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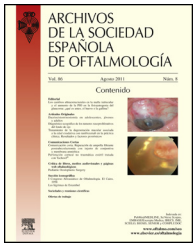

Review

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

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ABSTRACT

Objective: 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 VEFG 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.

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

Palabras clave:
Lexemas

RESUMEN

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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Bevacizumab
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Métodos: Se realizó una revisión amplia en Pubmed, Cochrane, Medline, utilizando las palabras factor de crecimiento vascular endotelial (VEGF), retinopatía del prematuro, tratamiento y bevacizumab.
Resultados: Se encontraron publicados casos y series de casos, revisiones, una revisión sistemática y un ensayo clínico controlado y aleatorizado sobre uso de bevacizumab intravítreo en ROP severa, como monoterapia o combinado con láser o vitrectomía.
Conclusiones: Aunque los resultados de la revisión han mostrado que la inyección intravítrea de bevacizumab es promisoria para el tratamiento de la ROP estadio 3+ en zona I o la ROP agresiva posterior, aún permanecen inciertas algunas cuestiones fundamentales como dosis máxima aceptada para prematuros, riesgo de efectos colaterales sistémicos y oculares a largo plazo, eficacia y bioactividad en un niño en desarrollo. En los reportes no hubo diferencias significativas en la tasa de recurrencia entre el tratamiento con bevacizumab intravítreo como monoterapia y tratamiento láser para el estadio 3 en zona II; este último es la mejor opción por seguridad y efectividad a largo plazo. En los estadios 1 y 2 de ROP no está indicado el tratamiento con bevacizumab intravítreo porque el riesgo de pérdida visual severa es bajo y el VEFG es necesario para el desarrollo de los vasos normales de la retina. Por otra parte, en estadios 4 y 5 debería ser contraindicado el uso de bevacizumab intravítreo porque acelera el desprendimiento de retina traccional.

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[4–15] after basic sciences involved the vascular endothelial growth factor (VEGF) in the pathogeny 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.[14,30]

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 pathogeny 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 cytosine 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 hyperoxia 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]