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REVIEWS

ANTI-VEGF THERAPY AND RETINOPATHY OF PREMATURITY

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ABSTRACT

INTRODUCTION: Nowadays, anti-vascular endothelial growth factor (VEGF) therapy is widely used as first-line therapy for retinopathy of prematurity (ROP) with very good therapeutic and visual results.

AIM: The aim of the present study is to compare the efficacy and safety outcomes between different anti-VEGF drugs.

MATERIALS AND METHODS: For the period January 2005–April 2023, in the available database (PubMed, Web of Science, Scopus), a systematic analysis of scientific publications examining the impact of anti-VEGF drugs on ROP was conducted.

RESULTS: Anti-VEGF drugs inhibit the second phase of pathogenesis of ROP, which is characterised by excessive production of VEGFs. In the last 15 years, many clinical trials comparing the efficacy of different concentraionts of the drugs, safety, ocular and systemic outcomes have been conducted.

CONCLUSION: There are several advantages of anti-VEGF therapy, such as easier application, earlier regression of ROP, peripheral vascularisation of the retina, and lower risk of myopia.

Keywords: *anti-VEGF therapy, retinopathy of prematurity, outcomes*

INTRODUCTION

Retinopathy of prematurity (ROP) is vasoproliferative multifactorial iatrogenic disease affecting the premature infants. It is the most important cause of treatable but irreversible blindness in premature children in both developed and developing countries. Each year more than 20,000 neonates are diagnosed with severe visual impairment and blindness due to ROP (1). The disease is characterised by retinal hypoxia and excessive production of vascular endothelial growth factor (VEGF), which cause retinal neovascularisation (RNV) in the severe stages. The main risk factors in the pathogenesis of the disorder are gestational age under 30 weeks, birth weight under 1500 g, and unregulated oxygen treatment. Early screening and treatment play a significant role in preventing the disease. Nowadays, anti-VEGF therapy is widely used as first-line therapy for ROP with very good therapeutic and visual results.

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AIM

The aim of the present study is to compare the efficacy and safety outcomes between different anti-VEGF drugs.

MATERIALS AND METHODS

For the period January 2005–April 2023, in the available database (PubMed, Web of Science, Scopus), a systematic analysis of published results of tri-

als about the effect of anti-VEGF drugs in managing ROP was conducted.

RESULTS AND DISCUSSION

The increasing use of anti-VEGF agents has revolutionised the approach to the disease management by reducing RNV, choroidal neovascularization (CNV), and vascular permeability. Nowadays, the main drugs used in ophthalmology are aflibercept, bevacizumab, pegaptanib, ranibizumab, conbercept, brolucizumab, and faricimab.

Bevacizumab

Bevacizumab is a recombinant, humanized monoclonal antibody (148 kDa) that binds all isoforms of VEGF-A, and first has been approved for the treatment of metastatic colorectal cancer in 2004 (2).

The first prospective multicentral randomised trial BEAT-ROP (Bevacizumab Eliminates the Angiogenic Threat of Retinopathy of Prematurity), which compared the effect of intravitreal administration of bevacizumab (0.625 mg in 0.025 mL of solution) versus laser therapy for ROP zone I or zone II posterior stage 3+ (stage 3 with plus disease), was conducted in 2011. In the trial were enrolled 150 infants. Recurrence of the disease was observed in 4 neonates in the intravitreal bevacizumab (IVB) group and in 19 neonates in the laser treatment group. Statistical significance was found only for ROP zone I ($P = 0.003$). In contrast to laser therapy, which coagulates the peripheral retina, intravitreal administration of bevacizumab allows further vascularisation of the entire retina (3).

Ranibizumab

Ranibizumab is a 48 kDa recombinant humanized monoclonal antibody with affinity towards all isotypes of VEGF-A. The lack of a fragment crystallizable (Fc) domain and its small molecule size might expand its affinity for more isoforms of VEGF-A (VEGF165, VEGF121, and VEGF110) and increase its diffusion within the retina and choroid (4).

The Ranibizumab Compared With Laser for the Treatment of Infants Born Prematurely With Retinopathy of Prematurity (RAINBOW) is the first randomised prospective clinical trial which compares the efficacy of intravitreal ranibizumab (IVR) (0.2 mg and 0.1 mg) and laser therapy. A total of 225 preterm babies divided into 3 groups were enrolled in the study. The first group received 0.2 mg IVR, the second group – 0.1 mg IVR, and the third group underwent laser therapy. Success was achieved in 80% in the first group, 75% in the second group, and 66% in the third group (4).

