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Bevacizumab versus diode laser in stage 3 posterior retinopathy of prematurity

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Editor,

Anti-VEGF agents, primarily bevacizumab, are emerging as a successful therapy for retinopathy of prematurity (ROP), particularly in aggressive posterior disease (Spandau et al. 2013). Concerns exist however regarding dosage, timing, duration of follow-up and long-term visual function.

We conducted a prospective case–control study in 14 infants with symmetrical zone 1 or posterior zone 2 Stage 3 + ROP; comparing intravitreal bevacizumab in one eye to laser therapy in the fellow eye. The purpose was to evaluate anatomic outcomes (regression or recurrence of ROP), and functional visual outcomes in the bevacizumab-treated eyes compared with laser-treated eyes, at one- and 2-year follow-up. We also evaluated ocular, systemic and developmental outcomes at one- and 2-year follow-up. Four infants had symmetrical Zone 1 Stage 3 + disease and 10 infants had Zone 2 Stage 3 + disease (Fig. 1).

We randomized the eyes into intravitreal bevacizumab (Avastin; Genentech Inc., South San Francisco, CA, USA) versus conventional laser therapy. All procedures were performed in the special-care baby unit (SCBU) under morphine sedation. Intravitreal injection with bevacizumab was performed under aseptic technique using a dose of 1.25 mg in 0.1 ml. After injection of bevacizumab, conventional 360° laser treatment was applied to the fellow eye.

The eyes were monitored weekly for 8 weeks, 3 monthly for a further 12 months, and 3–6 monthly thereafter. At 1- and 2-year follow-up, a full ocular examination was performed. Electrophysiology testing, visual evoked potential (VEP) and electroretinography (ERG), was performed on each eye where possible. All of the babies had a paediatric examination and magnetic resonance (MR) brain scan.

We observed rapid regression of ROP in all eyes injected with bevacizumab, as well as resolution of plus disease and flattening of the ridge by 48 hr postinjection in all eyes. Further vascularization was noted with complete regression taking up to sixty weeks in some eyes.

In our study, four of 14 eyes (28.6%) had recurrence of ROP; three eyes (21.42%) which had bevacizumab treatment and one eye (7.14%) with conventional laser therapy. There was a significant time delay to recurrence in the bevacizumab group compared with laser, with a mean age of 51 weeks PMA at time of recurrence in bevacizumab-treated eyes compared with 37 weeks PMA in the laser-treated eye. This delay in recurrence has also been reported by other studies including the BEAT-ROP trial. (Mintz-Hittner et al. 2011). Of the 3 bevacizumab-treated eyes with recurrence, two eyes received laser treatment where the ROP was peripheral. One eye with more posterior recurrence received a further intravitreal bevacizumab injection. In the eyes that received laser treatment, one eye (7.14%) demonstrated recurrent

