Comparison Of Intravitreal Injection Of Ranibizumab Versus Bevacizumab For Treatment Of Type 1 And Aggressive Retinopathy Of Prematurity

Introduction

Retinopathy of prematurity (ROP) is one of the leading causes of visual loss in children by means of macular dragging and retinal detachment. The first known description of the condition was in the 1940s. It occurs primarily in infants of low birth weight (≤1250 g) or gestational age of 30 weeks or less.[1] The disease process is associated with high levels of vascular endothelial growth factor (VEGF) secreted by the avascular retina which in turn leads to neovascularization, retinal detachment, and permanent visual loss.[2]

A committee for ROP classification was formed in1984, which proposed an international classification of ROP (ICROP) by dividing the retina into three zones, extending from posterior to anterior retina and describing the extent of ROP in clock-hours of involvement (International Committee for the Classification of Retinopathy of Prematurity 1984). [3]

However, with the advances in retinal imaging techniques, a revised ICROP classification was put forth which described the zones better (International Committee for the Classification of Retinopathy of Prematurity revisited 2005). For the purposes of localizing the disease, the retina is divided into 3 zones. Zone I, the posterior pole, is the retina within a circle centered on the optic disc with a radius equal to twice the disc-macula distance; zone II is concentric with zone I, whereas its radius extends to the distance from the disc to the nasal ora serrata; and zone III comprises the remaining crescent of temporal retina. Staging of ROP is based on the appearance of the clinically visible demarcation between the vascularized and avascular retina. This demarcation is a flat line in stage 1, a raised ridge in stage 2, and extraretinal neovascular proliferation overlying the ridge in stage 3. [4]

In more severe ROP, plus disease occurs which means that the blood vessels of the retina have become engorged and tortuous, indicating worsening of the disease. This is thought to be due to shunting through the areas of neovascularization. Presence of stage 3 ROP with plus disease in either 5 contiguous or 8 total clocks hours within zones I or II indicates ‘‘threshold disease’’—disease with a 50% chance of progression to retinal detachment and very poor visual prognosis (International Committee for the Classification of Retinopathy of Prematurity 1984). Retinal detachment is divided into subtotal (stage 4 ROP) or total detachment (stage 5 ROP).[5]

The Early Treatment for Retinopathy of Prematurity (ETROP) study defined type 1 ROP as cases with zone I ROP with plus disease, zone I stage III ROP, and zone II stage 2-3 with plus disease. The earlier treatment, within 72 hours, of those carefully selected cases results in an overall improved visual outcome. [6]

The Cryo-therapy for Retinopathy of Prematurity randomized trial demonstrated the efficacy of cryotherapy (vs. observation) as a treatment for threshold ROP, and it showed a marked reduction in the rates of unfavorable retinal structural outcomes and blindness (Cryotherapy for Retinopathy of Prematurity Cooperative Group 1988).[7]

Laser photocoagulation of the peripheral retina using indirect delivery system has proved to be an effective method of treatment according to the Early Treatment for Retinopathy of Prematurity (ETROP) study [8], however, in the same trial 9.1% of the patients had unfavorable structural outcomes. In addition,

a large area of peripheral retina is destroyed in the ablative process and normal vascularization generally cannot be achieved.[9,10]

A previous study reported significantly increased vitreal vascular endothelial growth factor (VEGF) levels in ROP patients. In the same study, an excess production of VEGF was shown to play an important role in ROP pathogenesis.[11] Bevacizumab treatment was found to be more effective than laser photocoagulation for ROP treatment, particularly in patients with zone 1 and 2 posterior disease (BEAT-ROP). [12] Moreover, other anti-VEGF therapies, macugen and ranibizumab, demonstrated efficacy in the treatment of ROP when used alone or in combination with laser photocoagulation. [13-15]

Bevacizumab is a larger, full-length immunoglobulin G (IgG) molecule with slower retinal clearance and therefore prolonged diffusion into the systemic circulation.[16] In contrast, the systemic half-life of a Fab molecule, such as ranibizumab, is a few hours, whereas that of a full-length IgG is up to 3 weeks in the general circulation. [17] Because of these structural differences, a much longer systemic half-life has been noted with bevacizumab compared with that of ranibizumab after intravitreal injection (20 days vs. 2 hours for bevacizumab and ranibizumab, respectively).[18,19]

The inhibition of VEGF raises concerns that these important physiologic effects associated with VEGF will be inhibited, leading to abnormal organogenesis or neurodevelopment. Based on our current data, the selection of an anti-VEGF with less systemic VEGF interference or reducing the dose of anti-VEGF agent or using an antiVEGF agent only once in ROP patients seems to be a safer choice because of the concerns mentioned above. [20-23]

In this prospective study, we compare the efficacy and reliability of bevacizumab and ranibizumab treatments for type 1 ROP, namely pattern of disease regression, recurrence of ROP, necessity of subsequent ablative procedures.

