CASE REPORT

Smouldering retinopathy of prematurity: a case treated by multiple antivascular endothelial growth factor therapy

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Accepted 13 August 2016

SUMMARY

A 13 months old female baby born at 24 weeks of gestational age (GA) presented with stage 4A retinopathy of prematurity (ROP) with plus disease in the right eye and stage 3 with plus disease in the left eye. The baby was diagnosed with stage 3 zone 2 ROP in both eyes with plus disease at 32 weeks of GA and received intravitreal bevacizumab in both eyes. The baby received intravitreal bevacizumab and ranibizumab injections at 39 and 57 weeks of postmenstrual age (PMA), respectively for recurrence. Laser treatment to peripheral avascular retina was carried out at 67 weeks of PMA. The right eye progressed to stage 4A and left eye developed pre-retinal haemorrhages. This case reports late recurrence treated with initial multiple antivascular endothelial growth factor (VEGF) injections alone. One should be cautious in using anti-VEGF agents as a monotherapy in cases of ROP that appear different from the current understanding of the natural course of the disease.

BACKGROUND

Antivascular endothelial growth factor (anti-VEGF) drugs have been used recently in the treatment for retinopathy of prematurity (ROP). There are various studies reporting the usefulness of this drug in regression of disease and vascularisation of retina thus preserving the field of vision which otherwise would be restricted by laser treatment. The major concerns with anti-VEGF injections are the systemic safety issues in preterm babies and the right dosage and timing of injection. The other ocular side effects noticed were the late recurrence and thus the need for long-term follow-up in such babies. This case reports a late recurrence in a baby who was treated with multiple anti-VEGF injections and raises the question on use of multiple injections of anti-VEGF drugs for ROP and to create awareness of its rational use in the treatment of ROP.

CASE PRESENTATION

A female baby with gestational age of 24 weeks and birth weight of 745 g presented to us at postmenstrual age (PMA) of 83 weeks. The baby had respiratory distress syndrome and hyberbilirubinaemia. She had received surfactant injection, oxygen therapy and was admitted in neonatal intensive care unit for 47 days. The baby had stage 3 zone 2 posterior ROP with plus disease in both eyes at 32 weeks of PMA and received intravitreal bevacizumab at 32 weeks of PMA. The baby was under regular follow-up at intervals of 1–2 weeks. The

baby was given repeated intravitreal bevacizumab (while patient was in the neonatal intensive care unit) and ranibizumab (after discharge from hospital) injections at 39 and 57 weeks of PMA, respectively, for recurrence of plus disease (different anti-VEGFs were used as per the medical insurance rules). The child received peripheral laser treatment at 67 weeks of PMA, as the peripheral retina was not getting vascularised. Despite the treatment with anti-VEGF injections and laser, the ROP recurred and progressed to stage 4 A ROP with disc drag and signs of mild plus (dilation and tortuosity of retinal vessels) in the right eye (figure 1) and localised preretinal haemorrhage in the inferotemporal quadrant with plus disease (dilation and tortuosity of retinal vessels) in the left eye. The fundus showed peripheral laser marks and a small strip of posterior avascular unlasered retina in both eyes. The child underwent lens sparing vitrectomy and additional laser in the right eye and only additional laser treatment of avascular retina in the left eye. At 90 weeks of PMA, the right eye showed signs of regression with no traction on the ridge (figure 2A) and reduced plus disease and the preretinal haemorrhages were resolving in the left eye with no plus disease (figure 2B).

TREATMENT

The child underwent lens sparing vitrectomy and additional laser treatment in the right eye and only additional laser treatment of avascular retina in the left eye.

Figure 1 Stage 4A ROP: fundus photo of the right eye showing tortuous vessels from disc, dragging of vessels and tractional retinal detachment temporally. ROP, retinopathy of prematurity.

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To cite: Balakrishnan D, Ambiya V, Jalali S, et al. *BMJ Case Rep* Published online: [please include Day Month Year] doi:10.1136/bcr-2016-216056

Figure 2 (A) Regressing stage 4A ROP after lens sparing vitrectomy: right eye fundus picture showing regressing ridge with reduced vessel tortuosity, minimal vessel drag and no traction on the ridge. (B) Left eye fundus showing resolving preretinal haemorrhage, laser marks and reduced vessel tortuosity. ROP, retinopathy of prematurity.

