**Review**

**Off-label use of intravitreal bevacizumab for severe retinopathy of prematurity**

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**ABSTRACT**

Objectives: To examine the quality of evidence and the variability in the off-label use of intravitreal bevacizumab for retinopathy of prematurity (ROP).

Methods: A wide review of the literature was performed using Pubmed, Medline, and Cochrane database, using the words vascular endothelial growth factor (VEGF), retinopathy of prematurity, treatment and bevacizumab.

Results: Case reports, case series, reviews, one systematic review and one randomized controlled trial were found on the use of intravitreal bevacizumab in severe ROP, as monotherapy or combined with laser and/or vitrectomy.

Conclusions: The results shown on the use of intravitreal bevacizumab in ROP stage 3+ in zone I or in aggressive posterior ROP are promising. However, uncertainty remains regarding its maximum tolerable dose in the neonatal group, its ocular and systemic safety profile, or its efficacy and bioactivity in a developing child. This report found no significant differences in the recurrence rates of ROP stage 3+ in zone II in patients treated with intravitreal bevacizumab monotherapy in comparison to laser, although the latter is the best option due to long-term safety and efficacy. The use of intravitreal bevacizumab is not indicated in stages 1 and 2 of ROP as the risk of severe visual loss is low and VEGF is necessary for normal retinal vessel development. On the other hand, the use of intravitreal bevacizumab would be contraindicated in stages 4 and 5 because the retinal detachment is accelerated.

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**Uso off-label de bevacizumab intravítreo en retinopatía del prematuro severa**

**RESUMEN**

**Palabras clave:** Bevacizumab, Retinopatía del prematuro, VEGF, Anti-VEGF, Tratamiento

Objetivo: Examinar la calidad de la evidencia y variabilidad en el uso off-label de bevacizumab intravítreo en retinopatía del prematuro (ROP).

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Introduction

Retinopathy of prematurity (ROP) is a progressive vasoproliferative disease that continues to be the main cause of severe visual impairment in children throughout the world due to traction of the macula or retina detachment.\(^1,2\) ROP incidence has increased globally due to significant developments in the care of low weight premature babies. A recent review on ROP incidence\(^3\) concluded that the incidence of entire ROP was of 60% in infants under 1500 g of weight in developed countries. The majority of ROP cases resolve spontaneously, but severe cases require treatment for preventing blindness. Higher numbers of prematures also survive in developing countries but even so the increased incidence of blindness due to ROP originates in late indication of adequate treatment.

To date, several encouraging studies have been published on the off-label use of intravitreal bevacizumab in newborns with severe ROP to\(^4-15\) after basic sciences involved the vascular endothelial growth factor (VEGF) in the pathogenicity of the disease\(^16-20\) and its successful use in proliferative diabetic retinopathy\(^21\) and age-related macular degeneration.\(^22\)

Accordingly, the application of intravitreal bevacizumab in ROP has been carried out as monotherapy\(^23-27\) or as a supplement for laser treatment or surgical procedures.\(^28,29\) However, there is a significant controversy about said applications.\(^30\)

The objective of the present study is to review, analyze and summarize clinical studies on the use of intravitreal bevacizumab for treating severe ROP in order to find the best evidence.

Materials and methods

A broad search was carried out in Pubmed, the Cochrane database and Medline utilizing the following keywords or combinations thereof: vascular endothelial growth factor (VEGF), retinopathy of prematurity, treatment and bevacizumab.

Results

Published case reports have been found as well as a retrospective studies, prospective case series, reviews, one systematic review and a controlled and randomized clinical trial on retinopathy of prematurity with ROP stages 1, 3, 4 and 5 treated with intravitreal bevacizumab as monotherapy or combined with laser or vitrectomy.