Rationale

Retinopathy of prematurity continues to be a major cause of childhood blindness worldwide. ROP has become a growing problem because of the increasing number of surviving preterm infants and the awareness of screening issues.

Although cryotherapy and laser photocoagulation can cure several cases of ROP, being relatively destructive to the peripheral retina, associated with high myopia, retinal dragging, anterior segment ischaemia, and vitreous heamorrhage, other lines of treatment have been tried.

Recently there is a shift of treatment to VEGF inhibitors which can regress ROP without destroying the peripheral retina. Yet, the best drug has not been identified.

Research question

Is the intravitreal ranibizumab monotherapy as effective in treatment of type 1 ROP as intravitreal bevacizumab monotherapy as regard disease regression, recurrence after single intavitreal injection and timing of total retinal vascularization?

Hypothesis

Intravitreal bevacizumab injection is better than intravitreal ranibizumab for treatment of type 1 ROP. Bevacizumab is a larger, full-length immunoglobulin G (IgG) molecule with slower retinal clearance and therefore prolonged diffusion into the systemic circulation, up to 3 weeks. In contrast, the systemic half-life of a Fab molecule, such as ranibizumab, is a few hours. Intavitreal ranibizumab is associated with higher chance of reactivations, need for additional laser therapy or more doses of IVR.

Aim of the Work

To evaluate the efficacy of intravitreal ranibizumab monotherapy compared to intravitreal bevacizumab monotherapy for treatment of type 1 ROP.

Objectives

- To report and compare the percentage of eyes achieving regression in each group (defined as: Regression of the ridge and venous dilation and arteriolar tortuosity of the posterior retinal vessels (plus disease)) after single intravitreal injection at one week post-injection and 55 weeks' postmenstrual age.
- To report and compare the percentage of eyes with relapse which necessitates additional treatment.
- To report and compare the percentage of eyes achieving regression at 55 weeks' postmenstrual age either by multiple intravitreal injections or additional laser therapy in each group.
- To detect, record and analyze any complications either related to the disease (progression into stage 4 or 5) or to the inravitreal injection procedure during the follow-up period of 6 months after initial injection.

Subjects and methods

Before initiating this study, all parents or guardians of the recruited infants will be provided with informed written consent. The investigator will explain to the parents the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks, benefits and the follow-up schedule.

The participants' parents will be informed that participation is voluntary, that he or she may withdraw from the study at any time and without giving reasons. The withdrawal will not affect the subsequent medical or conservative treatment or relationship with the treating surgeon. The participants' parents will be informed about the severity of disease, treatment options, and complications.

Technical Design

Setting: Abulreesh Children's Hospital Kasr Alainy, Cairo University and Zagazig University Hospitals.

Design: A prospective randomized clinical trial.

Subjects: Patients screened at neonatal intensive care unit (NICU) of Cairo University and Zagazig University Hospitals meeting the inclusion criteria of the study.

Sample size:

The sample size is calculated to be 36 eyes of 18 infants using open Epi confidence total 95%, power of the study 80% according to the following: the mean ±SD of axial length of patients with stage 3 ROP using bevacizumab versus ranibizumab (20.3±1.16 versus 19.4±0.36 mm).[24]

Inclusion Criteria:

Infants with a birth weight of ≤ 1500 g or geststional age of ≤ 30 weeks and selected infants with birth weight between 1500 and 2000 g or gestational age of more than 30 weeks with an unstable clinical course, including those requiring cardiorespiratory support. Patients with bilateral disease who will receive bilateral injections, are only included. Aggressive ROP (A-ROP) and Type 1 ROP according to ETROP study [6] which is defined as:

- Zone I ROP with plus disease.
- Zone I, stage 3 ROP without plus disease.
- Zone II, stage 2 or 3 ROP with plus disease.

Exclusion Criteria:

- Eyes with previous intravitreal injections.
- Eyes with previous laser therapy.
- Eyes with any other pathology, other than ROP.
- Eyes with ROP stage 4 or 5.
- Infants who will not be able to comply to the follow-up schedule.

Operational design:

Initial clinical evaluation:

History:

Data will be collected for each baby regarding date of birth, sex, single or multiple pregnancy, gestational age at birth, birth weight, age at which ROP is detected. Other data include oxygen and surfactant given or not, presence of common problems of prematurity, presence of intrauterine growth retardation, and duration of stay of infant in the Intensive Care Unit of the Neonatology Department.

