Serious adverse events and visual outcomes of rescue therapy using adjunct bevacizumab to laser and surgery for retinopathy of prematurity. The Indian Twin Cities Retinopathy of Prematurity Screening database Report number 5

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ABSTRACT

Aim To report serious adverse events and long-term outcomes of initial experience with intraocular bevacizumab in retinopathy of prematurity (ROP).

Methods Consecutive vascularly active ROP cases treated with bevacizumab, in addition to laser and surgery, were analysed retrospectively from a prospective computerised ROP database. Primary efficacy outcome was regression of new vessels. Secondary outcomes included the anatomic and visual status. Serious systemic and ocular adverse events were documented.

Results 24 ROP eyes in 13 babies, received single intraocular bevacizumab for severe stage 3 plus after failed laser (seven eyes), stage 4A plus (eight eyes), and stage 4B/5 plus (nine eyes). Drug was injected intravitreally in 23 eyes and intracamerally in one eye. New vessels regressed in all eyes. Vision salvage in 14 of 24 eyes and no serious neurodevelopmental abnormalities were noted up to 60 months (mean 30.7 months) follow-up. Complications included macular hole and retinal breaks causing rhegmatogenous retinal detachment (one eye); bilateral, progressive vascular attenuation, perivascular exudation and optic atrophy in one baby, and progression of detachment bilaterally to stage 5 in one baby with missed follow-up. One baby who received intracameral injection developed hepatic dysfunction. One eye of this baby also showed a large choroidal rupture.

Conclusions Though intraocular bevacizumab, along with laser and surgery salvaged vision in many otherwise progressive cases of ROP, vigilance and reporting of serious adverse events is essential for future rationalised use of the drug. We report one systemic and four ocular adverse events that require consideration in future use of the drug.

What is already known on this topic

- Bevacizumab, an antivascular endothelial growth factor agent, is a new treatment modality being reported for the treatment of vascularly active retinopathy of prematurity ROP in recent years.
- It may be beneficial in certain stages of the disease in half-adult dosages, though this is still under evaluation due to limited usage.
- Bevacizumab, as monotherapy and adjunctive therapy in relatively well-managed ROP babies seen in developed countries, are reported.

What this study adds

- Serious adverse events, especially systemic effects in preterm babies receiving bevacizumab, are not reported, and we report hepatic dysfunction for the first time.
- Serious ocular side effects on the choroidal tissue are reported only once earlier from Thailand, and we report the second case.
- The outcomes of adjunctive therapy in advanced, diverse and different spectrums of ROP that need management in developing countries have not been reported.

INTRODUCTION

Randomised controlled clinical trials[1 2] have established the role of retinal ablation, especially laser photocoagulation in eyes with vascularly active retinopathy of prematurity (ROP). However, even after laser treatment, some eyes fail to show adequate regression of pathology,[1–3] and are at high risk of progression to blindness. There are no definitive guidelines regarding management of such laser-failed cases or vascularly active retinal detachments (RD) that present late without being treated by laser photocoagulation, or having been treated with limited and inadequate laser.

The vascular activity in ROP is a complex phenomenon, and is contributed by numerous growth factors, the most important being the upregulation of vascular endothelial growth factor (VEGF) in the vitreous,[4] which leads to proliferation of new vessels, vitreous haemorrhage, tractional and exudative RD. Bevacizumab is an anti-VEGF agent being widely used as an off-label treatment over the last few years for adult vascular retinal disease. Published studies on intravitreal bevacizumab (IVB) in ROP have elucidated the efficacy and, rarely, complications of this treatment.[5 6] We started using

this off-label option from 2007 in selected cases. Data of all such cases were incorporated into our ongoing computerised prospective Indian Twin Cities ROP Screening (ITCROPS) database. The database was started in 1997 to assess the demography, risk factors and treatment outcomes of ROP,[3 7] and includes all babies screened and treated by the ROP team of the LV Prasad Eye Institute, Hyderabad, India. Institutional review board consent was taken for the ROP database analysis.