Marlow et al. published 2-year outcomes after ROP treatment with 0.2 mg ranibizumab. The study showed reduced risk of high myopia, strabismus and amblyopia, and better quality of life. After treatment with 0.2 mg IVR, high myopia was observed in 5% of the infants, while in the laser treatment group the frequency rate was 20% (5).

CARE-ROP (Comparing Alternative Ranibizumab Dosages for Safety and Efficacy in Retinopathy of Prematurity) is a multicenter, randomised, double-blind trial conducted from September 2014 to August 2016 in Germany. In the survey participated 20 infants with ROP zone I, stage 1 and 2 with plus disease, or stage 3 with or without plus disease, or ROP zone II stage 3 with plus disease, or aggressive ROP, who received different concentrations of ranibizumab (0.12 mg and 0.20 mg). The study demonstrates that the lower dose of the drug is as effective as the higher dose and better peripheral vascularisation is observed (4).

Long-term two-year follow-up of ophthalmologic status (first year) and neurodevelopment (second year) was performed in 16 of the preterm infants. Disease reactivation was found in only one of the children. Normal fixation and motility and mild myopia were observed in 15 of the preterm infants. At long-term follow-up, no negative impact on the overall development of the children was established. Due to the results of the study, ranibizumab is considered a safe medication for ROP treatment (4).

Aflibercept

Aflibercept (Eylea) is an ultra-purified and isoosmotic drug product that has been developed specifically for intravitreal injection for use in the treatment of various ophthalmological conditions. Aflibercept (VEGF-Trap), a recombinant human synthetic protein, acts as a soluble receptor that blocks a larger number of vascular endothelial factors.

In contrast to bevacizumab and ranibizumab, aflibercept binds not only to VEGF-A but also to VEGF-B and placental growth factor (PIGF), dem-

onstrating higher affinity for VEGF-A isoforms. As a result, more rapid blockage of VEGF-A- and PIGF-induced activation of VEGFR1 and VEGFR2 is observed as well as inhibition of endothelial cell migration (6-8).

In February 2023, aflibercept was officially approved by the FDA to treat ROP, following the publication of results from two global randomised trials: FIREFLEYE and BUTTERFLEYE, which compared the effect of intravitreal administration of 0.4 mg aflibercept and conventional laser therapy in ROP premature babies.

FIREFLEYE was the first global randomised open-label controlled phase 3 clinical trial, which compared the efficacy and safety profile of 0.4 mg intravitreal aflibercept (IVA) against laser therapy among 118 infants. They were diagnosed with ROP zone 1 stages 1 +, stage 2 and 3, stage 3+, ROP zone 2 stages 2+, 3+, and aggressive ROP.

Treatment success was 85.5% in the IVA group compared with 82.1% in the laser-treatment group. Additional treatment was required in fewer number of cases after IVA (4.8% vs 11.1%). Adverse ocular side effects were found in 13.3% of the cases in the IVA group compared to 7.9% in laser-treatment group. Systemic adverse reaction rate was 24.0% in IVA group and 36.8% in laser-treatment group (4,9).

Pegaptanib

Pegaptanib is an aptamer that selectively binds to and neutralises VEGF-A_{165} and was the first anti-VEGF therapy approved for the treatment of the exudative form of macular degeneration. Several articles have been published for the effect of IVP for treatment of ROP.

Autrata et al. reported a positive effect of the intravitreal administration of pegaptanib (IVP) in premature infants with ROP stage 3 with plus disease (10).

Conbercept

Conbercept is also a VEGF-Trap recombinant DNA protein with high affinity for all VEGFs and PIGF, which is approved for treatment of the exudative form of age-related macular degeneration (ARMD) (11).

SAFER

The increasing use of anti-VEGF drugs necessitates the publication of a practical guideline for proper administration and adequate follow-up of these patients. In order to optimize the safety of anti-VEGF treatment, a practical protocol, the so-called SAFER algorithm, has been published (12):

S (short needle) – the needle should be 32-gauge

A (antiseptics/antibiotics) – betadine 10 % or 5%, before and after injection

F (follow-up) – examination after 48 to 72 hours to check for ocular infection

E (extra attention to detail) – intravitreal injection should be performed at a precise distance from the limbus and under completely sterile conditions

R (re-check) – follow-up in 1–2 weeks until complete vascularisation of the peripheral retina

CONCLUSION

Anti-VEGF therapy provides several advantages and long-term benefits, such as easier application, earlier regression of ROP, peripheral vascularisation of the retina, and lower risk of myopia (13).

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