Examination:

The stage of ROP, the affected zone, and presence or absence of plus disease are recorded by binocular indirect ophthalmoscope and digital fundus images by RetCam.

Interventional procedure:

Dilating drops, 0.5% tropicamide and 2.5% phenylephrine, are instilled twice, 10 minutes apart, at least 30 minutes before the treatment.

Intravitreal injection will be performed under general (light inhalational anaesthesia) or topical anesthesia (Benoxinate hydrochloride 0.4%) in standard ophthalmic operating room under strict sterile

conditions. Povidone iodine 10% swab will be applied on the eyelids and eyelashes and sterile speculum will be inserted. Then, 5% povidone-iodine disinfectant for 3 minutes before intavitreal injection.

A dose of 0.25 mg/0.025 mL ranibizumab (Lucentis; Novartis, Basel, Switzerland) is injected in the left eye of the infant and 0.625 mg/0.025 mL bevacizumab is injected into the vitreous cavity of the right eye. The two injections are done sequentially on two consecutive days starting with the eye of more advanced disease.

A 31-gauge needle is used, aiming the needle directly toward the optic nerve in direction of visual axis 1.0 mm posterior to the superior/ inferior temporal limbus. Removal of the needle with simultaneous compression using a sterile cotton tip. All injections are done by the same surgeon.

Fundus examination will be conducted after injection with an indirect ophthalmoscope and a 28-D lens. The central retinal artery and the lens will be evaluated in addition to whether a retinal tear is present.

Postoperative moxifloxacin 0.4% drops will be prescribed 4 times daily for three days. Patients will be seen 24 hours after first injection, to monitor for any signs of infection. Risks of injection include endophthalmitis, lens injury, heamorrhage, retinal detachment and elevation of IOP.

Follow-up:

The follow-up period: at clinics is for six months after initial intravitreal injection.

Follow-up regimen:

All infants will be followed up weekly until the regression of ROP, after that every 2 weeks until full vascularization (vascularization reaching to the temporal ora serrata without an active component such as heamorrhage or exudation or clinically significant tractional elements) or additional treatment is given. Follow up is done by binocular indirect ophthalmoscope and digital coloured fundus images by RetCam (Clarity Medical Systems, Pleasanton, CA).

Primary and secondary outcome measures:

The primary outcome measurements include:

- The number of eyes that achieved regression either by single injection or multiple injections or additional laser therapy at 55 weeks' postmenstrual age.
- Total retinal vascularization time.

The secondary outcome measurements include:

- The number of eyes with recurrence of ROP (recurrent plus disease, recurrent neovascularization, or reformation of ridge despite treatment) in one or both eyes requiring retreatment before a postmenstrual age of 55 weeks.
- The number and kind of adverse events, the number of patients progressing to stage 4 or 5.

- The number of reinjections or laser spots and the number of eyes that need vitrectomy with/without lensectomy.

Results

Data were coded using the statistical package for the Social Sciences (SPSS) version 28 (IBM Corp., Armonk, NY, USA). Data was summarized using mean, standard deviation, minimum and maximum for quantitative variables and frequencies (number of cases) and relative frequencies (percentages) for categorical variables. Comparisons between groups were done using unpaired t test. For comparing categorical data, Chi square ($\chi 2$) test was performed. Exact test was used instead when the expected frequency is less than 5. *P*-values less than 0.05 were considered as statistically significant**.**

Discussion

Discussion will be done on results compared to relate relevant literatures and scientific researches to explain the reasons for getting such results.

Conclusion and Recommendation

They will be derived from the findings of the study.