MATERIALS AND METHODS

From the prospectively collected ITCROPS database, data was retrieved and analysed retrospectively, of all babies who had received bevacizumab (Avastin, Genentech, South San Francisco, California, USA) for vascularly active ROP with or without associated RD. To understand our initial experience and visual and anatomic results, the study period of current data was from September 2007 to November 2009. During this period, a total of 1587 preterm babies were evaluated: 581 babies had ROP, 105 babies had laser and 40 babies underwent surgery with or without previous laser.

Based on the fundus drawings of indirect ophthalmoscopy, ROP was classified in all cases as per the international revised ROP classification.[8 9] Documentation with fundus photographs or video indirect ophthalmoscopy was done whenever possible (see online supplementary table S1). All babies were assessed, treated and followed-up as per our screening and treatment protocols[3 7 10 11] by either one of the two trained ROP retinal surgeons (SJ and RPK). All babies with ROP who had vascularly active disease, where there was none or limited option of additional laser ablation, were offered the option of the new treatment modality of off-label and non-standard use of intraocular bevacizumab (IOB) as a rescue therapy. The following parameters were used to offer injections: (1) non-regressed, defined as persistent or progressive new vessels with plus at two or more consecutive visits 1 week apart, in spite of additional and confluent laser treatment, including posterior to ridge if possible;(2) vascularly active RD associated with plus disease. This included eyes with advanced disease where no laser was possible, or eyes where only limited laser was possible that was not sufficient to cause regression of the plus and the new vessels. Injection was administered in preparation for subsequent surgery that was deemed necessary in view of the progressive nature of such detachments. Vitreoretinal surgery was scheduled within 1 week of the injection.

Outcome measures

Primary efficacy outcome was complete regression of the new vessels. This was ascertained as no additional ablative or surgical treatment was required for eyes with attached retina. In eyes with RD, where the injection was given in preparation for subsequent surgery, alternative definition of drug efficacy included regression of new vessels with absence of intraoperative and postoperative intraocular haemorrhage or exudative RD.

Secondary outcome measures included the anatomical and visual outcomes at last follow-up, and any ocular or systemic adverse events.

Visual acuity was tested using Teller acuity cards (TAC) at each visit by trained optometrists. Dilated cycloplegic refractions were conducted at each visit after the pathology was stabilised. Prescription glasses, amblyopia management and vision training were attended to in collaboration with in-house paediatric ophthalmologists and vision rehabilitation specialists, starting from 1 week, postoperatively, and at each subsequent visit as deemed necessary. Visual acuity outcomes were interpreted as within or outside the normal range, based on age-related norms. For easier understanding of the Teller acuity values of vision (that are dynamic and age specific), the visual outcomes were grouped as good (TAC within the normal range for that age); fair (outside the normal range for age but the child can definitely perceive some TAC) and poor (where the child cannot perceive any TAC, or large objects and vision is only light perception).

After complete regression, further follow-up was scheduled at 1, 3, 6 and 12 months and yearly, thereafter. Examination under short anaesthesia was done whenever needed, especially to monitor intraocular pressure in surgical cases. More frequent follow-ups were advised as needed. Since preterm babies are known to have neurodevelopmental problems, comprehensive care of such babies is part of our ROP management programme. All preterm babies who are likely to have moderate or severe vision deficits, or show signs of any other developmental problems are managed simultaneously by the primary neonatologist along with our team of the retina, paediatric and vision rehabilitation specialists at each visit in our comprehensive 'Children's Eye Care Centre'. This often starts preoperatively and almost always from 1 week, postsurgery, in all surgical cases. Appropriate referrals, as needed with other related specialists, are carried out as part of the comprehensive management.

