Annals of Medical Research
DOI: 10.5455/annalsmedres.2018.08.152 2018;25(4)635-9

Original Article

Spectral domain-optical coherence tomographic assessment of macular changes following anti-vascular endothelial growth factor therapy in patients with retinopathy of prematurity

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Abstract

Aim: The purpose of this study was to investigate the effect of intravitreal ranibizumab (IVR) injection for type 1 and aggressive posterior retinopathy of prematurity (ROP) and to detect probable alterations in central foveal thickness, to analyze macular structural changes and to observe regression of ROP following IVR therapy.

Material and Methods: 40 eyes of 22 patients with type 1 or aggressive posterior ROP who received IVR injections and had macular spectral domain– optical coherence tomography (SD – OCT) images were included in the study. All eyes were scanned using a portable SD-OCT machine before treatment and 1st week, 1st month, 2nd month following IVR injection. All SD-OCT images were evaluated for central foveal thickness (CFT) and the development of cystoid macular edema (CME).

Results: Recurrence of plus disease was observed in 10 eyes of six patients after IVR injection. Interval time from initial injection to recurrence was between 7 and 10 weeks. Alterations in CFT and macular structure were observed in short term period following IVR injection for type I and APROP. CME was observed in all patients but at various times in their follow-up periods.

Conclusions: CME is a frequently seen finding in type I ROP and APROP. It might be a physiologic consequence of normal development of macula as well as part of pathologic process influenced by IVR injection. Even though recurrence rate of ranibizumab is higher than bevacizumab, we propose that ranibizumab may be a safer alternative agent than bevacizumab.

Keywords: Retinopathy of Prematurity; Vascular Endothelial Growth Factor; Cystoid Macular Edema; Ellipsoid Zone; Photoreceptor.

INTRODUCTION

Premature infants account for 10% of all newborn babies. Retinopathy of prematurity (ROP) is leading cause of potentially avoidable blindness in childhood period and characterized by proliferative vascularization of the retina (1). Prompt screening is an essential step to identify risk factors for ROP development and thus visual impairment and blindness may be avoided (2). Despite implementation of protective procedures and treatment, risk of visual function defects remains higher in preterm infants than in mature infants (3).

Spectral domain optical coherence tomography (SD-OCT) is an imaging system used for diagnosis and monitoring of many retinal disorders. Using SD-OCT tool, high resolution cross-sectional images from the retina and choroid are acquired (4). Although SD-OCT may provide valuable information of retina and choroid, it is difficult to use it in imaging of infants since these devices are designed for chin rest position which is suitable for adults and older kids. Fortunately, the development of portable OCT devices has been largely resolved positioning and fixation issues in infants (5). SD-OCT has been recently used to evaluate macula of premature infants (6,7).

During fetal development, due to higher oxygen demand for developing retinal tissue, vascular endothelial growth factor (VEGF) molecules are released and lead development of blood vessels from the optic disc to the ora serrata (8). Intravitreal injection of anti-VEGF agents solely or in combination with laser photocoagulation has been successfully employed to treat ROP (9,10). The

Received: 04.08.2018 **Accepted:** 17.08.2018 **Available online:** 03.09.2018
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key role of VEGF in development of ROP inspired clinical studies to explore efficiency and safety of intravitreal anti-VEGF treatment. Bevacizumab is the most commonly used anti-VEGF agent in ROP treatment (11). Ranibizumab which has been a recently introduced anti-VEGF agent in ROP treatment is thought to cause less systemic toxicity due to shorter half-life compared to bevacizumab (12).

Development of central retina may be affected in ROP (13). Apart from development of ROP, abnormal foveal photoreceptor layer, flatter foveal pit, macular structure alterations and thinning of retina nerve fiber layer may be observed in preterm infants (14,15,16).

Past studies performed in premature infants demonstrated that several macular changes such as cystoid macular edema cannot be observed in funduscopic examinations however same changes are detected using SD-OCT (17,18). Recent studies demonstrated that prematurity may cause persistent changes in central retina (14,19,20,21).

The purpose of this study was to investigate the effect of intravitreal ranibizumab (IVR) injection for type 1 and aggressive posterior retinopathy of prematurity (APROP) and to detect probable alterations in central foveal thickness, to analyze macular structural changes and to observe regression of ROP following IVR therapy.

