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# Time to consider a new treatment protocol for aggressive posterior retinopathy of prematurity?

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**ABSTRACT.**

***Purpose:*** **To discuss treatment modalities for aggressive posterior retinopathy of prematurity (AP-ROP).**

***Methods:*** **The medical charts of all infants with AP-ROP at Uppsala University Hospital, Sweden, during a 2-year period (2009 and 2010) were reviewed. Eight infants (16 eyes) with a mean gestational age of 23.8 weeks and a mean birth weight of 592 g were treated with laser and/or intravitreal injections of bevacizumab (0.4 and 0.625 mg). RetCam photography was used to document the retinal appearance before and after treatment.**

***Results:*** **All infants (16 eyes) had AP-ROP in zone I. Mean time at initial treatment was 34 weeks postmenstrual age. Two eyes (one infant) were only treated with laser, and six eyes (three infants) were treated with laser therapy or cryopexy and, because of lack of regression, with bevacizumab as salvage therapy. Eight eyes (four infants) were treated with a first-line bevacizumab injection and four of these eyes (two infants) with additional laser ablation for continued disease progression in zone II. Macular dragging occurred in one eye of one infant primarily treated with laser.**

***Conclusions:*** **Given the high complication rate of the extensive laser treatment for zone I ROP, it is worth considering anti-vascular endothelial growth factor treatment as an alternative therapy. Further knowledge concerning side effects and long-term ocular and systemic outcome is warranted before this drug becomes general clinical practice.**

**Key words:** aggressive posterior retinopathy of prematurity – bevacizumab – laser – retinopathy of prematurity

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## Introduction

Neonatal care has markedly improved during the past decade, resulting in increased survival rates for extremely preterm babies (Gilbert 2008). Recently, a Swedish national population-based study of infants born before 27 weeks of gestation during the period 2004–2007 reported a 1-year survival of 70% (The EXPRESS Group, JAMA 09). Such extremely preterm infants have a high risk of developing retinopathy of prematurity (ROP), which requires treatment (Austeng et al. 2009). They are also at risk of developing aggressive posterior ROP (AP-ROP), which is characterized by ROP in the posterior pole (zone I and posterior zone II) with flat neovascularizations and haemorrhages and sometimes a diffuse border between vascular and avascular retina (ICROP Arch Ophthalmol 05). Often, there is also rubeosis of the iris and unclear media.

Although laser ablation is usually a successful treatment option for classical ROP, progression of the disease to retinal detachment is common in AP-ROP, despite extensive and appropriate laser treatment (O'Keefe et al. 2003; Soh et al. 2008; Axer-Siegel et al. 2008; Kychenthal et al. 2006; Drenser et al. 2010). Further, there are well-known problems with laser therapy for AP-ROP because of persistent tunica vasculosa lentis, hazy vitreous, as well as difficulties in identifying the border between vascularized and non-vascularized retina. Another dilemma is that the extensive laser treatment required for AP-ROP may lead to a worse functional outcome of these eyes than for classical ROP. An alternative first-line therapy is therefore warranted.

Vascular endothelial growth factor (VEGF) plays an important role in

the pathogenesis of ROP (Smith et al. 1994). It is, therefore, not surprising that intravitreal injection of anti-VEGF has become an option for treatment of ROP. Bevacizumab is the most common anti-VEGF molecule used for ROP. (Chung et al. 2007; Honda et al. 2008; Lalwani et al. 2008; Mintz-Hittner & Best 2009; Dorta & Kychenthal 2010; Mintz-Hittner et al., 2011). In recent years, the indication spectrum for intravitreal injection of anti-VEGF has expanded from anterior segment neovascularization to 'classic' ROP (Lalwani et al. 2008; Mintz-Hittner & Best 2009; Dorta & Kychenthal 2010). Bevacizumab injection is now being used more often as a first-line treatment (Chung et al. 2007; Lalwani et al. 2008; Honda et al. 2008; Mintz-Hittner & Kuffel 2008). Further, Mintz-Hittner et al. (2011) have recently shown in a randomized study that treatment with bevacizumab for zone I ROP results in a better anatomical outcome compared with laser treatment. However, the long-term ocular and systemic effects of bevacizumab are still unknown.