SERIOUS ADVERSE EVENTS

Babies underwent detailed comprehensive ocular and systemic evaluation by the ophthalmologists (SJ/RPK) and the primary neonatologist, and by other specialists as needed, at each visit during the period of follow-up. Any serious ocular, systemic or developmental adverse event was recorded and managed as appropriate. Neurodevelopment screening was most commonly, but not uniformly, done using the Denver Development Screening Test by the neonatologists and the in-house vision rehabilitation specialists. Any specific abnormalities reported were entered in our database, and appropriate management instituted by the concerned specialists.

RESULTS

Complete patient details are provided in online supplementary table S1. Twenty-four eyes of 13 babies received IOB after informed consent of one parent. Stage of disease included severe stage 3 plus after failed laser for zone I ROP in 7 eyes, 4A plus in 8 eyes and 4B/ 5 plus in 9 eyes. Birth weight ranged from 780 to 1600 g, and gestational age at birth ranged from 27 to 33 weeks. Postconceptional age at time of injection was 34–42 weeks. Twenty-four eyes had laser done at less than 1–4 weeks before the injection. In two eyes, there was no scope for preinjection laser due to advanced RD at presentation. Fellow eyes of two uniocularly treated eyes (see online supplementary table S1, eyes 9 and 24) responded to laser alone, and did not need any additional treatment.

All injections were administered in the operating room with standard aseptic precautions by a single surgeon (SJ). General anaesthesia was used in the first four babies, while all subsequent babies received topical anaesthesia alone. Drug was injected intravitreally, 1.0 mm from limbus with a 29 G needle, in a lens-sparing vertical orientation in 23 eyes. One baby with RD extending to the retrolental space in one eye received, simultaneously, an intracameral injection (injection in anterior chamber) in this eye and intravitreal in the other eye. Dosage ranged from 0.75 mg in 0.03 ml in initial eight eyes of four babies to 0.63 mg in 0.025 ml (half an adult dose) in subsequent eyes, based on the ongoing literature reports being published at

that time. The first four babies also had paracentesis done, but this was deemed unnecessary in subsequent cases that were managed with reduced drug volume and mild ocular compression before and after the injection. Postinjection, all babies received topical tobramycin eye drops four times a day for 5 days.

Primary efficacy outcome

New vessels regressed in all 24 eyes within a week of the injection, and no eye needed additional injections or laser for new vessels.

Secondary efficacy outcomes

Seven eyes needed no further intervention and had complete regression, attached retina and vision salvage with no recurrence of new vessels (figure 1a,b and table 1). Fifteen eyes underwent the previously planned vitreous surgery. None of these eyes developed intraoperative or postoperative bleeding. Vision could be salvaged in 14 of 24 eyes that were at risk of total blindness, ranging from 20/2700 to 20/130 on TAC. In eight eyes, vision could not be restored due to failure to reattach or operate a progressive stage 5 RD. Two eyes had anatomical success with reattachment of retina, but loss of vision due to perivascular exudation and subsequent arterial narrowing with progressive optic atrophy. Except for these two eyes, in none of the other anatomically successful cases did we see any obvious adverse effects on the physiological vessels. Follow-up ranged from 12 to 60 months (mean 30.7 months).

Ocular adverse events

- Retinal breaks. One eye in stage 4B developed a large macular hole and a nasal retinal break leading to additional rhegmatogenous component noted at 1 week postinjection (figure 2 and table 2). This appeared to be due to the rapid contraction and traction of the regressing new vessels within the fibrovascular membranes.
- Two eyes of one baby who received 0.75 mg dose, showed vascular attenuation with subretinal perivascular exudates (figure 3a,b) following surgical reattachment for stage 5 detachments. Both eyes progressed to severe vascular attenuation, resolution of the perivascular exudation, optic atrophy and retinal degeneration with poor visual status after 2 years.(figure 3c,d)
- Retinal pigment epithelial (RPE)/choroidal rupture: On photographic review of fundus images, one eye was seen to have a linear RPE/choroidal rupture defect (figure 4).
- Disease progression. In two eyes of one patient, the detachment increased from stage 4A to inoperable stage 5 when the child failed to return on time for the planned surgery. It was difficult to ascertain whether this was due to the natural course of the advanced stage 4A plus at presentation, or there was any acceleration of the cicatricial process due to adverse effect of the drug.

