Timing of bevacizumab is a critical component of the therapy

by Sean Henahan in Orlando

A study showing therapeutic value for the anti-VeGF agent bevacizumab (Avastin, Genentech) in infants with retinopathy of prematurity (ROP) is stirring hope, and controversy.

Helen A Mintz-Hittner MD, professor in the Department of Ophthalmology and Visual Sciences, University of Texas Health Science Center-Houston Medical School, Houston, Texas, discussed the latest results of the BEAT-ROP study during a session of the annual meeting of the American Academy of Ophthalmology.

“This research was published recently in a landmark article in the New England Journal of Medicine. To say that it has generated some controversy among ophthalmologists, paediatricians and neonatologists would be an understatement,” noted Ken Nischal, MBBS, director of Children’s Hospital of Pittsburgh, Pennsylvania, US, in his introduction of the keynote address.

The BEAT-ROP (Bevacizumab Eliminates the Angiogenic Threat of Retinopathy of Prematurity) study is an ongoing prospective, controlled, randomised, stratified, multicentre trial that was designed to assess intravitreal bevacizumab monotherapy for Zone I or Zone II posterior stage 3+ retinopathy of prematurity. Infants received either intravitreal bevacizumab (0.625mg in 0.025ml of solution) or conventional laser treatment should be considered for the treatment of vision-threatening ROP in zone I patients by the people doing this kind of work.

“Indeed, I think it is inappropriate not to at least explain this drug to parents. It is a game changer in Zone I cases – with life-long consequences to vision,” Dr Mintz-Hittner commented.

Written informed consent Because the use of bevacizumab as monotherapy for vision-threatening ROP is an off-label indication, it is essential to obtain written informed consent from the parent or guardian. Records must reflect that Avastin is not FDA approved for this patient group or this disease. Clinicians need to keep a patient log with the pharmacy source and log numbers recorded by trained personnel. The drug must be administered using a sterile technique by an ophthalmologist trained to give intravitreal injections specifically for ROP, she emphasised, adding: “This is not something to be undertaken lightly.”

Timing of bevacizumab is a critical component of the therapy. Given too early in phase 1, before 31 weeks post-menstrual age (in Stages 1 and 2), patients may develop a severe retinal dystrophy causing cessation of retinal development. Given too late, beyond phase 2, after 45 weeks’ post-menstrual age, the drug may cause severe, rapid contraction of the membranes, producing an accelerated retinal detachment. The surgeon must be prepared to do a vitrectomy if administering the drug when severe tractional elements are present (in Stages 4 and 5), she explained.

“When the drug is given at just the right time, in the phase 2 of the pathogenesis of ROP (best when Type 1-ETROP), it reduces venous dilatation, arterial tortuosity, and intravitreal neovascularisation, and allows continuation of the retinal avascularisation into the avascular retina.”

Dose is also very important. If too low a dose is administered, the result could be recurrence of intravitreal neovascularisation. Too high a dose will stop the growth of retinal vascularityisation into the avascular retina. Patients in the BEAT-ROP protocol received half the adult dose of bevacizumab, 0.625mg in 0.025ml of solution.

Some commentators raised the issue of mortality in the BEAT-ROP study. Seven patients died before reaching the primary outcome of the study, 54 weeks’ post-menstrual age. Five of these had received intravitreal bevacizumab, and two had undergone laser treatment.

“Mortality comes up in editorials. It seems that a lot of people can count a lot better than they can read. I want to point out that three of the Avastin patients had non-Avastin related deaths. One was a do not resuscitate (DNR), which we did not know at the time of enrollment. A few days into the study, the mother asked for the baby to be taken off the ventilator. Two other patients were the only ones who went home on oxygen. The parents discontinued the oxygen, turned off the monitors and left the room. I do not consider those drug-related deaths. That leaves two deaths in each treatment group,” she said.

No ocular complications were observed in the study or in animal models or in human case reports. Nonetheless, it is essential that clinicians be looking for immediate traumatic events including: lens rupture, lens dislocation, retinal tears, and retinal detachment. They should also be vigilant for cataracts, and endophthalmitis, she stressed.

More studies needed “Systemic toxicity associated with intravitreal bevacizumab has not been demonstrated in pre-term infants with ROP. Nonetheless, we must have additional prospective studies. We need to have one or more large prospective studies to investigate the potential effects of anti-VeGF agents on the brain, lung and kidney,” she said.

She also cited a need for better pharmacokinetic studies, including studies of human plasma samples for at least 10 weeks following injections, although these may not reflect tissue levels because of natural organ development (eg, blood brain barrier). Future large, randomised clinical trials should also look for efficacy in patients with ROP in zone II, as well as for toxicity. There is also a need for a registry for those patients not treated in the context of a clinical trial that would track immediate complications, recurrence, long-term toxicity (ocular or systemic), and drug-related mortality.