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Research Article

Intravitreal Ranibizumab as a Primary Treatment for Type I Retinopathy of Prematurity. Local Experience from the United Arab Emirates

Ohood Al-Mazrouie* and Kais Al-Algawi

Department of Ophthalmology, Mafraq Hospital, United Arab Emirates

***Corresponding Author:** Ohood Al-Mazrouie, Department of Ophthalmology, Mafraq Hospital, United Arab Emirates.

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Abstract

Purpose: The aim of the study was to evaluate the efficacy and safety profile of intravitreal ranibizumab (IVR) monotherapy for advanced retinopathy of prematurity (ROP).

Methods: This is a prospective study including 40 eyes of 22 premature infants with advanced ROP disease that were treated with one intravitreal injection of 0.25 mg ranibizumab under light general anesthesia. No prior laser or other intravitreal therapy was done. Fundus examination was performed prior to the intervention and at each follow-up exam. Favorable outcome was defined as regression of the retinal neovascularization and plus disease, indicating good disease control. Unfavorable outcomes were signs of recurrence of the disease.

Results: The average gestational age and weight of patients at birth was 24.5 weeks and 686 grams, respectively. The gestational age at the date of treatment was 36.7 weeks. Average follow up period following IVR injections was 24 months. 100% of the eyes showed favorable outcome with complete retinal vascularization. None of the eyes developed recurrence of ROP except for one patient who required re-injection of both eyes as a top-up treatment to fasten regression.

Conclusion: This study showed a satisfactory response to monotherapy with intravitreal ranibizumab injection for the treatment of advanced Type I retinopathy of prematurity. However vigilant follow-up is necessary to ensure timely intervention should signs of regression be detected.

Keywords: *Retinopathy of Prematurity; Intravitreal Ranibizumab Injection; Recurrence; Regression; Threshold; Plus Disease*

Abbreviations

ROP: Retinopathy of Prematurity; VEGF: Vascular Endothelial Growth Factor

Introduction

Intravitreal injections of anti-VEGF drugs have increasingly been used for treatment of severe retinopathy of prematurity (ROP) [1]. These drugs inhibit the action of vascular endothelial growth factor (VEGF), an important signaling agent for new blood vessel development that was found to be present in excess in eyes of infants with severe ROP [1]. Neovascularization in the immature retina may lead to retinal traction, retinal detachment, hemorrhage and eventually, blindness. Initial results with anti-VEGF treatment are promising, but still long-term effect and safety profile are major concerns [2].

Many anti-VEGF drugs are available today, including bevacizumab (Avastin), ranibizumab (Lucentis), pegaptanib (Macugen) and aflibercept (Eylea) [3]. Currently, bevacizumab and to a lesser extent, ranibizumab are the most studied drugs for ROP treatment with encouraging results and very few ocular or systemic related complications [4].

Bevacizumab is a monoclonal antibody; whereas ranibizumab is an antibody fragment, and both bind to all VEGF-A isoforms [5]. There are pharmacokinetic differences between bevacizumab and ranibizumab, which may be of special safety importance in premature infants undergoing organogenesis.

ETROP study showed significant improvement in both primary and secondary (anatomical) outcomes when prethreshold ROP eyes were treated when compared to threshold disease [6]. In that study Type 1 ROP was summarised as:

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

This study reports our experience of intra-vitreal ranibizumab monotherapy for Prethreshold/Type I retinopathy of prematurity, with a special attention to assess the efficacy and safety profile.

Methods

Study design

This is an institutional-based prospective study conducted from March 2014-to January 2017 at Mafraq hospital, Abu Dhabi, United Arab Emirates.

Patients

The study included 40 eyes of 22 premature infants (55% male and 45% female). All were diagnosed with Type I ROP. Patients were either diagnosed at our hospital or referred from other governmental hospitals in Abu Dhabi for treatment. All had no prior laser or intravitreal therapy.

There were no exclusion criteria.

Ophthalmological examination and interventions

All patients were evaluated preoperatively by binocular indirect ophthalmoscopy. Birth weights, gestational age, gestational age on the day of treatment, classification of ROP in stages, zones, extension and severity, including any signs of Plus disease were registered.

Eighty two percent (82%) of our patients had bilateral severe ROP. Anti-VEGF therapy with IVR was performed in both eyes on the same day, or maximum of one week apart. The pupils were dilated with cyclopentolate 0.5% and phenylephrine 2.5%. Topical antibiotic drops (moxifloxacin) were applied before the administration of intravitreal injections.