Table 1 Interventions and anatomic outcomes of intraocular bevacizumab in retinopathy of prematurity

Stage	Eyes (n)	Laser/past laser	Surgery	Anatomic success	Anatomic failure
3 plus	7	7	0	7	0
4A plus	8	8	6	5	3*
4B/5 plus	9	7	9	4	5
Total	24	22	15	16	8

*Includes two eyes that were not operated as they progressed, because the child did not return for scheduled follow-up for surgery, and one eye with macular hole.

Systemic adverse event

Hepatic dysfunction of raised liver enzymes developed in one 3-month-old baby (see online supplementary table S1). The adverse event was detected 10 days after injection under topical anaesthesia, during routine preoperative laboratory investigations. Total bilirubin was normal (0.7 mg/dl; direct bilirubin to indirect bilirubin ratio (DB:IB) was 0.1 mg/dl:0.6 mg/dl) with no clinical jaundice, negative viral hepatitis antigens and normal hepatobiliary ultrasonography. Liver enzymes were raised more than five times the normal as compared with age-matched values: SGOT 236 U/l, SGPT 199 U/l, alkaline phosphatase 1662 U/l. This baby had received medication intracamerally in one eye and intravitreally in the other eye. The liver enzymes returned to normal for the baby's age in 3 weeks.

Systemic status

In 12 of the 13 babies, till the last follow-up (12–60 months), no obvious gross structural or functional abnormality of other organ systems was reported. One baby with history of birth hypoxia had hypoxic ischaemic encephalopathy manifesting clinically as mild increased spasticity of the lower limbs, and showing few areas of periventricular leukomalacia on brain scanning. The delayed motor development milestones were under treatment of a physical medicine specialist. Two blind babies were noted to have eye-poking behaviour.

DISCUSSION

Our initial experience with adjunctive IOB as a rescue therapy has been encouraging in that it was able to reduce the vascular activity and help in vision salvage in a number of eyes that could otherwise have progressed. However, few adverse events were encountered that needed consideration and vigilance as we

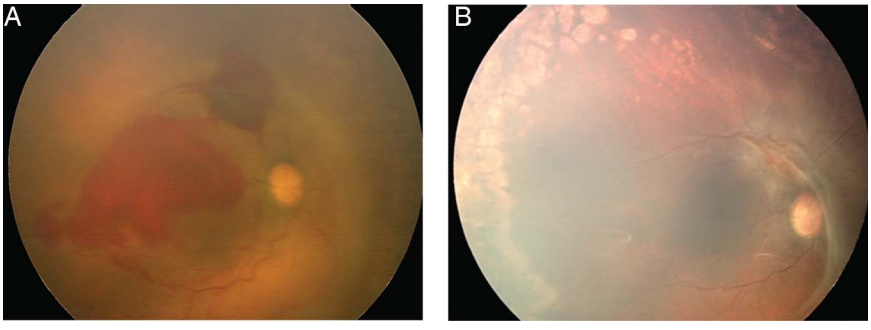

Figure 1 (a) Fundus photograph showing plus disease, premacular hemorrhage and active fibrovascular proliferation along upper temporal vessels in spite of multiple laser sessions. (b) shows complete regression with residual gliosis and normal-looking macula, 2 weeks after intravitreal bevacizumab.