The study was approved by the local ethics committee and performed in accordance with the ethical standards outlined in the Declaration of Helsinki. Informed consent was obtained from the parents of all participating subjects.

From August 2012 through December 2015, medical records of 1200 premature infants were retrospectively reviewed from database. Both eyes of 18 patients and single eye of 4 patients (40 eyes of 22 patients) with type 1 or aggressive posterior ROP which were applied initial single dose of intravitreal ranibizumab injection and which had SD-OCT images prior to and one week, one and two months following injection were included in the study. Infants with anterior segment anomalies like congenital cataract, congenital glaucoma, Peter's anomaly, and posterior segment anomalies like oculocutaneous albinism, choroidal coloboma, and morning glory disc anomaly were excluded from the study.

For all patients, one drop of 0.5% proparacaine HCl solution (Alcaine; Alcon Laboratories, Fort Worth, TX, USA) was applied for topical anesthesia preceding fundus examination. Lid speculum was placed to keep the eyelids open, and then fundus was examined with an indirect ophthalmoscope using a 20- or 28-diopter lens for each eye. Following indirect ophthalmoscopic examination, eyes were scanned using iVue (Optovue, Fremont, CA), which is a portable SD-OCT machine. As seen in Figure 1, provided with iVue is mounted on the iStand, SD-OCT imaging can be performed with the patient supine. Consecutive retinal SD-OCT images (2x6 mm) were captured with cross-line scanning pattern for each eye.

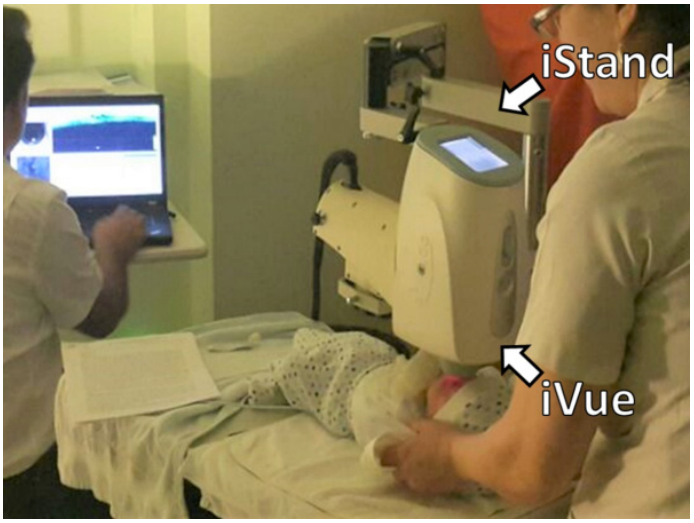

Figure 1. iStand (Optovue Inc.), a rolling floor stand option for the iVue SD-OCT system allows subjects to be scanned in the supine position.

For SD-OCT imaging, SD-OCT device was manually placed on the eye using real-time video guidance on the screen of the device. Eye of the subject was found on screen and iris was focused manually. Then, retina was detected and focused automatically using auto-adjust mode of the device. SD-OCT images of central retina and fovea were obtained. During scanning period, infants were held still by a nurse. During imaging process, to obtain a better image, cornea was irrigated with a saline solution when cornea becomes dry.

No additional sedative or anesthetic drug was used. When needed, we gave the infants a sucrose solution in a feeding bottle to calm them during scanning. It took 5 to 10 minutes to acquire images.

After converting the SD-OCT images into digital images, two experienced ophthalmologists (MKE, DT) evaluated them for the development of macular pathology including cystoid macular edema (CME) and presence of retinal layers and ellipsoid zone (EZ). Central foveal thickness (CFT), the distance from the internal limiting membrane to the retinal pigment epithelium was measured for each patient (6). The average of two measurements was used for thickness analysis.

Intravitreal ranibizumab (IVR) injections were performed 1 to 1.5 mm from the limbus with a 30-gauge needle. The dose of ranibizumab was 0.25 mg. In case of recurrence, laser photocoagulation under sedation or a second IVR injection was performed.