OUTCOME AND FOLLOW-UP

At 90 weeks of PMA, the right eye showed signs of regression with no traction on the ridge (figure 2A) and reduced plus disease and the preretinal haemorrhages were resolving in the left eye with no plus disease (figure 2B).

DISCUSSION

ROP is a multifactorial disease. The various factors that are known to be involved are VEGF, IGF1, erythropoietin etc.¹⁻⁴ Laser photocoagulation has been the treatment for ROP, but intravitreal anti-VEGFs are being increasingly used in the treatment of zone 1 and 2, type 1 ROP in recent years. Various studies and case reports have shown its beneficial role in the treatment of ROP.⁵⁻⁶ Even though initial studies on anti-VEGF in ROP were with bevacizumab, later studies have compared it with ranibizumab. Both the drugs were found to be effective, but bevacizumab was shown to be associated with more systemic side effects while recurrence was noted to be more with ranibizumab in one study.⁷⁻⁸ This could be because of the shorter systemic half-life of ranibizumab (2 hours) when compared with bevacizumab (20 days).⁷ The timing and dose of anti-VEGF injections are important to get the maximum benefits with fewer side effects. This is explained by the proposed pathogenesis of ROP, where abnormally high levels of VEGF in second hypoxic phase leads to abnormal proliferative phase of

ROP.¹⁻⁹ The use of anti-VEGFs cause regression of ROP, but multiple injections may hinder peripheral retinal vessel development, persistent peripheral avascular retina and recurrent intravitreal neovascularisation.¹⁰ The progression in the right eye to stage 4A and development of preretinal haemorrhage from NVE in left eye in the present case could be due to multiple anti-VEGF injections, avascular retina and delayed inadequate laser treatment at 67 weeks of PMA. However, there are cases where timely complete laser treatment immediately following anti-VEGF has also shown late recurrence.¹¹ The recurrence in one of the studies has shown to occur in the previously regressed ridge.¹²⁻¹³ Other factors like placental growth factors were found to be upregulated in hypoxia-induced retinopathy treated with anti-VEGF therapy.¹⁴ The levels of erythropoietin were found to be high in highly active ROP with high levels of VEGF suggesting its role in the pathogenesis of ROP.²

As mentioned in the report by Chen *et al*, the minimal increase in tortuosity of vessels after anti-VEGF injection should be taken as a sign of early recurrence and warrants to look for any skip areas of laser treatment that need to be added. It is important to perform confluent laser photocoagulation from the ridge to ora serrata without any skip areas. We found 84% favourable anatomical success when a strict protocol of timely screening (preterm babies with GA ≤ 35 weeks and birth weight ≤ 2000 g are screened by 30 days of life) and correct technique of confluent laser photocoagulation within 72 hours of diagnosis was carried out for zone 1 ROP.¹⁵ A study by Wu *et al*¹⁶ reported 89% regression of stage 3 ROP with bevacizumab monotherapy; 11% required rescue laser therapy at 2–3 weeks post injection in cases that did not show signs of regression. The present case points to the fact that multiple anti-VEGF injections without timely rescue laser therapy may become detrimental in some cases. The untimely use of anti-VEGF can cause fibrosis and tractional retinal detachment. The timing and indication of additional laser therapy in those babies who get recurrent ROP or persistent ROP need to be defined. The other systemic factors like reduced weight gain, anaemia and respiratory infections that are known to aggravate the ROP also need to be monitored.

Both eyes eventually regressed and were stable on follow-up, left eye stabilised with additional laser treatment to the avascular retina. This again highlights the need for additional laser treatment to avascular retina at any time of recurring ROP or non-regressing ROP.

To conclude, caution should be exercised in using anti-VEGF monotherapy in cases of ROP that appear to be different from the current understanding of the natural history. Long term and frequent follow-ups are needed for babies who received anti-VEGF injections. Timely adequate rescue laser therapy is to be considered in those preterm babies with signs of early recurrence of ROP following anti-VEGF treatment.

Learning points

- ▶ Antivascular endothelial growth factor (VEGF) injection should be used judiciously in cases of retinopathy of prematurity (ROP).
- ▶ Untimely injection can cause tractional retinal detachment.
- ▶ Laser treatment is to be considered if retina remains avascular or at early signs of recurrence of ROP than repeating anti-VEGF injections.
- ▶ Long-term follow-up is needed for babies who received anti-VEGF injections in view of late recurrences.

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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