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Is Avastin the right choice of treatment for retinopathy of prematurity?

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Anna Käll has no conflicts to declare.

Off-label use of intravitreal bevacizumab (Avastin®) is an increasingly popular treatment for retinopathy of prematurity (ROP). It has been described as a simpler, cheaper and more effective alternative to conventional laser therapy. But is it really safe to inject a cancer drug into the eyes of a premature infant? The use of bevacizumab is widely debated among neonatologists and ophthalmologists. We asked Christoph Bührer, professor of neonatology, at the Charité University Medical Center in Berlin, and Ann Hellström, professor of paediatric ophthalmology, at Queen Silvia Children's Hospital, Gothenburg, to share their views about the drug.

RETINOPATHY OF PREMATURITY AND BEVACIZUMAB

Retinopathy of prematurity (Fig. 1) is a leading cause of childhood blindness throughout the world. The disease mainly affects preterm infants of very low birth weight and occurs when abnormal blood vessels grow and spread throughout the retina. The blood vessels are fragile and can leak, scarring the retina and causing retinal detachment, which is the main cause of visual impairment in ROP. Today, peripheral retinal ablation with conventional laser therapy is the main treatment for advanced ROP.

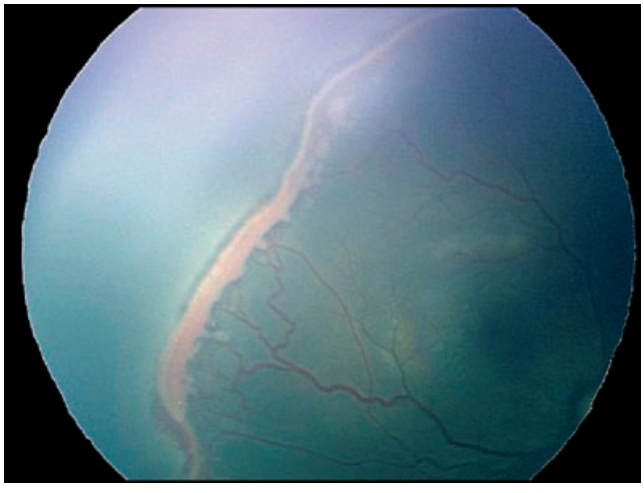

Figure 1 Retinopathy of prematurity, Fundus photograph, Ann Ells, Community Eye Health Journal 2006.

Bevacizumab is an anti-vascular endothelial growth factor (anti-VEGF) developed to treat cancer by choking off blood vessels to tumours. It has been approved since 2004, for the treatment for metastatic colorectal cancer and subsequently for other cancer forms. As ROP is a VEGF-driven disease, off-label bevacizumab was introduced as a possible treatment. Several studies have been published on the use of intravitreal bevacizumab for ROP, but it was not until February 2011 that the result from the first, and so far only, randomized controlled trial comparing bevacizumab with conventional laser therapy was published. The BEAT-ROP study included 150 infants with zone I or zone II posterior, stage 3 plus ROP. The study showed that bevacizumab was more effective than conventional laser therapy for zone 1 ROP, whereas no significant difference was found for zone II disease. The primary outcome was recurrence of ROP requiring retreatment before 54 weeks postmenstrual age.

HAVE SEEN PROMISING RESULTS IN ALL TREATED BABIES

After the publication of the BEAT-ROP study, Christoph Bührer (Fig. 2), professor of neonatology, and Antonia Joussen, professor of ophthalmology, at the Charité University Medical Center in Berlin, Germany, decided that there was evidence enough to start using bevacizumab.

- So far we have given bevacizumab to six infants. All of them had stage 3 ROP in zone II and were at an average gestational age of 35–36 weeks at the time of injection. We

Figure 2 Christoph Bührer.

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have seen promising results in all the babies. Our ophthalmologist was first heavily critical to the idea of using bevacizumab, but after the first injection, he was amazed how fast it worked. There were no scars, and it was almost like the disease was completely gone just after a few days, Christoph Bührer says.

The team copied the procedures from the BEAT-ROP study and used the dose 0.625 mg in 0.025 mL of solution, as it had proven to be effective.

- We follow the treated babies carefully to make sure there is not a recurrence. One of them had a late relapse after 2 months, so we decided that a second intervention was needed. We let the parents choose between laser therapy or a second injection of bevacizumab, and they opted for the injection. Which also tells us that the parents thought it was less invasive, Christoph Bührer says.