References

1. Kong L, Fry M, Al-Samarraie M, Gilbert C, Steinkuller PG: An update on progress and the changing epidemiology of causes of childhood blindness worldwide. J AAPOS 2012;6: 501–507.
2. Kwinta P, Bik-Multanowski M, Mitkowska Z, Tomasik T, Pietrzyk JJ: The clinical role of vascular endothelial growth factor (VEGF) system in the pathogenesis of retinopathy of prematurity. Graefes Arch Clin Exp Ophthalmol 2008;246:1467–1475.
3. An international classification of retinopathy of prematurity. The Committee for the Classification of Retinopathy of Prematurity. Arch Ophthalmol 1984;102(8):1130-1134.
4. An international classification of retinopathy of prematurity. II. The classification of retinal detachment. The International Committee for the Classification of the Late Stages of Retinopathy of Prematurity. Arch Ophthalmol 1987;105(7):906-912.
5. The International Classification of Retinopathy of Prematurity revisited. Arch Ophthalmol 2005;123(7):991-999. DOI: 10.1001/archopht.123.7.991
6. Good WV; Early Treatment for Retinopathy of Prematurity Cooperative Group. Final results of the Early Treatment for Retinopathy of Prematurity (ETROP) randomized trial. Trans Am Ophthalmol Soc. 2004;102:233-48.
7. Cryotherapy for Retinopathy of Prematurity Cooperative Group. Multicenter trial of cryotherapy for retinopathy of prematurity.Preliminary results. Arch Ophthalmol. 1988;106:471-479.
8. Early Treatment for Retinopathy of Prematurity Cooperative Group. Revised indications for the treatment of retinopathy of prematurity: results of the early treatment for retinopathy of prematurity randomized trial. Arch Ophthalmol 2003;121: 1684–1694.
9. Lu LX, Yon JH, Carter LB, Jevtovic-Todorovic V. General anesthesia activates BDNF-dependent neuroapoptosis in the developing rat brain. Apoptosis 2006;11:1603–1615.
10. Rizzi S, Carter LB, Ori C, Jevtovic-Todorovic V. Clinical anesthesia causes permanent damage to the fetal guinea pig brain. Brain Pathol 2008;18:198–210.
11. Villegas Becerril E, Gonzalez Fernández R, Fernández Molina F, Gallardo Galera JM. Growth factor levels and ROP. Ophthalmology. 2005;112(12):2238.
12. Mintz-Hittner HA, Kennedy KA, Chuang AZ; BEATROP Cooperative Group. Efficacy of intravitreal bevacizumab for stage 3+ retinopathy of prematurity. N Engl J Med. 2011;364(7)603-15.

Comment in: N Engl J Med. 2011;364(24):2359; author reply 2361-2; N Engl J Med. 2011;364(7):677-8. N Engl J Med. 2011;364(24):2360; author reply 2361-2.

13. Castellanos MA, Schwartz S, García-Aguirre G, Quiroz-Mercado H. Short-term outcome after intravitreal ranibizumab injections for the treatment of retinopathy of prematurity. Br J Ophthalmol. 2013;97(7):816-9.
14. Mota A, Carneiro A, Breda J, Rosas V, Magalhães A, Silva R, et al. Combination of intravitreal ranibizumab and laser photocoagulation for aggressive posterior retinopathy of prematurity. Case Report Ophthalmol. 2012;3(1):136-141.
15. Autrata R, Krejcírová I, Senková K, Holoušová M, Doležel Z, Borek I. Intravitreal pegaptanib combined with diode laser therapy for stage 3+ retinopathy of prematurity in zone I and posterior zone II. Eur J Ophthalmol. 2012;22(5):687-94.
16. Heiduschka P, Fietz H, Hofmeister S, et al. Penetration ofbevacizumab through the retina after intravitreal injection inthe monkey. Invest Ophthalmol Vis Sci 2007;48:2814–2823.
17. Mordenti J, Cuthbertson RA, Ferrara N, et al. Comparisons of the intraocular tissue distribution, pharmacokinetics, and safety of 125I-labeled full-length and Fab antibodies in rhesus monkeys following intravitreal administration. Toxicol Pathol 1999;27:536–544.
18. Bakri SJ, Snyder MR, Reid JM, et al. Pharmacokinetics ofintravitreal ranibizumab (Lucentis). Ophthalmology 2007;114:2179–2182.
19. Bakri SJ, Snyder MR, Reid JM, et al. Pharmacokinetics ofintravitreal bevacizumab (Avastin). Ophthalmology 2007;114:855–859
20. Been JV, Zoer B, Kloosterboer N, et al. Pulmonary vascular endothelial growth factor expression and disaturatedphospholipid content in a chicken model of hypoxiainduced fetal growth restriction. Neonatology 2010;97:183–189.
21. Dvorak HF. Vascular permeability factor/vascular endothelialgrowth factor: a critical cytokine in tumor angiogenesis anda potential target for diagnosis and therapy. J Clin Oncol 2002;20:4368–4380.
22. Ferrara N. VEGF and the quest for tumour angiogenesis factors. Nat Rev Cancer 2002;2:795–803.
23. Ferrara N. Vascular endothelial growth factor: basic scienceand clinical progress. Endocr Rev 2004;25:581–611.
24. S Kimyon, A Mete. Comparison of bevacizumab and ranibizumab in the treatment of type 1 retinopathy of prematurity affecting zone 1. Ophthalmologica 2018;240(2), 99–105.