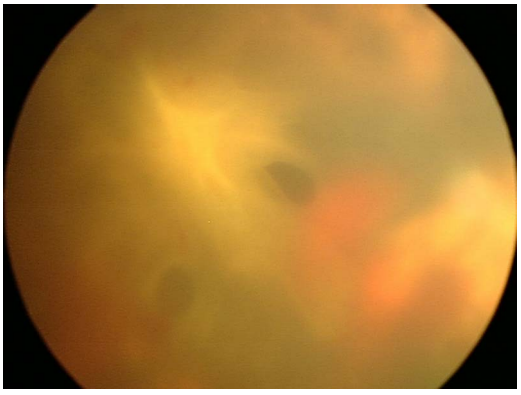

Figure 2 Fundus photograph showing macular hole and an additional nasal retinal break after intravitreal bevacizumab for plus disease with tractional retinal detachment and vitreous haemorrhage in untreated retinopathy of prematurity.

improve our knowledge and experience with this new modality of treatment in ROP. As VEGF is a prominent factor in ROP pathogenesis, use of anti-VEGF drugs, like IOB, would be a logical management option. Systematic analysis of reports of early experiences[5] showed that the drug caused rapid regression of new vessels and helped in treatment of severe disease states, like zone 1 ROP and vascularly active ROP RDs as an adjunct to laser/surgery. The early reports did not show any major ocular adverse events except worsening of pre-existing traction on retina,[5] because the drug acts only on the vascular component and not on the biomechanical vitreous and fibrotic/gliotic component that causes RDs.[5 12] In recent years, numerous articles are being published on the use of bevacizumab in ROP that seems to have gained rapid popularity in treatment of vascularly active ROP. An excellent review article by Mintz-Hittner *et al*[12] provides detailed information regarding the problems with the current standard of care, that is, laser treatment in ROP, the role of VEGF in ROP pathogenesis, effect of IOB on retinal tissues on immunohistopathology, role of IOB as monotherpy or rescue therapy in various stages of ROP, and effects of bevacizumab on the developing ocular vasculature and tractional status of the vitreous. While the new vessels as seen in ROP show regression with IOB in most studies, questions about safety, dosage, timing, indications, recurrences and effects of anti-VEGF drugs on a developing immature ocular and systemic vasculature have been areas of concern in the literature. Our preliminary experience data shows that the primary efficacy outcome of regression of new vessels and plus disease was achieved in all 24 eyes. Both, 0.75 mg and 0.63 mg doses given bilaterally, worked well. Some reports recommend IOB as a monotherapy for aggressive posterior ROP,[6 12 13] but caution about late recurrence of new vessels in up to 6% eyes,[12] and also progressive RDs with late recurrences.[14] We did not see any early or late recurrences possibly due to use of simultaneous laser ablation or the subsequent surgical intervention. The smallest baby treated in our rescue therapy series was 34 weeks postconceptional age, and 1800 g at time of injection. These parameters will reduce if we use IOB as the primary treatment, and may raise more concerns regarding ocular and systemic safety and dosage.

The visual and anatomical outcomes in 12 eyes of compliant patients, with stages 3 and 4A plus disease were good (see online supplementary table S1). The visual outcome, as expected in stage 4B/5 was poor,[15 16] but ambulatory vision could be salvaged in 2/9 eyes, and this was encouraging. Previous reports on bevacizumab have not reported visual or developmental outcomes. None of our patients showed any other organ system abnormality over the short follow-up of 12–60 months. However, our data on neurodevelopment status is not presented, as it is limited due to very small sample size, retrospective retrieval, developmental screening done individually by each treating neonatologist and by our rehabilitation specialists, and the need for longer follow-up data with uniform developmental assessment protocols done at a specific age.

Table 2 Details of babies who had serious adverse events after adjunctive bevacizumab therapy

