patients treated with IVB, whereas laser has a long track record. Proof of systemic safety in premature infants who already have multiple medical problems would require thousands of patients, and it is thought to be unlikely this evidence will be available in the near future.
(9) Bevacizumab is not approved for use in ROP by Health Canada or the US Food and Drug Administration and this is considered off-label use. This drug is a humanized monoclonal antibody that was originally developed for the treatment of colorectal cancer but was also found to be effective in treating eye diseases that result in abnormal blood vessel proliferation, such as age-related macular degeneration.

Additional Considerations

The ROP practitioner's relationship with a patient's family often is not established until significant disease is noted. Families are frequently not present when practitioners perform examinations and usually do not meet the ophthalmology service unless treatment is warranted. The onus is on the ophthalmologist to involve the family in the decision-making process, ensure the parents fully understand the rationale for treating ROP and the potential risks and benefits associated with any treatment option. In our experience, this is an iterative process and may require several conversations. Ideally, to facilitate this process, educational material that explains ROP and its treatment should be distributed to families at the time of the initial ROP screening. Parental comprehension of complex medical information given during the consent process can be variable and frequently their "confidence in the medical team" is the most important factor when providing consent.[43] For patients who may be candidates for treatment, it is important to involve the neonatologist and the nursing team to help better engage the family in the treatment discussion. Neonatalogists and nursing teams typically have a much closer relationship with the patient's family and can help to further educate them. This is particularly salient in the neonatal intensive care unit setting, where families often are experiencing significant stress because of their child's multiple medical problems.

Conclusions

Treatment of ROP using IVB is gaining popularity internationally, at least for selected cases. A rigorous informed consent process is the foundation on which to

proceed with any new treatment modality. To this end, we have developed the consent recommendations based on our survey results and personal experience.We also recommend that the ROP community establish a registry to collect long-term data on visual and structural outcomes and systemic comorbidities in neonates treated with bevacizumab and laser. It is important to regard IVB in ROP with caution and responsibility. It is our hope that the proposed guidelines outlined in this editorial with help facilitiate that goal.

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