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Analysis of the Recurrence of Plus Disease after Intravitreal Ranibizumab as a Primary Monotherapy for Severe Retinopathy of Prematurity

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Purpose: To assess the outcomes of severe retinopathy of prematurity (ROP) in zone I or posterior zone II, and of aggressive posterior ROP treated with a single dose of intravitreal ranibizumab (IVR) as monotherapy.

Design: Retrospective study.

Participants: The study included premature babies diagnosed with aggressive posterior ROP or ROP 3+ in zone I or posterior zone II.

Methods: Intravitreal injection of 0.25 mg (0.025 mL) ranibizumab was performed in the operating room. A disposable 1-mL syringe with a 30-gauge needle was used.

Main Outcome Measures: Favorable outcome was considered regression of ROP after treatment (meaning regression of the retinal neovascularization and plus disease). Unfavorable outcome was progression to stages 4 and 5 of ROP.

Results: The study included 43 infants (85 eyes). The mean birth weight and gestational age were 1276±302 g and 29.7±2.0 weeks, respectively. The mean postmenstrual age at ROP diagnosis was 36±2.7 weeks and at treatment was 37.2±2.2 weeks. All 85 eyes demonstrated total regression of plus disease after a single dose of IVR. Twelve infants (29.2%) developed full vascularization of the peripheral retina in both eyes. Twenty-two infants (43 eyes [53.6%]) developed ROP reactivation at a mean interval of 7.1±3 weeks (range, 3–15 weeks) after IVR and needed rescue laser treatment of the peripheral avascular retina. The mean postmenstrual age at rescue laser was 43±3.2 weeks (range, 35.5–54.5 weeks). Six patients (11.6%) had persistent peripheral avascular retina in zone II for >6 months (or 24 weeks) after IVR treatment.

Conclusions: Although there was complete regression of plus disease in all treated eyes, only 29.2% of the patients reached complete peripheral retinal vascularization. There was a disease reactivation in 53.6% of the patients and they needed additional laser therapy. The results of IVR treatment in severe ROP, even when initial control of the disease was achieved, did not eliminate the risk of late reactivation of the disease by retinal neovascularization. Some of the treated patients may achieve a permanent interruption in the development of the peripheral retinal vascularization. *Ophthalmology Retina 2017;■:1–6 © 2017 by the American Academy of Ophthalmology*

Retinopathy of prematurity (ROP) is an avoidable cause of childhood blindness in many middle- and low-income countries in Latin America and Eastern Europe that have introduced neonatal intensive care services, thus improving survival of high-risk neonates.[1–5]

Laser photocoagulation remains the gold standard for the treatment of severe ROP in threshold or in type 1 pre-threshold ROP with good anatomical and functional results, as established after the Cryo-ROP[6] and ETROP[7] randomized trials. Unfortunately, when the disease is located in zone I or posterior zone II, or in patients affected by aggressive posterior (AP)-ROP, visual results with conventional laser treatment are usually unfavorable.[8–12]

Anti–vascular endothelial growth factor (VEGF) therapy with intravitreal bevacizumab (IVB) or with intravitreal ranibizumab (IVR) are new options in the search for a treatment with better structural and functional outcomes for ROP located in zone I or posterior zone II, or for patients affected by AP-ROP. The BEAT-ROP study, the first prospective, randomized, multicenter trial, assessed the efficacy of IVB monotherapy in the treatment of severe ROP in zone I or posterior zone II compared with conventional laser therapy and concluded that IVB showed significant benefit for zone I but not for zone II disease, as compared with laser photocoagulation.[13] One of the potential benefits of anti-VEGF therapy is that it allows for the development of peripheral vessels of the retina and is associated with less

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myopia and greater preservation of the peripheral visual field than laser therapy.[14–16] Previous studies have shown that anti-VEGF therapy promotes regression of the disease with some minor potential adverse effects, but this treatment remains off-label for ROP and, until now, the exact dose and long-term ocular and systemic side effects have been unknown.[13–16]

Most studies of anti-VEGF therapy in ROP report the use of bevacizumab (Avastin, Genentech, South San Francisco, CA). Initially, it was thought that the entire monoclonal antibody bevacizumab 149 kDa had lower penetration in the retina and, therefore, less systemic absorption than the 40 kDa antibody ranibizumab (Lucentis Genentech).[17] However, recent reports showed that serum levels of VEGF are suppressed for 2 months after the use of IVB in patients with type 1 ROP, showing leakage of the bevacizumab to the systemic circulation.[18] Both molecules reach the systemic circulation. The longer half-life of bevacizumab has a clearance from the systemic circulation of $\geq$2 months,[17–19] whereas ranibizumab reduces plasma VEGF levels up to 1 week after treatment.[20]

This study aims to assess the outcomes of patients treated with a single dose of IVR as monotherapy in cases of severe ROP in zone I, posterior zone II, and AP-ROP.