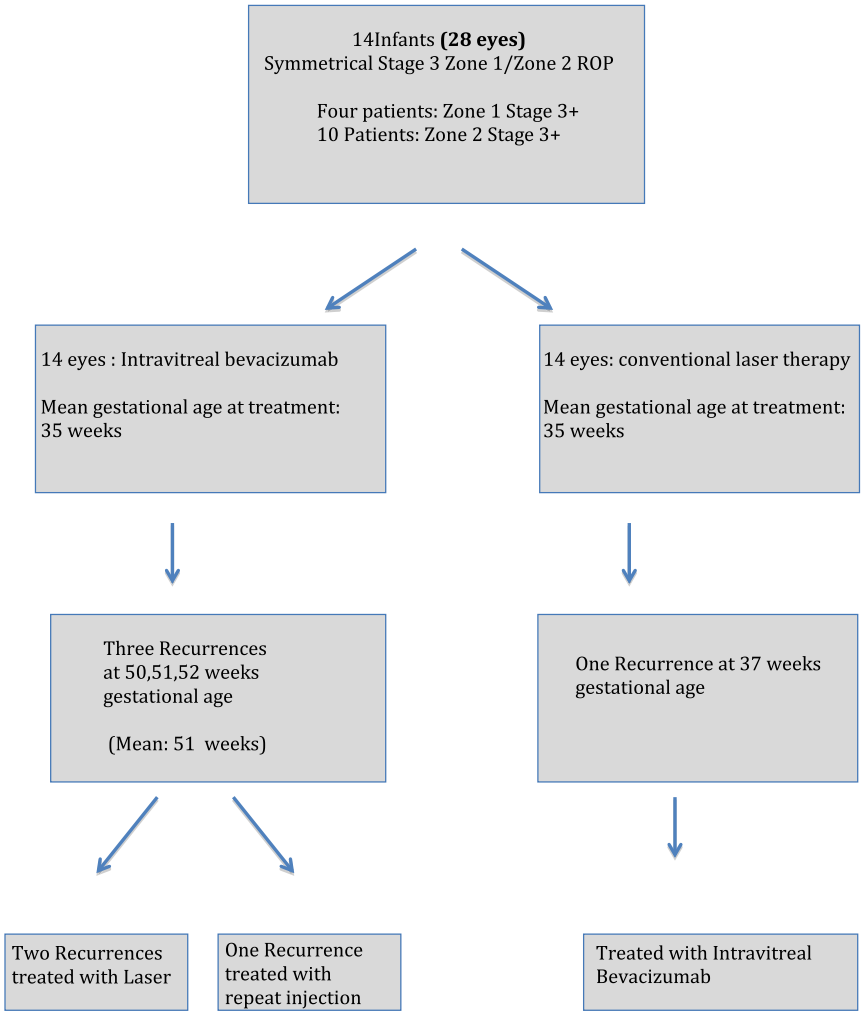

Fig. 1. Summary of eyes treated, including recurrences, bevacizumab and laser.

and progressive ROP 1 week following laser treatment (37 weeks PMA) and was treated with intravitreal bevacizumab at this time. At one- and 2-year follow-up, ocular and paediatric assessment including MR brain scans showed no abnormality that could be attributed to bevacizumab.

Our study demonstrates efficacy of bevacizumab in treatment for posterior ROP. At 2-year follow-up, we have not observed any adverse ocular or systemic events. Since completion of this study, we have successfully treated a further 12 infants with bevacizumab, using a lower dose of 0.625 mg.

We believe intravitreal bevacizumab is the treatment of choice in Zone 1 and posterior Zone 2 ROP. It is less invasive, inexpensive, easily administered, and has a rapid effect. Drawbacks include delayed vascularization, need for prolonged monitoring (Mireskandari et al. 2013), the risk of ocular side-effects during and after administration, (Shima et al. 2008) as well as uncertainty regarding systemic effects (Jalali et al. 2013). Longer follow-up is necessary to assess outcomes such as visual acuity, refractive errors, retinal status and potential delayed systemic effects.

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Subretinal tissue plasminogen activator injection to treat submacular haemorrhage during age-related macular degeneration

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Editor,

We reviewed the records of patients who were admitted at the University Hospitals Leuven between November 2008 and July 2012 with submacular haemorrhage due to AMD and treated using 23-G vitrectomy with subretinal tPA (0.5–1 ml injection through a 41-G microcannula) and air tamponade to displace the haemorrhage downwards from the fovea. This treatment was followed by standard-of-care intravitreal anti-VEGF injection treatment.

Inclusion criteria were as follows: unilateral submacular haemorrhage larger than one disc diameter, but smaller than the area between the two vascular arcades; and preserved vision capable of more than counting fingers in the fellow eye. The study included 74 eyes of 74 patients. The mean age was 79.65. A total of 27 patients were pseudophakic; all 47 phakic patients (64%) underwent combined cataract surgery. Most of the patients underwent surgery within a few days after presentation, but time of presentation at our department varied greatly. The mean delay between the onset of symptoms and the surgery was 22.68 days (1 day to 5 months).

Follow-up visits were performed 1 day, 1 week and 6 weeks (mean follow-up: 53 days) after the surgery. The final follow-up visit varied from 18 days to over 4 years.

At baseline, visual acuity (VA) ranged from 20/40 (0.3 logMAR) to light perception [mean VA: 20/800 (1.6 logMAR)]. After surgery, VA improved by 0.34 logMAR units at the 6-week follow-up visit, indicating an improvement of 23.5% ($p < 0.0001$).

In 14 of the patients (19%), VA worsened, and 11 patients (15%) maintained their preoperative VA.

A mean improvement of 0.24 logMAR units was recorded at the end of follow-up.

The scatter chart in Fig. 1 displays the pre- and postoperative outcomes along the *X*- and *Y*-axes. VA tended to decrease with the length of follow-up; the final VA was 0.1 logMAR units worse than the 6-week postoperative VA.

Delays in surgery are associated with significantly worse visual outcomes. There was a deterioration of VA of 0.003 logMAR units/day of delay at the 6-week follow-up ($p = 0.040$).

No intra-operative complications were recorded, but adverse events occurred postoperatively. Two patients developed vitreous haemorrhage and hyphema that required reintervention. A total of seven patients suffered from retinal detachment: four of these patients presented 4 weeks after surgery, and the other three patients presented with proliferative vitreoretinopathy 8 weeks postoperatively. Two

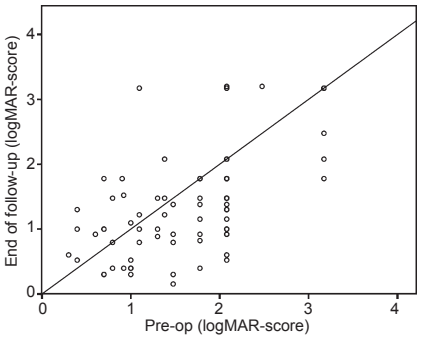

Fig. 1. Scatter chart: Visual acuity pre- and postoperative (LogMAR).