S. no. of the eye	Eye	Zone*	Stage	PCA at first visit	GA	BW	PCA at laser (weeks)	PCA at surgery (weeks)	PCA at Avastin (weeks)	Days after laser	Visual outcome*	Final teller visual acuity*	Follow-up (months)	Remarks/ complications
3	OD	Open	5+	40	28	1030	35	42	41	30	Poor	PL and follow light	36	Arterial attenuation, exudation, attached retina
4	OS	Open	5+	40	28	1030	35	42	41	30	Poor	PL and follow light	36	Arterial attenuation, exudation, attached retina
5	OD	Open	5+VH	39	29	1500	No laser	40	39	NA	Fair	20/960	32	Elevated liver enzymes, choroidal/ RPE rupture, attached retina
14	OD	II	4A+	39	33	1600	39		39	5	Poor	PL	17	Did not return for timely surgery, no surgery
15	OS	II	4A+	39	33	1600	39		39	5	Poor	PL	17	Did not return for timely surgery, no surgery
17	OS	I	4A+, APROP	39	30	1100	39	46	42	14	Poor	PL	60	Macular and tractional hole, rhegmatogenous detachment

*'Open' refers to stage 5 detachment configuration as 'open funnel'.
APROP, aggressive posterior ROP; BW, birth weight; GA, gestational age; OD, right eye; OS, left eye; PCA, post conceptional age; PL, perception of light only; RPE, retinal pigment epithelial; ROP, retinopathy of prematurity; S. no., serial number. Eyes 3, 4 and 14, 15 are bilateral in same babies.

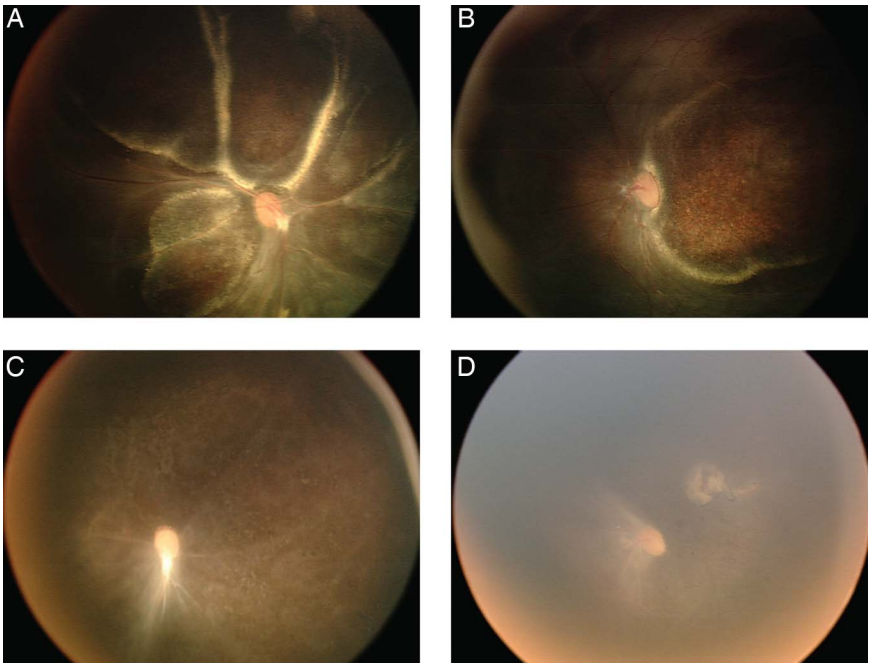

Figure 3 Fundus photographs showing postoperative perivascular subretinal exudates but with perfused retina and optic discs 3 months after retinal reattachment surgery in (a) right eye and (b) left eye after bilateral intravitreal bevacizumab preoperatively; (c) and (d) same eyes at 2 years postoperative. Note the severely increased vascular attenuation, resolution of exudates and advanced disc pallor at this stage.