The aim of this paper is to discuss and elucidate a new treatment policy, with bevacizumab as first-line therapy for AP-ROP instead of laser, by reviewing the literature and describing our own experiences.

# Methods

A retrospective review of infants with aggressive posterior ROP, AP-ROP, in the NICU at Uppsala University Hospital during the past 2 years was performed. According to the revised International Classification of Retinopathy of Prematurity, aggressive posterior ROP, AP-ROP, is characterized as zone I disease (but may also occur in posterior zone II), prominent plus disease and often ill-defined retinopathy (ICROP 2005).

### Screening protocol for ROP

The first examination was scheduled when the infant was 5 weeks old. The screening protocol advocated weekly examinations. We followed the Early Treatment for Retinopathy of Prematurity Cooperative Group (ETROP 2003) recommendations concerning criteria for treatment. Subsequent examinations and laser treatments were also scheduled following Early Treatment ROP recommendations. RetCAM photography was used for documentation when possible.

### Treatment protocol for AP-ROP

When treatment criteria were reached, laser therapy was given in the presence of an adequate fundus view. If the fundus view was poor, we performed cryo therapy and added laser ablation 1–2 weeks later, as soon as the fundus view improved.

If there were media opacities or zone I retinopathy, intravitreal bevacizumab injections were initiated in 2009, primarily as salvage treatment and later as first-line therapy. If the disease progressed in zone I, a new injection was given unless the retinal vascularization had reached zone II. If the progression occurred in zone II, laser ablation was performed.

### Laser therapy

Treatment was performed under general anaesthesia. The laser technique used was indirect transpupillary photocoagulation (Keeler Multilase and Iris Medical Oculight SLX). All patients underwent diode laser photocoagulation of the peripheral avascular retina extending from the ridge of extraretinal proliferation to the ora serrata. All eyes received an almost confluent laser pattern.

### Intravitreal injections of bevacizumab

The injections were administered in an operating theatre under general anaesthesia. After instillation of 4% chlorhexidine and insertion of a lid speculum, a dose of 0.4 or 0.625 mg bevacizumab was injected 1 mm posterior to the limbus. The dosage of 0.625 mg was chosen according to the recommendations of the BEAT-ROP study (Mintz-Hittner et al. 2011). The 0.4-mg dosage was determined based on a mathematical calculation of the volume of a neonate eye, being one-third of the adult eye (axial length of a 34-week gestational age (GA) neonate eye = 16 mm (Ehlers et al. 1968)). The usual dosage for the adult is 1.2 mg, and the size-adjusted dosage for the neonate is therefore 0.4 mg.

Before initiating the off-label treatment with bevacizumab for each infant, consensus was reached among the screening paediatric ophthalmologist, the retinal surgeon and the responsible neonatologist. Thorough oral information was given to the parents, and verbal consent was required. The 'experimental nature' of the off-label use of bevacizumab was explained, including the known and possible ocular and systemic side effects, and the need to participate in ophthalmic and general long-term follow-up to puberty was explained.

### Follow-up

A prolonged and focused monitoring up to puberty is performed in the departments of paediatrics and ophthalmology, including general health, developmental outcomes, orthoptic status and electroretinography (ERG).

# Results

During the past 2 years, there were 16 eyes of eight patients (Six boys and two girls) with AP-ROP at our hospital. Gestational age at birth of the infants ranged from 23 to 26 weeks (mean 23.8 weeks), and the birth weights varied from 494 to 721 g (mean 592 g). The timing of the first treatment ranged from postmenstrual age 32–36 weeks (mean 34 weeks).