SYSTEMIC EFFECTS MAY NOT BE OBVIOUS UNTIL DECADES AFTER THE TREATMENT

Ann Hellström (Fig. 3), professor of paediatric ophthalmology at the Institute of Neuroscience and Physiology, Queen Silvia Children's Hospital, Gothenburg, Sweden, is deeply concerned about the increased use of intravitreal bevacizumab for the treatment for ROP.

- The systemic long-term effects of bevacizumab may not be obvious until decades after the injections. Preterm infants are still undergoing organogenesis at the time of ROP treatment, and VEGF plays an essential role in organ development. We know that intravitreal bevacizumab leaks through the retinal-blood barrier into the circulation. A recently published study showed that bevacizumab was found in serum at least 2 weeks after intravitreal injection, and bevacizumab levels were correlated with reduced serum VEGF. On the basis of the animal studies, we can suspect that bevacizumab still can be found in the circulation 8 weeks after administration and inhibit VEGF at a time when it is important for a normal development of kidneys, lungs, brain and other organs, Ann Hellström explains and continues:

- I am also concerned about the dosing. Half the adult dose (0.625 mg/eye) seems to be the most commonly used, although one-hundredth of the dose had an effect on diabetic retinopathy in adults. It is important to note that in most patients, ROP regresses after laser treatment. The effects of laser are limited to the eye. It has been used for many years with proven efficacy except in the most severe cases, she says.

Christoph Bührer has a different opinion.

- Just because laser has been historically used as opposed to bevacizumab doesn't mean it is superior. It has just been known for a longer period of time. Laser treatment is irreversible, whereas anti-VEGF isn't. With laser you take away parts of the retina to save other parts of the retina, whereas with bevacizumab you are not destroying anything. If bevacizumab doesn't work you still have the option of laser, but if you have already damaged the retina by laser you cannot redo it. Another positive thing with bevacizumab is that you avoid central anaesthesia, and by doing that you do something good for the brain, he says.

Figure 3 Ann Hellström.

BEVACIZUMAB VERSUS RANIBIZUMAB

In addition to the question whether anti-VEGF should be used at all for treatment for ROP, it has also been discussed if bevacizumab is really the right choice of anti-VEGF. The antibody fragment ranibizumab (Lucentis®) is licensed for the treatment for macular degeneration, a leading cause of blindness in adults.

- Ranibizumab may be a better alternative for premature infants, although it is almost 40 times more expensive. It has a much shorter half-life in serum and was developed for concerns of systemic adverse effects of bevacizumab, Ann Hellström says.

Christoph Bührer is not so concerned about the longer half-life of bevacizumab.

- Not as we only give one or two injections. I would rather like to acknowledge Helen Mintz Hittner et al. for using bevacizumab and not ranibizumab in the BEAT-ROP study. By choosing the cheap anti-VEGF, it will be possible to use this treatment also in the developing world, he says.

TIME TO ESTABLISH AN INTERNATIONAL REGISTER

Ann Hellström's conclusion is that infants who can be treated successfully with laser should not receive anti-VEGF until further studies have been carried out.

- We need experimental studies on animal species with VEGF that binds to bevacizumab, at the developmental stages corresponding to the human third trimester, regarding adverse effects on developing organs. Bevacizumab may be an option, but only in case of laser failure for infants with very severe ROP. In that case the treated infants should be included in controlled pharmacokinetic, dose – efficacy and safety trials, and serum concentrations of VEGF should be monitored, Ann Hellström says.

Christoph Bührer, on the other hand, thinks bevacizumab can be used as an alternative to laser, with careful follow-up.

- We have seen that it has effect. Now we need to determine the optimal dose and find out if it has any rare side effects. I think the best way would be to establish an international register where data from many patients can be compiled. Observational studies are sometimes a better option than randomized controlled trials. The declaration of Helsinki stipulates that a patient can only be enrolled in one randomized clinical trial at a time. Many of the premature infants have several ongoing diseases and require treatment with a number of off-label medicines, which all needs to be evaluated, Christoph Bührer says, and draw a parallel with extracorporeal membrane oxygenation (ECMO) treatment:

- Extracorporeal membrane oxygenation was never studied in a randomized controlled trial, but there is a huge ECMO register. Virtually everything we know about ECMO comes from that register. It is probably going to be the same for bevacizumab, he says.