Very few reports mention adverse events, possibly due to retrospective studies, small samples or failure to carry out comprehensive evaluations. Due to well-defined ongoing protocols, we could prospectively assess and record adverse events in our cases. One baby showed arterial narrowing, perivascular exudates and progressive disc pallor in both eyes. It was difficult to attribute this precisely to disease, the injection procedure or toxicity to the drug. Over the follow-up, the exudates regressed, but there was progressive disc pallor and increasing arterial attenuation with poor vision. Transient bilateral retinal vascular sheathing was reported recently from Taiwan.[17] Systemic bevacizumab has been reported to cause Reversible Posterior Leukoencephalopathy Syndrome (RPLS) in 0.1% of clinical cases. RPLS[18] is a rare brain capillary leak syndrome associated with hypertension, fluid retention and cytotoxic effects of immunosuppressive drugs on vascular endothelium. This complication was noted from less than 1 month up to 12months postsystemic injections. The perivascular leakage in our case could be a cytotoxic effect of bevacizumab on the retinal capillaries. On the other hand, subretinal exudation and arterial narrowing could be a consequence of a reattached exudative component in the ROP detachment which is not uncommonly seen in ROP. However, absence of any exudative detachment, preoperatively, and the limited distribution of the exudates to perivascular region and not all over the fundus makes the second reason less plausible than the first one. After retinal reattachment (figure 3c,d), the progressive loss of vascularity and increasing disc pallor over the next 2 years is inexplicable to us. Our patient did not have any other systemic and especially central nervous system signs or symptoms, and did not have any neurodevelopmental issues so far. Except for this case, in none of the other anatomically successful cases did we see any obvious adverse effects on the physiological vessels. As VEGF is needed for normal angiogenesis, a delayed vascularisation has been noted in other studies using bevacizumab as a monotherapy,[6 12–14] but due to simultaneous laser and surgery, such an event was not noted in our few cases.

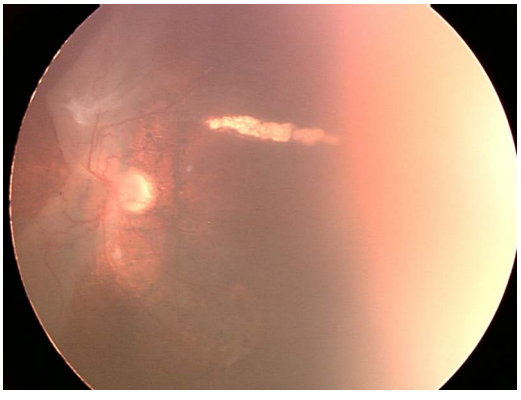

Figure 4 Fundus photograph showing linear retinal pigment epithelial/choroidal rupture after retinal reattachment following intravitreal bevacizumab preoperatively.

One baby developed retinal breaks including macular hole. Similar cases have been reported in adults and are postulated to be due to rapid contraction of a vascularly active fibrovascular frond or, alternatively, due to acute posterior vitreous detachment resulting from 'forceful' injections.[19] This is a serious adverse event because retinal breaks in ROP converts an operable tractional detachment to an inoperable and blinding rhegmatogenous RD. The injection must be administered slowly, so as to reduce the chance of such an adverse event. We inject all drugs very slowly as part of our protocol, not only to avoid acute vitreous disturbance but also to prevent acute rise of intraocular pressure. In spite of a slow injection, macular hole or other tractional tears can occur, as seen in our case, possibly due to increased vitreous contraction from rapidly regressing fibrovascular tissues. Two eyes of another baby with delayed follow-up in stage 4A progressed to stage 5. Sometimes, due to systemic comorbidities, babies may be unfit for general anaesthesia for the scheduled surgery 3–7 days postinjection, and this delay can result in progressive traction and fibrotic reaction. Increased traction has been reported in adults and in ROP, postulated to be due to a rapid regression and contraction of active fibrovascular fronds, especially when there is some pre-existing

traction.[20 21] It is understood that anti-VEGF drugs can only regress the vascular component of ROP, while the fibrovascular component does not have VEGF-related growth and, hence, this tractional component can be ongoing and indeed gets aggravated due to rapid regression of vasculature within the fibrovascular component.[12 20 21]It was difficult for us to assess this as attributable to drug or the natural course of the advanced disease in our case, and was possibly due to both factors. However, based on our experience in this series, we subsequently modified our protocol and now consider the alternative of giving intravitreal bevacizumab intraoperatively at end of the surgery rather than preoperatively, whenever we think there is a possibility of increased traction in eyes with significant preexisting traction.