RESULTS

Twenty-two infants (12 males, 10 females) diagnosed with Type 1 ROP or APROP were included in the study. Sixteen patients (7 male, 9 female) had type 1 ROP and, six patients had APROP (5 males, 1 female). Mean gestational age was 27.6 ± 1.8 weeks (range: 23 to 32 weeks) and mean birth weight was 942 ± 445 g (range: 560 - 1590 g). Post-menstrual age (PMA) with a diagnosis of type 1 or APROP ranged from 33 to 37 weeks. Mean follow-up time was 13.4 ± 6.5 months for all patients. Except for bilateral eyes of one patient, plus disease was regressed in a week after IVR injection in all patients. Recurrence of plus disease was observed in 10 eyes of six patients. Interval

time from initial injection to recurrence was between seven and 10 weeks. Both eyes of one patient were treated with IVR injection and remaining patients were treated with laser photocoagulation following disease recurrence. No additional treatment apart from the initial single dose IVR was applied to 30 eyes without recurrence. In our study, 85% of CME were seen in type 1 and AP ROP. CME resolution was observed in all but six eyes at the end of the second month (Figure 2). All eyes with recurrence of ROP had hyper reflective foci in the vitreous or retina (Figure 3). Delay in ellipsoid zone formation was observed in the IVR injected eye compared to un-injected eye in one patient (Figure 4). The graphic of CFT thickness before treatment and after IVR injection of first week, first and second months of patients is shown in Figure 5.

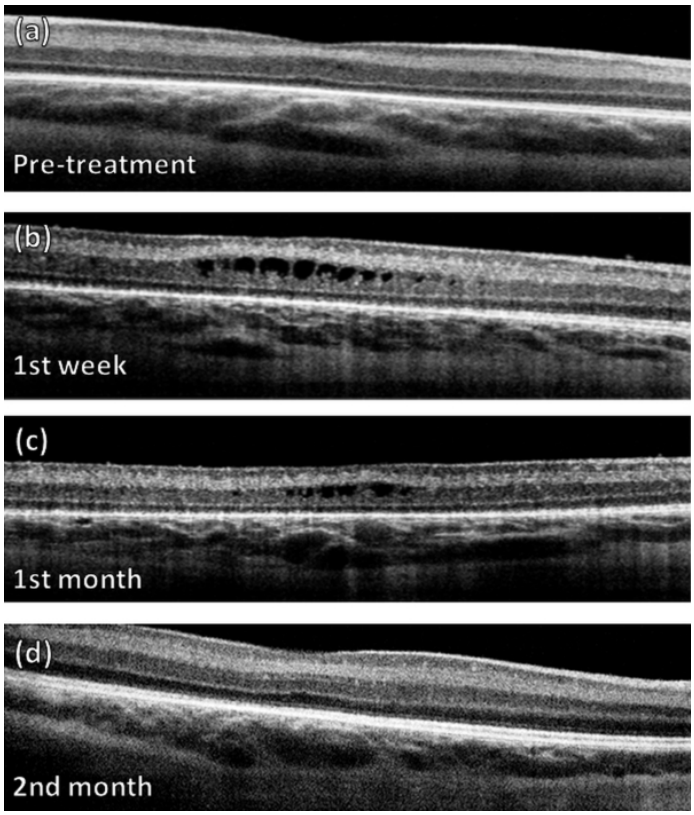

Figure 2. Spectral domain-optical coherence tomography (SD-OCT) images from right eye of a 30-week postmenstrual age, 1100 gr infant with type I retinopathy of prematurity. SD-OCT images are shown including initial scans (a), first week (b), first month (c) and second month (d) scans following intravitreal ranibizumab injection

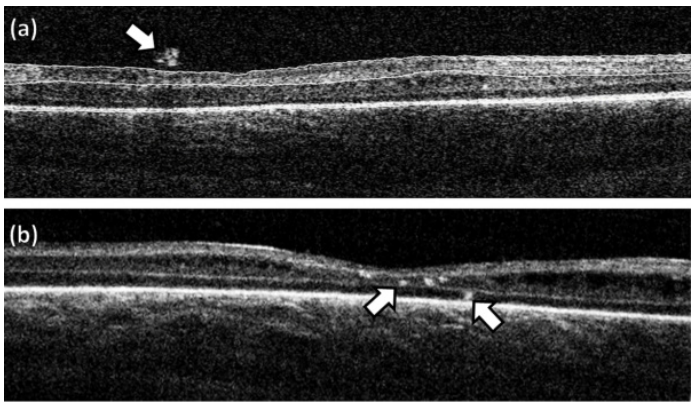

Figure 3. Examples of hyperreflective foci in the vitreous (a) and retina (b) of different patients with recurrence

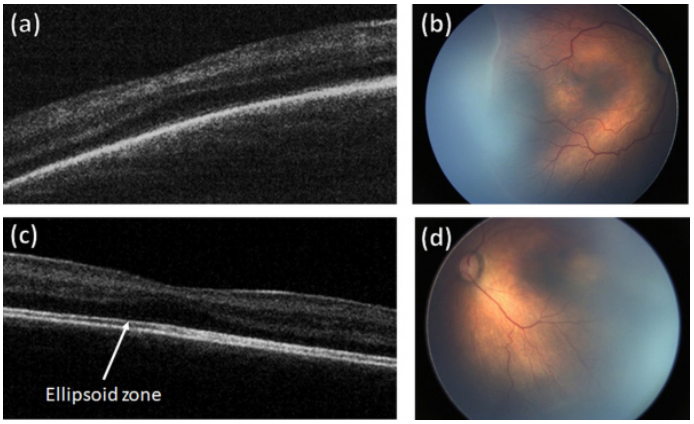

Figure 4. Spectral domain-optical coherence tomography (SD-OCT) and photographic images of retina in a 29 weeks postmenstrual age and 970 grams infant. (A), initial fundus image of right eye with type I retinopathy of prematurity (b). SD-OCT images of the untreated left eye captured the same session with left eye revealed ellipsoid zone formation (c) and initial fundus image of left eye (d)

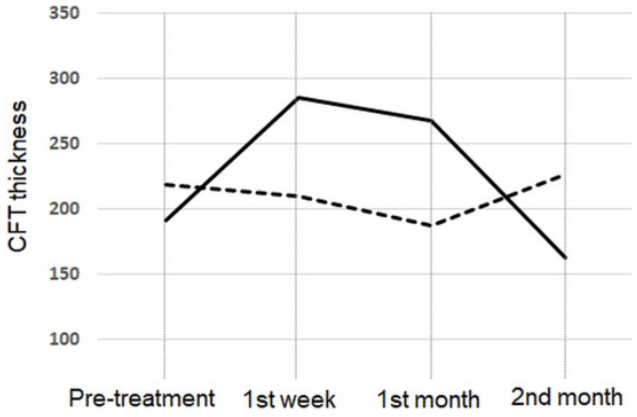

Figure 5. Central foveal thickness of patients with (dotted line), and without recurrence (continuous line) of retinopathy of prematurity (ROP) before and after intravitreal injection within 1st week, 1st ve 2nd months

DISCUSSION

In the current study, effects of intravitreal ranibizumab (IVR) injection on central foveal thickness as well as macular structure in patients with type 1 and aggressive posterior retinopathy of prematurity (APROP) and improvement of the disease following IVR therapy were investigated. Our study results showed that CFT and macular structural changes occurred following IVR injection. Although effectiveness of anti-VEGF agents for ROP has been proven by many studies, safety knowledge about these agents is limited. It has been reported that anti-VEGF agents may cause deficiency in central nervous system development. Also, anti-VEGF molecules, inhibits expression of some proteins in photoreceptors (14,22,23). Following bevacizumab administration, leakage into the systemic circulation from eye may occur and this may cause decrease in serum level of VEGF in ROP patients (24). However, Carneiro et al. reported that IVR injection does not alter systemic VEGF levels in adults (25,26). In our study, IVR injection was applied to 40 eyes of 22 patients with type I ROP and APROP. Plus disease regressed in 38 eyes of 21 patients in a week following IVR injection.

Recurrence of plus disease was observed in 10 eyes of 6 patients with an interval time of 7 to 10 weeks of follow-up. Sukgen et.al. performed IVR injection to 31 infants with a diagnosis of type I ROP or APROP in their study. They reported that, although ROP recurred in 14 infants, only four of them needed further treatment (27). Castellanos et al. performed single dose IVR injection to 6 patients with ROP disease and observed no recurrence during follow-up visits. (28). Wong et al. performed IVR injection to 6 patients with ROP. Although they observed regression of the ROP in all patients initially, they reported that ROP was reactivated in 5 (83%) patients in a mean time of 5.9 weeks (11). Our study demonstrated that ranibizumab can be used for ROP treatment. Our study showed that IVR injection for type I and APROP resulted in alterations in CFT and macular structure in short term. Knowledge of foveal development was limited particularly in ROP patients and based on solely postmortem histological analyses so far (29). Recent SD-OCT imaging studies in preterm infants provided further investigations about foveal development process in vivo (30). CME in preterm period is also known as macular edema of prematurity (18). The etiology of CME in premature infants has not yet been fully understood (31). It has not been known whether CME was a pathological process or part of normal foveal development in premature infants (32).

CME is considered to be associated with either neurohumoral factors such as VEGF or thought to be caused by mechanical traction (32,33,34). While CME cannot be observed by binocular indirect ophthalmoscopy method which is gold standard for screening of ROP, it can be detected by SD-OCT (35). Maldonado et al. reported 18 CME of the 31 ROP patients in a study with only one SD-OCT imaging session for each eye (34). Vinekar et.al reported a correlation between stage of the ROP and the severity of the CME (33). In contrast to their study results, no relationship was reported between the stages of ROP and the CME by several studies (18,32) . In the current study, CME was observed in all patients at various SD-OCT imaging session during follow-up period. This result may be related to our longer follow-up time and severity of the ROP which only Type I and APROP were included in the study.

Another interesting finding in our study was that presence of hyperreflective foci (HRF) in SD-OCT images of all ROP patients having a recurrence. While HRF is not observed in normal retina and vitreous it may exist in various retinal diseases including age-related macular degeneration, diabetic retinopathy, Stargardt disease and retinitis pigmentosa (36). HRF is considered to be caused by inflammation or the breakdown of retinal vessel barriers. Amount of HRF is known to be reduced in age-related macular degeneration after anti-VEGF agent injection (37). We propose that these HF are caused by increased inflammation and vascular permeability due to high VEGF concentrations.

There was a delay in photoreceptor maturation following anti-VEGF injection (Figure 4). EZ ,also known as IS-OS junction, is formed by longitudinal-oriented mitochondria that appear as a hyper-reflective band on OCT which can be seen in central retina approximately PMA 33 weeks (6). It has been reported that EZ could be used for predicting visual acuity after vitreoretinal surgery in adults (38). There is a fact that photoreceptor maturation is delayed in premature infants. Delayed photoreceptor development may be responsible for visual function defects in premature infants (14).

Mean CFT was increased due to edema following IVR injection in type I ROP or APROP patients without recurrence in early post-injection period (Figure 5). There was no increase in CFT in patients with recurrence of ROP in early post-injection period. We concluded that alterations in CFT may result from serum VEGF levels. Due to unknown mechanisms, suppressed VEGF levels in those who were applied IVR injection, might be a reason for retinal edema occurrence in eyes of premature infants. Recurrence of ROP might be due to excessive amounts of serum VEGF levels and since this high serum level of VEGF cannot be suppressed by IVR injection, it does not alter CFT. Our study results showed that after IVR injection retinal thickness alterations can be detected by SD-OCT. In patients with APROP and type 1 ROP, comparison of the CFT by SD-OCT, before and after injection may play a role in predicting recurrence of disease. Thus, we propose that more frequent follow-up examinations in those who are more likely to have recurrence may be beneficial.

Our study had some limitations, including small sample size, retrospective design, and short follow-up period. In addition, the iVue does not have a tracking system. We could not acquire repeated SD-OCT images from the exact same place. We only evaluated one cross-line image. Further studies including a larger sample size with a longer follow-up period are necessary to understand “clinical importance of these macular changes.

CONCLUSIONS

In conclusion IVR injection for type I and APROP resulted in alterations in CFT and macular structure in short term. CME is a frequently seen finding in type I ROP and APROP. It might be a physiologic consequence of normal development of macula as well as part of pathologic process influenced by IVR injection.

Competing interests: The authors declare that they have no competing interest.
Financial Disclosure: There are no financial supports
Ethical approval: This work has been approved by the Institutional Review Board.

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