The injections were administered in the operating theater, under sterile preparations and light general anesthesia. A dose of 0.25 mg (0.025 mL) of ranibizumab was injected 1.5 - 2 mm posterior to the corneal limbus using a 30 G needle in all eyes. After administering IVR injection, topical antibiotic drops (moxifloxacin) were used every 6 hours for 5 - 7 days.

All babies treated were ROP type I diseases. All received the treatment by the same surgeon (KA), except for 2 babies. One of these two babies needed top up injections in both eyes while the other showed delayed regression who did not need any further treatment.

Outcomes evaluated and follow-up

The outcome was considered favorable when signs of regression of the ROP after treatment, including the resolution of the Plus disease and regression of the retinal neovascularization were confirmed. This means good control of the disease.

The minimal follow up evaluations were performed on days 1, 3, 7 and 14 and then at 1, 2, 3, 6 and 12 months. At times, the follow up visits varied according to the progress of the disease.

Ocular or systemic adverse effects registered

Short- and long-term (after 2-year follow-up) ocular adverse effects were looked for and documented. These include signs of intraocular inflammation, intraocular pressure elevation, and secondary cataract formation.

Systemic adverse effects were closely monitored during perioperative and postoperative periods in the Neonatal Intensive Care Unit and then at the Pediatric Clinics. Related blood investigations were done before and after injection and during the follow up visits including; complete blood with differential counts, electrolytes, liver function test, kidney function test, and coagulation profile.

Ethical aspects

In all cases, babies' parents or their representatives signed a consent form before the treatment.

The approval of the Ethical Committee of Mafraq Hospital was obtained before submitting our results.

Results

Twenty-two patients (40 eyes) were included in the study. All diagnosed with severe Type I ROP. Fifty five percent (55%) of our patients were male. Mean GA at birth was 24.5 weeks (range: 23 - 27 gestational weeks). Mean birth weight was 686gs (range: 510 to 1200g) and gestational age on the day of treatment 36.7 weeks (range: 33 to 46 weeks) (Table 1).

Number of patients	22
Number of eyes	40
Males	12
Females	10
Mean gestational age (wk)	24.5 weeks
Mean birth weight (g)	686gs
Mean gestational age at date of treatment (wk)	36.7 weeks

Table 1: *Demographic of patients receiving ranibizumab treatment.*

None of the 40 eyes showed any signs of unfavorable outcome. All showed complete regression of ROP. Resolution started on day 3 with reduction in plus disease activity and signs of significant regression were noticed in 5 - 7 days after the injection. None developed retinal detachment, hemorrhages, high myopia or cataract (Table 2).

			Right Eye					Left Eye				
Patient	**Gender**	**GA**	**Stage**	**Zone**	**Plus**	**Rx**	**Age of Rx**	**Stage**	**Zone**	**Plus**	**Rx**	**Age of Rx**
1	F	24+3	2	2		Yes	33+6	2	2		Yes	33+6
2	F	25	2			No	-	2			Yes	35+1
3	M	26+2	2	2		Yes	38+3	2	2		Yes	38+3
4	M	24+1	3	2		Yes	36+3	3	2		Yes	36+3
5	F	25	3	2		Yes	36+6	3	2		Yes	36+6
6	F	26	2	2		Yes	40	2	2		No	-
7	M	24	2	2-3		No	-	2-3	2		Yes	38+3
8	M	26	2	2		Yes	46+4	3	2		Yes	46+4
9	F	24+2	3	2		Yes	34+5	2	2		No	-
10	M	25	3	2		Yes	37	3	2		Yes	37
11	F	23+1	1	2		Yes	35+5	1	2		Yes	36+1
12	M	23+6	3	2		Yes	40+3	3	2		Yes	40+3
13	M	25	2	2		Yes	35+6	2	2		Yes	35+6
14	M	23+3	3	Retinal hmg		Yes 2nd inj	33+2 44+3	3	Retinal hmg		Yes 2n inj	33+2 44+3
15	M	27	3	2		Yes	37	3	2		Yes	37
16	M	24+4	3	2		Yes	35+2	3	2		Yes	35+2
17	F	24+2	3	2		Yes	35+5	3	2		Yes	35+5
18	M	24+6	3			Yes	36+3	3			Yes	36+3
19	M	26	3	2			38+2	3	2			38+2
20	F	24+3	3	2		Yes	37	3	2		Yes	37+6
21	F	25	3	2		Yes	39+4	3	2		Yes	39+4
22	M	23+4	3	3		Yes	34	3	3		Yes	34

Table 2: *Patients receiving antivitreal ranibizumab injection.*

One out of the 40 eyes developed slight dragging of the macular vessels with thin fibro- vascular membrane. This may well be due to late treatment at the age of 46+6 weeks. The baby was referred to us late from elsewhere. No effect on the visual attention of that eye was reported.