Discussion

Angiogenesis factors and pathogenicity of retinopathy of prematurity

The pathological process in ROP comprises 2 stages: the first, induced by oxygen, involves vasoconstriction and vascular obliteration.\(^31\) It takes place between postmenstrual weeks 22 and 30. In the second stage which is hypoxic, the non-perfused retina produces angiogenic factors which give rise to the development of neovessels, from postmenstrual weeks 31–44.\(^32\)

VEGF is an angiogenic cytokine which is crucial in both stages. In a normally developing retina, this factor is released in response to the oxygen demand by the neuroretina, which promotes the development of normal vessels toward the periphery. In the first stage, due to the relative hypoxia compared to the intrauterine hypoxia, VEGF levels diminish whereas in the second stage hypoxia increases the VEGF levels causing the development of neovessels from the retina toward the vitreous with fibrovascular proliferation.\(^33,34\)
In most of the severe ROP forms, vascular changes include abnormal dilatation and tortuosity of retinal vessels, which is the mark of the plus disease. The severity of the plus disease increases with time and could be correlated to endothelial cell proliferation.

**Bevacizumab**

Bevacizumab is a complete 149 kD monoclonal antibody which joins VEGF and prevents it from joining its receptor. Intravitreal injection of anti-VEGF molecules has demonstrated a significant reduction of neovascular activity in animal models. In 2004, the Food and Drug Administration approved the use of intravenous bevacizumab for treating colorectal cancer with metastasis. The drug reduces the size and number of metastasis neovessels. Bevacizumab was also used, although without approval, for treating age-related macular degeneration, proliferative diabetic retinopathy and severe retinopathy of prematurity.

Some issues on the use of intravitreal bevacizumab in severe ROP are yet unsolved, including systemic effects, dosage, frequency, adequate administration time and adjuvant therapies. Considerable blood relations were found in the literature on these issues.

**Efficacy of intravitreal bevacizumab in retinopathy of prematurity**

Posterior aggressive ROP is characterized by its severity, by being located in posterior zone I or II and by its rapid progression. The Early Treatment for ROP (ETROP) study proposed laser treatment although subsequent results were poor because, as reported in several clinical trials, the recurrence rate is higher.

Mintz-Hittner et al. of the Bevacizumab Eliminates the Angiogenic Threat of Retinopathy of Prematurity cooperative group (BEA T-ROP) carried out a prospective, controlled, multicenter and randomized study to assess the efficacy of intravitreal bevacizumab as monotherapy for treating ROP stage III in zones I and II with plus. Overall, 50 children were randomized and assigned conventional laser or bilateral intravitreal bevacizumab (0.625 mg in 0.025 ml solution). The result being controlled was ROP recurrence in one or both eyes requiring treatment before week 54 of postmenstrual age. They reached the conclusion that, compared to conventional laser, intravitreal bevacizumab monotherapy in children with ROP 3+ exhibited significant benefits in zone I but not in zone II. The recurrence rate for the former was 42% for laser and 6% for bevacizumab. Zone II did not exhibit significant differences. Vessel development toward the periphery continued after intravitreal bevacizumab injection but not after laser treatment. Said authors admitted that the study is too small to ensure safety and reported that they did not observe systemic or local effects attributable to the intravitreal bevacizumab injection, although the follow-up time was short.

Even though numerous authors have published their experience with intravitreal bevacizumab, at the time of writing this study the authors found only one controlled and randomized clinical trial, carried out by BEA T-ROP. Even though one paper was published reporting the use of intravitreal bevacizumab in ROP stage I, numerous authors have reported that if intravitreal bevacizumab is indicated at a very early stage it would interfere with normal vascularization development.

When bevacizumab is administered at later stages such as 4 and 5, membrane contraction is accelerated rapidly causing retina detachment.

Xu et al. recommend intravitreal trail bevacizumab injection prior to vitrectomy as it effectively reduces neovascular activity in ROP stage 4 and facilitates pars plicata vitrectomy.

**Adverse effects and long-term complications**

It is well proven that intravitreal bevacizumab reaches systemic circulation and remains in blood over 8 weeks. A study reported that, after the first intravitreal injection, VEGF in circulation diminishes over 42%. It is important to emphasize that, in contrast with adults, premature babies have normal angiogenesis, which is crucial for organ genesis, osteogenesis and central nervous system development. Angiogenesis during embryo growth and development requires VEGF as its absence leads to tissue death. Accordingly, possible adverse effects must be considered in VEGF-dependent developing organs such as kidneys, brain, lungs and others.