The first four infants (cases 1–4) were treated with first-line laser ablation (Table 1). Cases 2, 3 and 4 were given intravitreal injections of bevacizumab as salvage treatment because of the lack of regression of ROP. The left eye of one infant (case 4) developed a macular heterotopia.

After our positive experiences with salvage treatment with bevacizumab in cases 2–4, and to avoid the central destruction of retinal tissue by laser (Fig. 1), a decision was made to change our treatment policy as follows. For AP-ROP with zone I retinopathy, intravitreal anti-VEGF would be used as first-line therapy. If vascularization reached zone II and if there was a continued disease progression, we would perform laser ablation if necessary.

The following infants (cases 5–8) were treated with first-line intravitreal bevacizumab (Fig. 2). In two infants (cases 5 and 6) (four eyes), the ROP

**Table 1.** Treatment details for preterm infants in the present case review.

| No. | GA (w) | BW (g) | 1st treatment (w) | 2nd treatment | 3rd treatment | 4th treatment | Anatomical outcome |
|---|---|---|---|---|---|---|---|
| 1 | 22 | 523 | w 34<br>R: 1686 spots<br>L: 1386 spots (600 mW) | w 36<br>R: 1529 spots<br>(500 mW) | | | w 74<br>R: good<br>L: good |
| 2 | 26 | 514 | w36<br>R: 2183 spots (700 mW)<br>L: Cryo (hazy media) | w37<br>R: 837 spots + 0.625 mg bevacizumab<br>L:490 spots + 0.625 mg bevacizumab (700 mW) | | | w47<br>R + L: good |
| 3 | 25 | 648 | w34<br>R + L: Cryo (hazy media) | w35<br>R:734 spots<br>L:704 spots (800 mW) | w36<br>R + L:<br>Cryo + 0.625 mg bevacizumab | w37<br>R + L:<br>Cryo + 0.625 mg bevacizumab | w39<br>R + L: good |
| 4 | 24 | 721 | w33<br>R: 3118<br>L: 2472 (700 mW) | w35<br>R: 788 spots<br>L: 415 spots<br>(600 mW) | w37<br>R + L: 0.625 mg bevacizumab | | w39<br>R: good<br>L: macular dragging |
| 5 | 23 | 495 | w34<br>R + L: 0.4 mg bevacizumab | | | | w65<br>Good, vascularized until zone III |
| 6 | 23 | 585 | w34<br>R + L: 0.4 mg bevacizumab | | | | w93<br>Good, fully vascularized |
| 7 | 23 | 555 | w34<br>R + L: 0.625 mg bevacizumab | w36<br>R + L: 0.625 mg bevacizumab | w38<br>R: 1859 spots<br>L: 1730 spots (600 mW) | | w45<br>Good |
| 8 | 24 | 700 | w32<br>R + L: 0.625 mg bevacizumab | w36<br>R + L: 0.625 mg bevacizumab | w43<br>R: 1800 spots<br>L: 1800 spots (600 mW) | | w44<br>Good, vascularized into zone II |

Spots = laser spots; w = postmenstrual age in weeks; R = right eye; L = left eye.