4 out of 40 eyes (2 patients), initially showed good response but subsequently had slower regression with residual avascular temporal retinae 6 - 8 weeks after the initial treatment. One patient required second intravitreal ranibizumab injections for both eyes as a top up treatment to speed up regression and the other 2 eyes of the second patient continued to have slow regression till resolution. The 4 eyes had complete stable resolution.

2 infants deceased during follow up period from other prematurity complications, not related to ROP treatment.

The mean follow-up period was 12 months. No short, or long, term ocular or systemic adverse effects were registered in this cohort of 22 treated patients.

Discussion

An increase in VEGF levels is one of the main mechanisms underlying ROP development [7]. Anti-VEGF drugs have been used as mono-therapy agents or in addition to laser photocoagulation, with successful results [7]. The majority of studies have reported the results of bevacizumab therapy and less on ranibizumab therapy [8].

Castellanos., *et al*. [9] treated 6 eyes with high-risk pre-threshold and threshold ROP disease by intravitreal ranibizumab without laser photocoagulation and demonstrated a single dose of intravitreal ranibizumab was sufficient to regress retinal neovascularization with no recurrences observed after a 3-year follow-up period.

Furthermore, Odalis Arambulo treated 57 eyes grouped in 2 groups; 16 eyes received only Intravitreal ranibizumab treatment and 41 eyes received combined IVR and laser photocoagulation. Patients were followed for mean of 12.8 months. He demonstrated favorable outcomes in 14 eyes (87.5%) in IVR only group and 43 eyes (75.4%) achieved regression of ROP in both groups [4].

Two major concerns led us to the idea of treating severe ROP with intravitreal ranibizumab. The first; laser photocoagulation or cryo-therapy require trained surgeons to deliver the treatment. Furthermore conventional laser therapy resulted in permanent destruction of the vessels in the peripheral retina beyond the affected zone, whereas intravitreal anti VEGF allowed for continued, though slow, vessel growth into the peripheral retina towards the temporal ora serrate. It also has many disadvantages such as; cataract formation, anterior segment and vitreous hemorrhage, intraocular inflammation and fluctuating intraocular pressure [10]. In the long term, high myopia, peripheral field loss and strabismus are major side effects of laser therapy [11].

Secondly; Ranibizumab seems to have a short systemic half-life and the antibodies lack a crystallizable fragment (Fc). Therefor using ranibizumab reduces the risk of systemic adverse events and complement-mediated toxicity [12].

As Anti-VEGF leaks to the systemic circulation, it may suppress serum VEGF, which plays positive roles related to neural, vascular, and lung development in the premature infant. Wu., *et al*. [13] and Myung Hun Yoo [14] Compared the levels of VEGF after Bevacizumab and Ranibizumab for the treatment of retinopathy of prematurity and concluded that serum level of VEGF in patients with type I ROP suppressed for 2 months after treatment with IVB and were less affected after IVR treatment.

Recently Hoerster and colleagues tested serum VEGF levels in a premature infant after one injection of ranibizumab to treat ROP 3 plus in zone I. They found suppressed systemic VEGF levels below detection limit for about 2 weeks post-injection. An impaired blood-retina barrier of the immature retina might explain this suppression at this age, as ranibizumab does not seem to change systemic VEGF levels in adults. Hoerster., *et al*. found that four weeks after bilateral treatment, systemic VEGF levels returned to normal values [15]. In a case series of 11 eyes treated with bevacizumab, systemic VEGF levels were suppressed for at least 7 weeks post-injection. This data suggests ranibizumab might have a better safety profile.

Recent studies have shown that VEGF is not the only growth factor upregulated in the eyes with ROP. Insulin-like growth factor-1, angiopoietin-1, and angiopoietin-2 have also been identified. Vascular growth factors have compensatory mechanisms in ROP, and therefore, the inhibition of VEGF expression alone may be unable to induce regression in all ROP cases [16,17].

One of the important problems in anti-VEGF treatment of ROP is recurrence after the initial inactivation of ROP. Therefore, long-term follow-up of these patients is needed following such treatment [18].

Conclusion

We found that intravitreal ranibizumab injections were effective and well tolerated in infants with Type I ROP. All of our cases, apart from one, needed a single injection of ranibizumab to show significant regression of the ROP. Only one patient required a 2nd injection in each eye as a top up treatment to speed up regression. Otherwise no short-term systemic or major ocular side effects were identified.

Studies with more cases and a longer follow-up period are warranted.

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Conflict of Interest

No specific financial support was available for this study.

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