RETINOPATHY OF PREMATURITY CLASSIFICATION

The severity and location of retinopathy of prematurity have been classified by an international committee (ICROP). In summary, ROP is classified into five stages ranging from mildly abnormal blood vessel growth (stage 1) to complete retinal detachment (stage 5). In addition, 'plus disease' may be present at any stage. 'Plus disease' means that the blood vessels of the retina have become enlarged and twisted. Early stages of ROP may improve without treatment. The location of the disease is divided into three zones (Fig. 4). Threshold disease is considered to be present when stage 3 ROP is found in either zone 1 or zone 2, and plus disease is present. Aggressive posterior ROP (AP-ROP) is an aggressive form observed in the lowest birth weight infants.

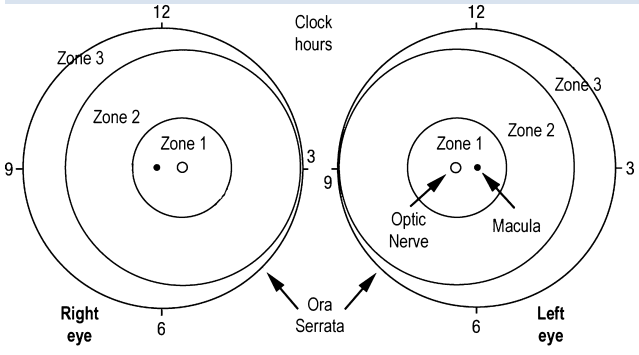

Figure 4 Scheme of retina showing zones and clock hours used to describe the location of retinopathy of prematurity.

HISTORIC PAPER IN ACTA PAEDIATRICA

During 1930s, it was noted that preterm infants often suffered from apnoea, which could be treated with oxygen (Fig. 5A,B). Therefore, oxygen was introduced. That resulted in a better survival of preterm infants. However, a new disease – retrolental fibroplasia (nowadays ROP) – was discovered. This caused blindness among numerous preterm infants. Various theories to explain this disease were proposed, for example, hypoxia.

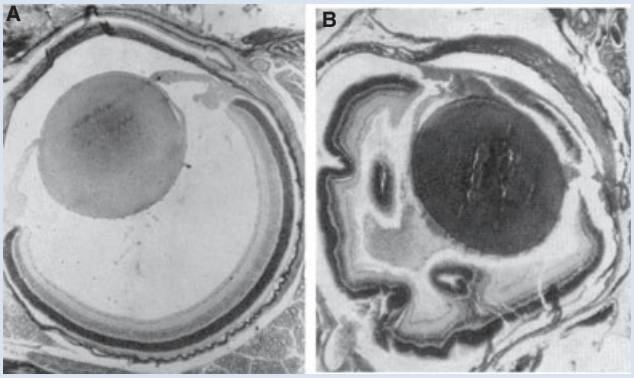

Figure 5 (A) Control animal, 11 days old. Normal eye. (B) After oxygen exposure.

However, an Australian doctor discovered high incidence of the retrolental fibroplasia in private hospitals, where oxygen was given frequently to preterm infants, when compared with public hospitals, where oxygen could not be afforded. The paediatrician, Bo Hellström, together with the histologist and also famous author, Lars Gyllensten, tested the idea that the oxygen tension could be of importance for the pathogenesis of retrolental fibroplasia.

Full-term newborn mice were kept in sealed boxes with a continuous flow of 100% oxygen during 48-h interval interrupted with intervals of 24 h in ordinary air during 1–3 weeks. The most consistent findings were haemorrhages in the vitreous body and detachment of optical retina. The authors were not able to explain these findings, but they speculated that the increased oxygen tension might cause the inner layer of the retina and the vascular tissue of the eye to overgrow with secondary haemorrhages.

This brief report is often referred to as the first animal study showing the deleterious effect of hyperoxia on the developing eye.

HUGO LAGERCRANTZ

Reference: Lars J. Gyllensten and Bo E. Hellström. Retrolental Fibroplasia – Animal Experiments, The effect of intermittingly administered oxygen on the postnatal development of the eyes of full term mice. A preliminary report. *Acta Paediatr* 1952; 41: 577–582.