Methods

Study Design

This institutional-based retrospective study was conducted from July 2009 to December 2014 at the University Hospital of Maracaibo, Venezuela.

Patients

The study included all preterm infants diagnosed with AP-ROP or ROP 3+ in zone I or posterior zone II, as defined according to the International Classification of ROP revisited from 2005,[21] treated with a single dose of IVR in the institution. Inclusion criteria in the protocol for IVR monotherapy were AP-ROP, ROP 3+ in zone I or posterior zone II, and severe disease that prevented conventional laser treatment by lack of iris dilation (rigid pupil) or media opacity (as vitreous or retinal hemorrhages). There were no exclusion criteria.

Ophthalmologic Examination and Interventions

All patients were evaluated preoperatively by binocular indirect ophthalmoscopy and by fundus retinal digital documentation with Retcam Imaging System (Clarity Medical Systems, Pleasanton CA). Gestational age (GA); birth weight (BW); classification of ROP in stages, zones, extension, and disease severity; postmenstrual age (PMA) at presentation; and PMA at treatment were recorded.

Anti-VEGF therapy with IVR was performed in all patients in the operating room with vital signs monitoring. Intravitreal injection of 0.25 mg (0.025 mL) of ranibizumab, one half the adult dose, was performed at 1.5 mm posterior to the corneal limbus. A disposable 1-mL syringe with a 30-gauge needle was used to inject ranibizumab. Topical povidone iodine 5% was applied for cutaneous and conjunctival asepsis. Topical anesthesia with proparacaine eye drops was used. Lid speculum under surgical microscope and evaluation of changes in cornea, anterior chamber, and lens before and after injection were always performed. All sterile materials and equipment for the second eye simultaneous treatment were exchanged. After administering IVR injection, antibiotic and steroid eye drops were used every 6 hours for 7 days.

Outcomes Evaluated and Follow-up

A favorable outcome was regression of ROP after treatment (meaning regression of the retinal neovascularization and plus disease). Unfavorable outcomes were progression to stages 4 and 5 of ROP. Follow-up evaluations were performed at 24 hours, 48 hours, 1 week, 2 weeks, 1 month, 2 months, 3 months, 6 months, 12 months, or more after treatment until the peripheral retinal vascularization was fully completed in zone III. Binocular indirect ophthalmoscopy was used for eye fundus examination in all patients. Patients with persistent avascular peripheral retina, or with retinal neovascularization after 6 months of initial treatment with IVR, were referred to fluorescein angiography examination. Retreatment criteria for laser therapy was reappearance of plus disease and neovascularization.

All patients were evaluated before, during, and after treatment by a neonatologist or pediatrician analyzing signs of respiratory distress, neurologic disorders, or heart distress, and were evaluated by a pediatric neurologist between months 3 and 6 after treatment.

Data were analyzed using the statistical program GraphPad Instat (GraphPad Software, Inc, Cary, NC).

Ethical Aspects

This study was conducted with a protocol approved by the institutional ethics committee and adhered to the Declaration of Helsinki, 1995 (revised in Edinburgh in 2000). A parental consent form was obtained for all patients before treatment.

Results

A total of 43 infants (85 eyes) were included in the study. Twenty-five patients were female. The mean GA at birth was 29.7±2.0 weeks (range, 26–34 weeks) and the mean BW was 1276±302 g (range, 800–1900 g). The mean PMA at diagnosis of ROP was 36±2.7 weeks and mean PMA at treatment was 37.2±2.2 weeks (Tables 1 and 2).

No intraocular adverse events occurred at the time of IVR injection, and no cardiorespiratory complications were observed during the treatment. No systemic side effects were observed in the short term, but 1 infant (2.4%) previously diagnosed with pulmonary dysplasia died 2 months after treatment from respiratory complications (patient 8). One infant (2.4%) developed cataract in the left eye 5 months after treatment and needed cataract surgery. No postoperative vitreous or retinal hemorrhages were registered after treatment.

One week after treatment, all eyes showed complete regression of plus disease. Within the first 6 months of follow up, only 12 infants (29.2%) developed complete vascularization of the peripheral retina (in zone III). A total of 22 infants (53.6%) had reactivation of plus disease in both eyes and required treatment with laser photocoagulation in zones II or III, but none in zone I. Five infants (11.6%) showed persistent absence of vascularization in zone II and zone III for >6 months (or >24 weeks) after treatment. One infant needed laser treatment in zone II after 135 weeks of follow-up. One infant developed bilateral ROP stage 5 within the first 2 months after IVR. In this patient, plus disease regressed, but then the patient developed a component of fibrosis in the posterior pole and subsequent retinal detachment. Two infants were lost to follow-up. The mean follow-up period was 22 months (range, 12–72) or 88 weeks.