Postnatal VEGF blockage causes growth inhibition and increases mortality due to kidney failure as well as dete-
riorations in organ development whereas experimental blockage in young primates produces ovary failure and halting of growth due to alterations in the epiphysis growth plate chondrocytes. Increased risk of arterial hypertension and thrombembotic events have been reported with the use of intravitreal bevacizumab including myocardial infarct and cerebrovascular accidents.

The BEA T-ROP group did not observe any ocular or systemic collateral effects although they admitted the study was too small to address safety-related issues.

Numerous ocular complication case reports have been published involving choroidal ischemia, exudative retinal detachment, fibrous traction membrane and tractional retina detachment in the larger vascular arches following neovascular activity regression. Jalali et al. described severe complications with the use of intravitreal bevacizumab as adjuvant therapy for laser or surgery including macular hole, retinal tears causing rhegmatogenous retina detachment, bilateral vascular attenuation, perivascular exudation, optical atrophy and progression to stage V with bilateral retina detachment in one case in which follow-up was lost. In addition, one premature exhibited liver dysfunction and large choroidal rupture in one eye.

**Dose and localization of intravitreal bevacizumab injection**

With regard to the dose for each eye, published studies exhibit broad variability: 0.75 mg; 0.625 mg in 0.025 ml; 0.4 mg; 0.375 mg; 0.25 mg.

A recent editor note in Ophthalmology questioned the localization of the intravitreal bevacizumab injection at 2.5 mm posterior to the limbus of the BEA T-ROP study warning
that, in premature babies, pars plana injection should not exceed 1.5–2.0 mm posterior to the limbus because otherwise it would traverse the entire thickness of the retina.76

Recurrence periods

There is a great difference between the recurrence period of patients treated with laser and those treated with intravitreal bevacizumab: 16 ± 4.6 weeks for bevacizumab and 2.2 ± 5.7 weeks for laser.54 The average between the initial treatment and the requirement for retreatment was 14.4 weeks, with a minimum of 4 and a maximum of 5 weeks.79 Careful and longer follow-up must be carried out in patients treated with intravitreal bevacizumab. Close follow-up is required for at least 9 months even though ROP regression is observed due to the high risk of tractional retinal detachment.72

Tahija et al.80 recommend caution because, even though intravitreal bevacizumab can be effective for resolving posterior zones I and II, the peripheral retina remains avascular for years, thus making it advisable to carry out follow-up with retinofluorescein graph as this device has demonstrated its safety for newborns.81,82 Henaine-Berra et al.83 reported that in some patients extremely peripheral retinal vessels may never develop, even though patients with these findings did not exhibit pathological neovascularization.

Refraction

Harder et al.84 reported that eyes treated with intravitreal bevacizumab exhibited less myopization than those treated with laser, although the patients were followed up for only one year. In contrast, Tseng et al.85 reported large refraction defects probably caused by intravitreal bevacizumab injection in premature patients with ROP.

Even though said review results have demonstrated that intravitreal bevacizumab injection is promising for treating ROP stage 3+ in zone I or posterior aggressive ROP, some fundamental issues remain unresolved such as the maximum acceptable dosage for premature, risk of long-term systemic or ocular collateral effects, efficacy and bioactivity in a developing infant.

The reports did not differ significantly in recurrence rates between treatment with intravitreal bevacizumab in monotherapy and laser treatment for stage 3 in zone II; the latter is the best therapeutic option due to its safety and long-term effectiveness.

In ROP stages 1 and 2, intravitreal bevacizumab treatment is not indicated because of the risk of severe visual loss is low and VEGF is necessary for the development of normal retina vessels.

On the other hand, intravitreal bevacizumab should be contraindicated in stages for and 5 because it accelerates tractional retinal detachment.

Even though the literature includes some reports on the use of intravitreal bevacizumab associated to laser treatment and vitrectomy, there are no controlled clinical trials verifying the efficiency and long-term safety of said treatment.

Conflict of interests

No conflict of interest has been declared by the authors.

REFERENCES