Bilateral choroidal ruptures in ROP after intravitreal bevacizumab have recently been reported.[22] The adverse effects of anti-VEGF on choroidal vascular development have been postulated because VEGF is also needed for the developing choroid.[22] So far, most of the ROP basic science and clinical literature have not evaluated the choroidal vascular development, but have mainly reported on the retinal vascular development. Choroidal vascular development in preterm babies and the in vitro effects of anti-VEGF drugs on the developing choroid need to be studied in detail to understand such side effects. We did not observe this side effect, but after reading the publication, we reviewed all our retinal photographs of IOB eyes and detected RPE/choroidal rupture in one eye (figure 4). Fortunately, it was not in the macular area. This emphasises the need for constant vigil, documentation and reporting of adverse events.

We are highly concerned about the raised liver enzymes in one baby who received intracameral bevacizumab at 3 months of age, when physiological derangement is not expected. Currently, a causative relation in our patient has not been confirmed by our observation. Liver enzyme derangements have been reported in cancer patients receiving systemic bevacizumab.[23] Raised liver enzymes are attributed to acute hepatic injury either directly by drug itself or due to an indirect ischaemic insult from altered vascularity after anti-VEGF treatment. Another report has attributed monoclonal antibodies to be causative of postinjection hepatic toxicity. The very little knowledge about the pharmacokinetics and systemic safety of bevacizumab has been critically summarised in an excellent review by Hard A *et al*.[24] The drug has a large molecule, and is known to enter the systemic circulation when injected intravitreally.[24] It is possible that systemic toxicity would be more if the drug is injected in the anterior chamber, (intracamerally) as in our case, and could have more access to systemic circulation due to rapid egress as there is no blood-retinal barrier.[24] None of the ROP-IOB studies included liver enzymes in their monitoring protocols, and so, exact incidence of this complication in ROP babies remains unknown. A prematurely born infant receiving anti-VEGF drugs is at a stage when growth and differentiation are intense, and numerous other organs have been shown to have significant VEGF expression. These include kidney, lung, brain and so on, where VEGF has angiogenic and neuroprotective effects. Any derangements in these organs at this critical stage of development could have long-lasting effects that may not be evident in the short follow-ups of these babies so far.[24]

We would like to highlight that our series of cases deals with advanced ROP, often presenting late. While ideally we would like all preterm babies to be screened and managed early, and have been working hard over the last decade in our twin cities and in our country to achieve this goal,[3 7 10 11] lack of awareness, resources and manpower in many geographic areas lead us to a diverse, different and difficult spectrum of ROP that needs management in developing countries. Bevacizumab, as an adjunct, has provided an additional armentarium to the ROP surgeon to tackle these difficult cases. However, since this is a new drug, it is imperative to use it judiciously and monitor the babies closely, and report the good and the adverse outcomes.[24 25]

CONCLUSIONS

Though uniocular or binocular IOB used as an adjunct therapy to laser and surgery, at half adult dose, was able to rescue vision in many otherwise progressive or advanced selected cases of ROP, continued vigilance and reporting of any serious adverse events is essential for improving the future rationalised use of the drug. Informed consent and monitoring for any other ocular or systemic side effects, including liver enzymes, is needed. This may be especially critical if the injection is used much earlier in the course of the disease as a monotherapy, when babies will be of lesser weight and postconceptional age with more immature retinal, choroidal and systemic development, and high levels of circulating VEGF. We report one systemic and four ocular adverse events after bevacizumab that require considerations in future use of the drug. We also believe that more basic science studies are required to get more information on the effect of bevacizumab on developing tissues of prematurely born infants.

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Competing interests None.

Ethics approval Institutional review board of L V Prasad Eye Institute.

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Data sharing statement The ROP database is maintained at the L V Prasad Eye Institute, and access is through the corresponding author only.

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