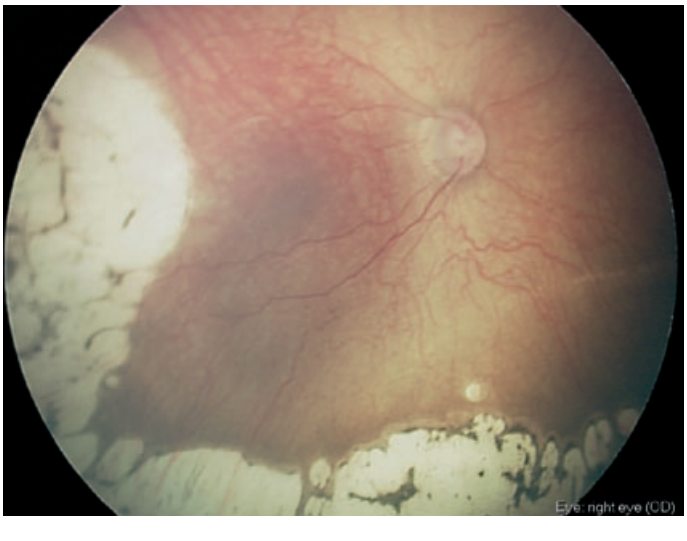


**Fig. 1.** Fundus photograph of case 4. This infant was treated with laser ablation followed by intravitreal bevacizumab. The photograph of the right eye was taken 12 weeks after the treatment. The laser effects are very close to the posterior pole and the macula.

regressed after a single injection. In two infants (cases 7 and 8) (four eyes), there was a lack of regression and a second injection was given. In the latter, there was a progression of the ROP after vascularization had reached zone II and the infants were consequently treated with laser ablation. All eyes ($n$ = 8) of the infants treated with first-line bevacizumab had a favourable anatomical outcome (Fig. 2).

## Discussion

During the past 2 years, there were eight cases with AP-ROP in the neonatal unit at Uppsala University Hospital. The first four cases were initially treated with laser or cryo. Intravitreal injection was used as a salvage therapy in a later session in three of the cases because of lack of regression of the disease, with a good effect. The long-term retinal and visual functions, as well as the size of the remaining visual field, are a great worry in such eyes with very central location of the disease and extensive retinal destruction after confluent laser treatment from zone I to the ora serrata. In our latest cases with AP-ROP, all below 25 weeks of gestation, injection with bevacizumab was, therefore, used as first-line treatment. We hypothesize

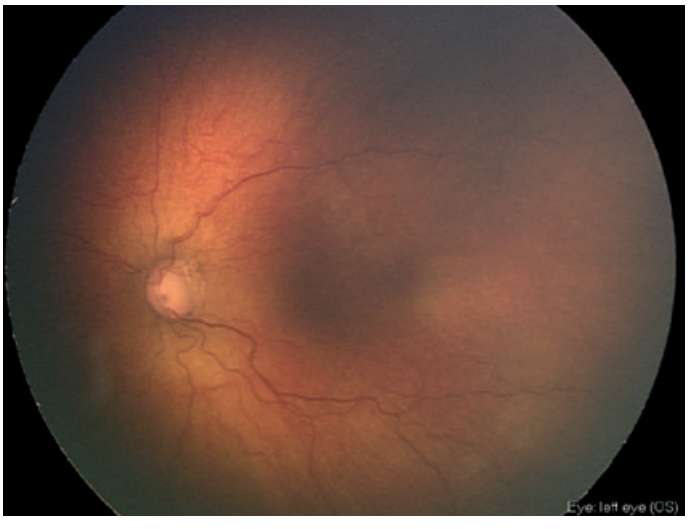


**Fig. 2.** Fundus photograph of case 5. This infant was treated with intravitreal bevacizumab only. The photograph was taken 4 weeks after the treatment. The retina is already vascularized into zone II.

that this management will preserve retinal tissue and future retinal and visual function.

Laser treatment is the conventional and efficient treatment for ROP in the huge majority of cases, which is illustrated by the fact that 94% of the ROP regressed after laser treatment in a recent Swedish population-based study of 500 infants born before 27 weeks of gestation (Austeng et al. 2010b). In AP-ROP, however, progression of the disease is common, despite extensive laser treatment (Soh et al. 2008; Kychenthal et al. 2006; Micieli et al. 2009; Drenser et al. 2010; Mintz-Hittner et al. 2011). The results of our small series of infants with AP-ROP are in line with those of Mintz-Hittner et al. (2011) regarding the anatomical outcome. One eye in one of our infants initially treated with laser developed macular heterotopia, but this occurred in none of the eight eyes primarily treated with bevacizumab. Several other authors have reported poor experiences with laser ablation for AP-ROP (Soh et al. 2008; Axer-Siegel et al. 2008; O'Keefe et al. 2003; Drenser et al. 2010). They found a more or less poor anatomical and functional outcome of laser-treated eyes, with a high prevalence of retinal detachments ranging from 13% to 100%. Chung et al. (2007), Lalwani et al. (2008) and Honda et al. (2008) used combined laser/bevacizumab therapy and achieved much better results.

