We are IntechOpen,
the world's leading publisher of
Open Access books
Built by scientists, for scientists

4,800

Open access books available

122,000

International authors and editors

135M

Downloads

Our authors are among the

154

Countries delivered to

TOP 1%

most cited scientists

12.2%

Contributors from top 500 universities

CLARIVATE ANALYTICS

BOOK CITATION INDEX

INDEXED

WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com

Therapeutic Options in Retinopathy of Prematurity

Simona Delia Nicoară

Abstract

Preterm babies may develop retinopathy of prematurity (ROP) in various stages. Most of them regress spontaneously without treatment, and a small proportion develops severe ROP that can lead to visual loss if not treated promptly. Less than 10% of the ROP cases require treatment worldwide. Before 1980, the only treatment for ROP was vitreoretinal surgery for retinal detachment in advanced stages of the disease. Around this time, cryotherapy started to be used in order to ablate the peripheral retina and interrupt the pathogenic chain in ROP, but there were no indications correlated with the severity of the disease. Few years later, cryotherapy was replaced by indirect laser photocoagulation of the nonvascular retina that became the golden standard of treatment for ROP. During the last years, efforts have been made in order to find therapeutic methods to induce the regression of new vessels with minimal side effects. Among these, intravitreal injections of anti-vascular endothelial growth factor (VEGF) became increasingly popular in the treatment of ROP worldwide. Personal experience in treating aggressive posterior ROP (APROP) with laser versus intravitreal anti-VEGF is presented. Intravitreal anti-VEGF proved its superiority in treating APROP as compared to laser, with no systemic and/or local side effects in our series.

Keywords: retinopathy of prematurity, laser, bevacizumab, cryotherapy, blindness

1. Introduction

All high-risk pregnancies are on the rise, and most of them result in a premature birth which is induced either due to maternal factors or fetal factors. Moreover, theoretically there could be more instances where retinopathy of prematurity (ROP) can develop because there has been a lot of development as well as success in management of preterm babies. Progress in neonatal care was associated with higher survival rates of low birth weight and low gestational age newborns.

Retinopathy of prematurity (ROP) is an important threat for the vision of the premature infants, especially for those born at low postconceptional ages (PCAs) and with low birth weights (BWs) [1, 2].

Following progress in neonatal care, the prevalence of ROP is increasing in the developing world, justifying the identification of ROP as a leading cause of visual impairment in children in the developing world, by the World Health Organization (WHO) [1].

In the developed countries, ROP accounts for 4% of childhood blindness, whereas in the developing ones, ROP generates 40% of it [1].

Many preterm babies will develop ROP in various stages. Most of them regress spontaneously without treatment, and a small proportion develops severe ROP that can lead to visual loss if not treated promptly [3]. ROP is one of the few largely preventable causes of visual impairment in children [3–5].

Fortunately, a treatment is available that can significantly reduce the rate of unfavorable outcomes [1]. The early detection of ROP and the prompt treatment are crucial for the prevention of blindness. Currently, there are two therapeutic methods to treat ROP: intravitreal injections with anti-vascular endothelial growth factor (VEGF) agents and indirect laser photocoagulation of the nonvascularized retina [2].

2. