

Structural, Visual and Refractive Outcomes of Intravitreal Aflibercept Injection in High-Risk Prethreshold Type 1 Retinopathy of Prematurity

Abdelrahman G. Salman Aza M. Said

Department of Ophthalmology, Ain Shams University, Cairo, Egypt

Key Words

Retinopathy of prematurity · Intravitreal injection · Aflibercept

Abstract

Purpose: To study the structural, visual and refractive outcomes of intravitreal injection of aflibercept monotherapy in patients with high-risk prethreshold type 1 retinopathy of prematurity (ROP). **Design:** Prospective nonrandomized interventional case series study. **Patients and Methods:** 1 mg/0.025 ml intravitreal aflibercept was administered for patients with high-risk prethreshold type 1 ROP. The primary outcomes studied were unfavorable structural outcome, unfavorable visual outcome and unfavorable refractive outcome. The secondary outcomes were absence of recurrence, ocular and systemic adverse events. **Results:** Twenty-six eyes were enrolled in the study; all had completed 1 year of follow-up. The mean birth weight was 991 ± 266 g (range: 875–1,105 g); the mean gestational age at birth was 26.33 ± 2.1 weeks (range: 24–30 weeks); 9 eyes were graded as ROP with stage 2+, zone I retinopathy, 14 eyes had stage 3+ disease in zone II and 3 eyes were diagnosed with stage 3 disease in zone I. Twenty-five eyes (96.2%) showed a favorable structural and 21 (80.1%) a favorable visual outcome, and the median refractive error after 1 year was 0.75 dpt (range: –9.5 to +4). **Conclusions:** Intravitreal injection of aflibercept monotherapy is an easy, safe and effective alternative mo-

dality of therapy for high-risk prethreshold type 1 ROP. A further multicenter study with a longer duration of follow-up is required.

© 2014 S. Karger AG, Basel

Introduction

Retinopathy of prematurity (ROP) is a proliferative vascular retinopathy affecting infants with a young gestational age (GA) and low birth weight (BW) [1]. No standard guidelines for the treatment of ROP existed before the multicenter trial of Cryotherapy for Retinopathy of Prematurity (CRYO-ROP) [2, 3]. Subsequently, the Laser ROP Study group and other studies found that laser photocoagulation (LPC) has been used for peripheral retinal ablation with at least equal success and is now the preferred method of ablation [4, 5].

More recently, the Early Treatment for Retinopathy of Prematurity Randomized Trial (ETROP) confirmed the efficacy of treatment of prethreshold type 1 ROP to improve retinal and visual outcomes at 9 months corrected age and redefined the guidelines for treatment of ROP [6]. The investigators defined type 1 and type 2 ROP from the cohort of prethreshold eyes and recommended treatment for type 1 prethreshold ROP.

Vascular endothelial growth factor (VEGF) plays an important role in the development of ROP [7]. Many stud-

ies were done on the role of anti-VEGF agents in ROP such as bevacizumab [8–10], ranibizumab [11, 12] or pegaptanib [13, 14] with approval of their safety and efficacy as alternative treatment. Aflibercept is a soluble decoy receptor, engineered by fusing VEGF receptors 1 and 2 to the Fc portion of human immunoglobulin G1, allowing it to bind all isoforms of VEGF-A, VEGF-B and placental growth factor [15]. The binding affinity of aflibercept for VEGF is substantially greater than that of either bevacizumab or ranibizumab [15], and mathematical modeling has predicted its potential for a longer duration of action in the eye [15]. Intravitreal aflibercept has recently gained popularity and has been approved by the US Food and Drug Administration for intraocular use in the treatment of some ocular neovascular diseases in adults [16, 17] without known serious ocular systemic adverse events.

Our study aimed to examine the structural, visual and refractive outcomes of intravitreal aflibercept injection monotherapy in patients with high-risk prethreshold type 1 ROP.

Patients and Methods

This prospective interventional nonrandomized study enrolled 26 eyes of 15 patients with high-risk prethreshold type 1 ROP. Type 1 ROP was defined according to the ETROP Study [6] as follows: (1) zone 1 stage 1 or 2 ROP with plus disease, (2) zone 1 stage 3 (fewer than 5 contiguous or 8 cumulative clock hours) ROP with plus disease, (3) zone 2 stage 2 ROP with plus disease, and (4) zone 2 stage 3 (fewer than 5 contiguous or 8 cumulative clock hours) ROP with plus disease. High risk was determined using a model based on the CRYO-ROP natural history cohort ($\geq 15\%$) [3].

We obtained written informed consent from the parents, including disclosure of the off-label use of the drug, its unknown safety and efficacy for this indication, and its unknown effects in children as an alternative to LPC treatment. This study was conducted in accordance with the declaration of Helsinki in 1975 and approved by the hospital medical and ethics committees.

All patients received a single dose of intravitreal aflibercept 1 mg/0.025 ml also known as VEGF Trap-Eye (Eylea[®], Regeneron Pharmaceuticals Inc., Tarrytown, New York, USA) which is half of the adult dosage. Inclusion criteria were high-risk prethreshold type 1 ROP with GA of 32 weeks or less and BW of 1,500 g or less according to the screening protocol of the Royal College of Pediatrics and Child Health and the Royal College of Ophthalmologists [18]. A minimum follow-up of 12 months was required. Exclusion criteria were refusal of a parent or guardian, any previous intravitreal injection, laser, cryotherapy or surgical procedure and presence of traction and detachment (stage IV or V) or any associated ocular or systemic disorders that could confound the interpretation of study results. Intravitreal aflibercept injection was performed according to the guideline of intravitreal injection by the Royal College of Ophthalmologists of 2009 [19]. We gave the injection 1.5 mm posterior to the limbus in the temporal inferior quadrant.

Follow-up examinations were performed by funduscopy daily for 1 week, weekly for 1 month, then monthly for 1 year postoperatively. This included both eyes even if the other eye was normal to detect any crossover effect of the injection in the sound eye. During the examinations, fundus photographs were taken with a Ret-Cam 120 digital fundus camera (Clarity Medical Systems Inc., Pleasanton, Calif., USA). The follow-up chart included demographic data, ocular data [the anatomical status of the retina, zone of ROP, the circumferential extent of extraretinal proliferation (ERP), changes in tortuosity, dilatation of retinal vessels, neovascularization] or any other abnormalities. Best-corrected visual acuity, spherical equivalent refraction (spherical value plus half the cylinder value) in each eye, presence of strabismus and duration of follow-up in months were recorded. Details of further injection, LPC or vitreoretinal surgeries, if any, and their results were noted as well as systemic data: number of ventilated days, presence of intraventricular hemorrhage and sepsis or any other systemic side effects of the drug. Systemic monitoring was performed along with the neonatal and pediatric doctor.

The technique employed to evaluate grading acuity with the Teller acuity card procedure as used previously in the CRYO-ROP study [3, 20] and ETROP study [6] and the Snellen equivalent were noted. Cycloplegic retinoscopy with cyclopentolate 1% eyedrops (Alcon Laboratories Inc., Fort Worth, Tex., USA) was made before injection, after 1 month and then every 6 months during the follow-up.

All patients were eligible to receive LPC in the form of 810-nm diode laser (Iris Medical Instruments Inc., Mountain View, Calif., USA) at any time if there were sustained vascular changes, tortuosity and dilatation after 2 weeks from the injection or progression to neovascularization in the anterior or posterior segment according to BEAT-ROP study recommendations [10]. In case of recurrence after complete resolution of ROP, another injection of aflibercept of the same dose was given. A masked physician was assigned to assess adverse events, supervise the masked assessment of efficacy and decide on the need for reinjection or shift to laser treatment.

The primary outcomes studied were: (a) unfavorable structural outcome, defined as per the CRYO-ROP study [2], (b) unfavorable visual outcome, defined as visual acuity of less than 20/200, and (c) unfavorable refractive outcome, i.e. high myopia, defined as myopia ≥ 5 dpt. The secondary outcomes were absence of recurrence within 1 year as suggested by the ETROP study [6], ocular and systemic adverse events.

Statistical Analysis

All data were recorded in preformatted data collection forms and analyzed; the software used to perform statistical calculations was SPSS version 18.0 (SPSS Inc., Chicago, Ill., USA). The results were considered statistically significant with descriptive levels of $p < 0.05$ and highly significant when $p < 0.001$.

Results

Twenty-six eyes of 15 infants were enrolled. All completed 1 year of follow-up with a range of 12–19 months. The mean BW was 991 ± 266 g (range: 875–1,105 g), the mean GA at birth \pm SD was 26.33 ± 2.1 weeks (range:

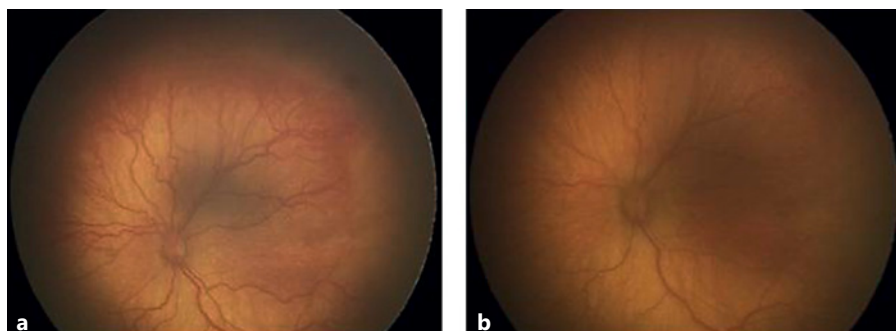


Fig. 1. **a** Zone 1, stage 3+, before bevacizumab injection. **b** Same eye, a few days after intravitreal aflibercept injection.

24–30 weeks), other demographical data are shown in table 1. Seven infants were excluded, 3 died within 3 months of treatment and 4 were lost to follow-up.

Structural Outcome

Regression of the disease occurred in 25 eyes (96.2%) after a single aflibercept injection. The successfully treated eyes showed a regression of plus disease within 2–6 days after the intravitreal injection, a decrease in pupillary rigidity, a resolution of any tunica vasculosa lentis, if present prior to the injection, and a complete regression of the retinal neovascularization within 2–3 weeks. The 25 eyes reached full vascularization 6–8 weeks after the injection. Among those with a favorable structural outcome, 2 eyes (7.7%) had disk dragging, with macular heterotopia. Figure 1 shows an eye before and after injection.

One eye (3.8%) had an unfavorable structural outcome with a single intravitreal aflibercept injection and was shifted to LPC in a near-confluent manner using a diode laser indirect ophthalmoscope and was retreated to cover the skipped areas after 1 month due to poor response; however, it progressed to stage 4A (extrafoveal partial retinal detachment) with reattached posterior pole after pars plana vitrectomy but with severe dragging of the macula and disk. For an unfavorable structural outcome, lower postconceptional age (PCA) at treatment ($p = 0.03$) and zone I disease ($p < 0.001$) were significant. The mean ERP in the 26 eyes was 4.0 ± 1.2 h (range: 2–7 h). However, BW, GA and number of ventilated days were not found to be significant risk factors for an unfavorable structural outcome.

Visual Outcome

Unfavorable visual outcome, i.e. visual acuity $< 20/200$, was present in 5 (19.2%) eyes. Two eyes had dragged disk and macular heterotopias. One eye had severe dragging of the disk and macula, and 2 eyes had anisometropia. The significant risk factor was zone I disease ($p = 0.002$).

Table 1. Characteristics and treatment of 26 eyes with ROP by intravitreal aflibercept injection

Case No.	Sex	BW, g	GA, weeks	Zone and stage		PCA at treatment, weeks
				OD	OS	
1	M	875	24	II, 3+	II, 3+	35
2	M	940	26	II, 3+	II, 3+	35
3	M	1,090	30	I, 2+	NROP	36
4	F	1,075	24	II, 3+	II, 3+	35
5	F	995	26	NROP	II, 3+	34
6	M	960	27	II, 3+	II, 3+	32
7	F	950	26	II, 3+	II, 3+	34
8	M	965	29	I, 2+	I, 2+	36
9	F	1,050	29	I, 2+	I, 2+	35
10	M	945	24	I, 3	NROP	33
11	M	1,105	25	I, 2+	I, 2+	35
12	M	965	27	NROP	II, 3+	34
13	F	935	26	II, 3+	II, 3+	35
14	M	1,060	27	I, 3	I, 3	34
15	M	955	25	I, 2+	I, 2+	35

PCA = Postconceptional age; NROP = no retinopathy of prematurity.

Other systemic or ocular risk factors were not found to be significant for an unfavorable visual outcome. Figure 2 shows the visual outcome.

Refractive Outcome

On cycloplegic retinoscopy, the median refractive error after 1 year was 0.75 dpt (range: -9.5 to $+4$). Fifteen (57.7%) eyes had nonsignificant hyperopia (range: 0.25–4 dpt) and 4 (15.4%) eyes had no refractive error (spherical equivalent: 0 dpt). Six (23.1%) eyes had low myopia (< -5 dpt; range: -0.25 to -4.25). Unfavorable visual outcome (> -5.0 dpt) was seen in only 1 (3.8%) eye. This eye had 9.5-dpt myopia. Two (7.7%) eyes had esotropia and

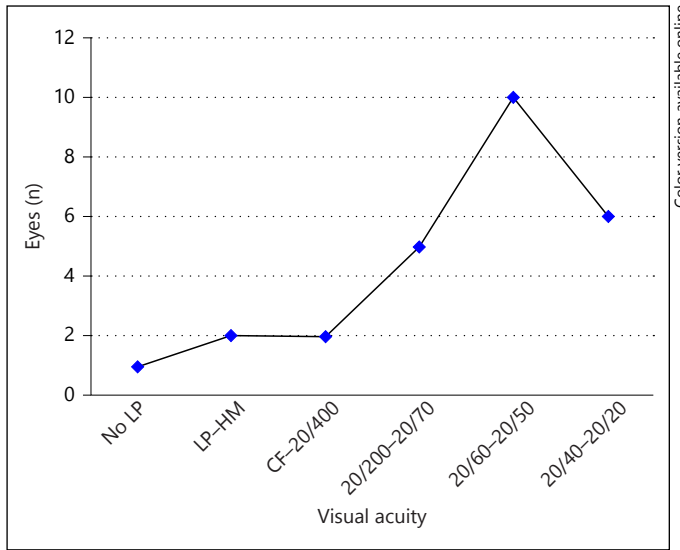


Fig. 2. Visual outcome of 26 eyes with ROP after 1 year of intravitreal aflibercept injection. LP = Light perception; HM = hand movements; CF = counting fingers.

2 (7.7%) eyes exotropia. Full cycloplegic refraction was given for them in the form of spectacles. Zone I disease ($p = 0.001$) and lower PCA at treatment ($p < 0.001$) were the only significant risk factors for high myopia.

Twenty-three (88.5%) eyes remained stable during the follow-up and no further treatment was necessary and no recurrence was present in the first year. Two eyes (7.7%) had recurrence of the plus disease after 21 weeks and the other after 19 weeks, and both were stage 2+ in zone I and were given another injection of aflibercept of the same dose, and no recurrence occurred later on. Ocular complications were preretinal hemorrhage of treatment in 1 eye (3.8%), which eventually resolved spontaneously after 3 weeks. Two eyes (7.7%) had subconjunctival hemorrhage which disappeared spontaneously after 2 weeks. No adverse effect in the other healthy eye from the crossover effect and no notable systemic complications that were related to the intravitreal aflibercept injection were observed during the follow-up period.

Discussion

The number of infants with ROP is increasing, likely due to the better medical management of premature infants worldwide. Also more infants are now eligible for ROP screening. In our study the mean BW was 991 ± 266 g, and the mean GA was 26.33 ± 2.1 weeks which were much

higher than the mean BW of 703 g and the mean GA of 25 weeks for the ETROP cohort [6]. As the infants treated in the present study were heavier and older, the disease profile and outcomes in these infants are likely to be different. To our knowledge this is the first study about the use of intravitreal aflibercept as a primary treatment in ROP.

The half-lives of bevacizumab, ranibizumab and aflibercept are calculated to be 4.32, 4.75 and 7.13 days in human eyes [21]. Meyer et al. [22] concluded that both concentrations of 1.5 and 3.0 mg of unbound anti-VEGF (bevacizumab) had the same pharmacokinetic characteristics which was no longer statistically significant after 6 weeks in the presumed extended biological active concentration, and the application of twice the dosage does not double the duration of its efficacy.

In our study, males were more likely to have an unfavorable structural outcome than females ($p = 0.054$). However, Foroozan et al. [23] did not find gender to be a significant risk factor. We found a favorable structural outcome in 25 eyes (96.2%). This was a higher rate in comparison with other forms of anti-VEGF in the treatment of ROP such as bevacizumab [8–10], ranibizumab [11, 12] or pegaptanib [13, 14]. This may be explained by the effective and long duration effect of intravitreal aflibercept and its work in both VEGF-1 and VEGF-2 receptors and the choice to treat prethreshold, not threshold disease.

In comparison with other forms of treatment, the efficacy of intravitreal aflibercept monotherapy was nearly the same or higher than LPC with 87.5–92% [6, 10] and better than cryotherapy (40%) [2, 3]. This could be explained by the role of aflibercept to block VEGF, which is already produced and is present in the vitreous body, while LPC prevents any further production of VEGF in addition to the inflammation induced with cryotherapy. The successfully treated eyes in our study group showed a regression of plus disease within 2–6 days after the intravitreal injection, a decrease in pupillary rigidity, a resolution of any tunica vasculosa lentis, if present prior to the injection, and a complete regression of the retinal neovascularization within 2–3 weeks, and they were comparable with the bevacizumab-treated eyes in the BEATROP study [10]. We found 4 (15.4%) eyes with disk dragging and with macular heterotopias, and it was severe in one of these which progressed to stage 4A (extrafoveal partial retinal detachment) and had a reattached posterior pole after pars plana vitrectomy. This was comparable with other studies [8–12].

Favorable visual outcome was present in 80.8% which was comparable with other types of anti-VEGF treatment [8, 10] and LPC [24]. We studied various risk factors for

structural, visual and refractive outcomes and found zone I disease to be the most important risk factor for all 3 unfavorable outcomes. In our study, the correlation of abnormal retinal structure with poor visual outcomes was statistically significant ($p = 0.001$), and zone I disease was present in 12 (46.2%) eyes. The adverse effect of ROP in zone I on the structural outcome was also observed in the ETROP study [24] in both conventionally treated and early treated prethreshold high-risk eyes. Axer-Siegel et al. [5] made similar observations regarding structural outcome but did not evaluate the effects statistically. This was in contrast to Foroozan et al. [23] who did not find zone I disease to be a statistically significant risk factor for unfavorable structural outcome. Disease in zone I was the only risk factor for unfavorable visual outcome in our study. This was comparable with the conventional arm of the ETROP study but was not statistically significant [24]. We found zone I disease to be a strong risk factor ($p < 0.001$) for high myopia. This was also observed in the ETROP study, i.e. that in the conventionally treated eyes, both myopia and high myopia ≥ 5 dpt were higher in zone I eyes compared with zone II eyes [24].

Previous studies have reported that the prevalence of myopia is positively correlated with a lower BW and greater severity of ROP and the development of myopia is linked to cicatricial retinal changes and retinal residuals of ROP [24, 25]. In the present study, the regression of ROP was seen without structural retinal sequelae, which may also account for lower rates of myopia. The extent of ERP was not found to be significant for unfavorable structural, visual or refractive outcomes; this was in contrast to treatment in threshold ROP where the extent of ERP was a significant risk factor for high myopia [23, 25]. Bourla et al. [26] reported that abnormal retinal structure rarely causes poor visual outcomes after laser therapy for ROP compared to factors such as strabismus, amblyopia and perinatal neurological events. Strabismus is common in ROP-treated subjects and may be seen in 16.3–39% [23–25]. The ETROP study reported strabismus in 22.8% of prethreshold eyes with a bilateral favorable outcome [6]. The low rate of strabismus in our study (15.4%) might be attributed to the short follow-up duration, predominant symmetric presentation and early start of treatment.

The correct injection timing is important. Kim et al. [8] reported that due to the interaction of an anti-VEGF drug and retinal vascular development, the timing of anti-VEGF therapy should be later than 30 weeks of PCA. In our study PCA was 34.5 ± 0.7 weeks. The recurrence rate in our study was 7.7% which was comparable with that of the BEAT-ROP group [10], where bevacizumab

injection had a recurrence rate of 6% in combined retinal zones I and II compared with a 26% recurrence rate in laser treatment. Data from the CRYO-ROP trial [2, 3] and the ETROP trial [6] and BEAT-ROP group [10] suggested that recurrence of ROP generally occurs before 55 weeks postmenstrual age.

In our study there were no serious systemic adverse effects. This was comparable with intravitreal anti-VEGF agents in other studies [8–14] although continued extensive evaluations of infants are warranted for possible long-term effects with measuring the level of VEGF in the peripheral blood before and after the injection. An intravitreal anti-VEGF agent might also avoid complications that can be seen with laser such as the onset of visual field loss, macular burn or anterior segment ischemia, although LPC had the advantage of an absence of systemic side effects.

Drawbacks of our study were first the short time of follow-up of approximately 1 year, which was still relatively short, so the study did not allow conclusions about the long-term effects and side effects of the therapy. Second, there was the high cost of aflibercept even in comparison with other anti-VEGF drugs. Third, the method of measuring visual acuity was subjective, and the number of children included was relatively small, which does not allow any statements on the safety of the therapy.

Conclusions

In a 1-year follow-up, a single intravitreal injection of aflibercept was an easy and effective modality of therapy for high-risk prethreshold type 1 ROP disease with highly favorable structural, visual and refractive outcomes. However, further prospective, randomized, controlled clinical trials with a larger number of enrolled patients and a longer follow-up are necessary to determine the best choice of drug as well as the optimal dose and timing, the need for repeat treatments, the possibility of ocular or systemic complications and the persistence of the effect.

Acknowledgment

We thank those who gave a donation and do not want us to mention their names. This article has been funded by Ain Shams University.

Disclosure Statement

The authors have no financial interest.

References

- 1 Palmer EA, Flynn JT, Hardy RJ, Phleps DL, Phillips CL, Schaffer DB, et al: Incidence and early course of retinopathy of prematurity. *Ophthalmology* 1991;11:1628–1640.
- 2 Cryotherapy for Retinopathy of Prematurity Cooperative Group: Multicenter trial of cryotherapy for retinopathy of prematurity. Preliminary results. *Arch Ophthalmol* 1988;106:471–479.
- 3 Palmer EA, Hardy RJ, Dobson V, et al; Cryotherapy for Retinopathy of Prematurity Cooperative Group: 15-year outcomes following threshold retinopathy of prematurity: final results from the multicenter trial of Cryotherapy for Retinopathy of Prematurity. *Arch Ophthalmol* 2005;123:311–318.
- 4 Laser ROP Study Group: Laser therapy for retinopathy of prematurity. *Arch Ophthalmol* 1994;112:154–156.
- 5 Axer-Siegel R, Maharshak I, Snir M, Friling R, Ehrlich R, Sherf I, et al: Diode laser treatment of retinopathy of prematurity. Anatomical and refractive outcomes. *Retina* 2008;28:839–846.
- 6 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.
- 7 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.
- 8 Kim J, Kim SJ, Chang YS, Park WS: Combined intravitreal bevacizumab injection and zone I sparing laser photocoagulation in patients with zone I retinopathy of prematurity. *Retina* 2014;34:77–82.
- 9 Harder BC, Schlichtenbrede FC, von Baltz S, Jendritza W, Jendritza B, Jonas JB: Intravitreal bevacizumab for retinopathy of prematurity: refractive error results. *Am J Ophthalmol* 2013;155:1119–1124.
- 10 Mintz-Hittner HA, Kennedy KA, Chuang AZ; BEAT-ROP Cooperative Group: Efficacy of intravitreal bevacizumab for stage 3 retinopathy of prematurity. *N Engl J Med* 2011;364:603–615.
- 11 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;97:816–819.
- 12 Orozco-Gómez LP, Hernández-Salazar L, Moguel-Ancheita S, Ramírez-Moreno MA, Morales-Cruz MV: Laser-ranibizumab treatment for retinopathy of prematurity in umbra-preumbra disease. Three years of experience. *Cir Cir* 2011;79:207–214, 225–232.
- 13 Autrata R, Senková K, Holoušová M, Krejčířová I, Doležel Z, Borek I: Effects of intravitreal pegaptanib or bevacizumab and laser in treatment of threshold retinopathy of prematurity in zone I and posterior zone II – four years results. *Cesk Slov Oftalmol* 2012;68:29–36.
- 14 Autrata R, Krejčířová 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;22:687–694.
- 15 Papadopoulos N, Martin J, Ruan Q, et al: Binding and neutralization of vascular endothelial growth factor (VEGF) and related ligands by VEGF Trap, ranibizumab and bevacizumab. *Angiogenesis* 2012;15:171–185.
- 16 Brown DM, Heier JS, Clark WL, Boyer DS, Vittori R, Berliner AJ, Zeitz O, Sandbrink R, Zhu X, Haller JA: Intravitreal aflibercept injection for macular edema secondary to central retinal vein occlusion: 1-year results from the phase 3 COPERNICUS Study. *Am J Ophthalmol* 2013;155:429–437.
- 17 Holash J, Davis S, Papadopoulos N, et al: VEGF-Trap: a VEGF blocker with potent antitumor effects. *Proc Natl Acad Sci USA* 2002;99:11393–11398.
- 18 Royal College of Pediatrics and Child Health and Royal College of Ophthalmologists: Retinopathy of prematurity guideline. May 2008. <http://www.rcophth.ac.uk/core/>.
- 19 Royal College of Ophthalmologists: Guideline of intravitreal injection by Royal College of Ophthalmologists. February 2009. <http://www.rcophth.ac.uk/core/>.
- 20 Dobson V, Quinn GE, Biglan AW, et al: Acuity card assessment of visual function in the Cryotherapy for Retinopathy of Prematurity trial. *Invest Ophthalmol Vis Sci* 1990;31:1702–1708.
- 21 Stewart MW, Rosenfeld PJ, Penha FM, Wang F, Yehoshua Z, Bueno-Lopez E, Lopez PF: Pharmacokinetic rationale for dosing every 2 weeks versus 4 weeks with intravitreal ranibizumab, bevacizumab, and aflibercept (vascular endothelial growth factor Trap-eye). *Retina* 2012;32:434–457.
- 22 Meyer CH, Krohne TU, Holz FG: Intraocular pharmacokinetics after a single intravitreal injection of 1.5 mg versus 3.0 mg of bevacizumab in humans. *Retina*. 2011;31:1877–1884.
- 23 Foroozan R, Connolly BP, Tasman WS: Outcomes after laser therapy for threshold retinopathy of prematurity. *Ophthalmology* 2001;108:1644–1646.
- 24 The Early Treatment for Retinopathy of Prematurity Group; Good WV, Hardy RJ, Dobson V, et al: Final visual acuity results in the Early Treatment for Retinopathy of Prematurity Study. *Arch Ophthalmol* 2010;128:663–671.
- 25 Sahní J, Subhedar NV, Clark D: Treated threshold stage 3 versus spontaneously regressed subthreshold stage 3 retinopathy of prematurity: a study of motility, refractive, and anatomical outcomes at 6 months and 36 months. *Br J Ophthalmol* 2005;89:154–159.
- 26 Bourla DH, Gonzales CR, Valijan S, Yu F, Mango CW, Schwartz SD: Association of systemic risk factors with the progression of laser-treated retinopathy of prematurity to retinal detachment. *Retina* 2008;28(suppl 3):S58–S64.