In addition to the high complication rate, laser therapy for AP-ROP is technically/practically demanding because of media opacities and difficulties in identifying the border between vascularized and non-vascularized retina. Furthermore, because of the very central location of AP-ROP, an extensive part of the central and peripheral retina is destroyed by laser treatment. When examining the fundus after treatment (Fig. 1), it is easy to imagine that such treatment will be of functional disadvantage in the future, both regarding central retinal function and peripheral visual fields. Because of the negative results of laser ablation for AP-ROP, a search for new treatment modalities is logical.

The anti-VEGF drug bevacizumab is an attractive alternative to laser treatment for AP-ROP. Retinopathy of prematurity is a proliferative disease of the developing retinal vessels. Vasoactive substances, in particular VEGF, are involved in the hypoxia-induced vessel proliferation (Smith et al. 1994). Many studies of proliferative retinopathies, such as diabetes or central retinal vein occlusion (CRVO), have demonstrated an anti-proliferative effect of bevacizumab (Arevalo & Garcia-Amaris 2009; Spaide et al. 2009). It is therefore not surprising that several groups have reported positive effects of first-line bevacizumab therapy for AP-ROP, with a favourable anatomical outcome and no retinal detachments (Mintz-Hittner & Kuffel 2008; Drenser et al. 2010; Dorta & Kychenthal 2010).

The aforementioned studies, however, are all retrospective and non-randomized studies with a limited number of cases. Therefore, a recent prospective and randomized multicenter study by Mintz-Hittner et al. (BEAT-ROP study) has provided evidence of a positive anatomical outcome of bevacizumab therapy with a significant reduction of retinal detachments, at least in zone I ROP stage 3 with plus disease. The authors found significantly lower recurrence rates of zone I disease after first-line treatment with bevacizumab (6%) compared with laser (42%) in 31 and 33 infants, respectively. In eyes with zone II disease, there was no significant difference in recurrence rates between the treatments (5% versus 12%). Importantly, for zone I disease, the authors also reported significantly fewer complications such as macular dragging and retinal detachments after intravitreal injections of bevacizumab than after laser treatment (3% versus 54%). Recently, drawbacks of the study by Mintz-Hittner et al. have been pointed out, such as modification of primary outcome, a too short follow-up time and a lack of safety data (Good & Palmer 2011; Moshfeghi & Berrocal 2011).

The findings of the BEAT-ROP study support our change of policy regarding treatment for AP-ROP. In our first four infants, laser was used as primary treatment. Because of our negative experiences with macular heterotopia in the left eye of case 4, we re-evaluated our treatment protocol for AP-ROP. With the intention to rescue central retinal tissue and to promote further outgrowth of the retinal vessels (Figs 1 and 2), intravitreal injection with bevacizumab was used as first-line treatment in the following four cases with AP-ROP (cases 5–8). Two of these cases (cases 5 and 6) regressed after one single injection, while the other two (cases 7 and 8) needed a second injection. The latter two cases progressed after outgrowth of vessels in zone II and were treated with laser ablation (Table 1). None of the eyes in these last four infants developed retinal detachment or macular dragging. We have now changed our treatment protocol so that AP-ROP in zone I is initially treated with intravitreal bevacizumab, while zone II retinopathy is still treated with laser

ablation. In case of lack of regression of zone I disease, a re-injection of bevacizumab is given. If the retina has become vascularized into zone II and if further treatment is warranted, laser ablation is performed.

There are several reservations regarding anti-VEGF treatment. One disadvantage of bevacizumab treatment is a much later recurrence, that is, deterioration with new proliferations, compared with laser treatment. According to data from the CRYO-ROP and ETROP studies, recurrence occurred before 55 weeks of age in eyes treated with cryo or laser (ETROP 2003; ICROP 2005; ETROP 2010).

Our knowledge concerning the course of retinal vascularization in eyes with AP-ROP treated with bevacizumab is, however, still limited. In the BEAT-ROP study the mean time of a recurrence was 16 ± 4.6 weeks in the bevacizumab group and only 6.2 ± 5.7 weeks in the laser group (Mintz-Hittner et al. 2011). The mean follow-up for bevacizumab-treated infants should, therefore, be at least 10 weeks longer than that for laser-treated infants. These results are confirmed by other studies: Dorta & Kychenthal (2010) report an arrest of the vascularization at zone III with a follow-up time up to 48 weeks GA in eyes treated with bevacizumab. In the present study, one of our infants (case 5), who was examined at 65 weeks GA, had a full nasal vascularization in both eyes, but there was an arrest in the retinal vascularization in zone III with a dot haemorrhage. The clinical relevance of these findings is difficult to interpret, but they emphasize that infants who have been treated with anti-VEGF need an extended follow-up.

A major dilemma with bevacizumab therapy is that although it may be a good alternative to laser ablation, its long-term ocular and systemic effects are unknown. We know from studies on newborn humans and macaques that VEGF is reduced in the plasma for 8 weeks after an intravitreal injection of bevacizumab (Lee et al. 2011; Miyake et al. 2010). Vascular endothelial growth factor plays an important role in the developing eye and body. It is not only important for the physiological angiogenesis of the neonate, and in particular of the eye, lungs and brain but also for the neuroprotection of the developing body (Storkebaum et al. 2004; Ribatti 2005). It plays a critical role in the physiological development of the retinal vasculature and photoreceptors (Smith et al. 1994; Saint-Geniez et al. 2008). Unfortunately, there have not yet been any long-term follow-up studies of bevacizumab concerning retinal and visual function. A low rate of systemic adverse events is documented in adults (Bakri et al. 2007), whereas cerebrovascular accidents have been reported in 0.21% of neonates (Micieli et al. 2010).

Another important drawback is the limited knowledge concerning the 'correct' dose of intravitreal bevacizumab. In the BEAT-ROP study, a dosage of 0.625 mg was recommended, but the rationale for this dosage was not reported (Mintz-Hittner & Kuffel 2008; Mintz-Hittner et al. 2011). Several studies have used a dosage of bevacizumab between 0.4 and 0.7 mg (Honda et al. 2008, Kong et al. 2008, Dorta & Kychenthal, 2010, Mintz-Hittner et al. 2011). In our small group of infants, one single intravitreal injection of 0.4 mg bevacizumab was sufficient to treat the retinopathy in two infants (cases 5 and 6), while two infants (cases 7 and 8) required an additional laser ablation, despite two injections of 0.625 mg. Recently, Harder et al. (2011) showed good anatomical results after a single injection of 0.3 mg bevacizumab in 23 eyes with type 1 ROP. These experiences reveal that apparently half of the dosage recommended in the BEAT-ROP study could be sufficient to treat zone I ROP. But why not inject 0.1 mg, or only 0.05 mg? The dosage question is of great importance as VEGF plays such a vital role in the development of the neonate. Therefore, a separate study that titrates the minimal dosage is indeed warranted.

In view of the high complication and recurrence rate of laser therapy in zone I ROP and an available alternative treatment with anti-VEGF, it is worth to re-evaluate the current treatment policy. There are, however, many concerns regarding anti-VEGF treatment such as dosage, timing, duration of follow-up and long-term functional outcome of the eye. In addition, more knowledge is warranted regarding ocular and systemic side effects before these drugs become general clinical practice.

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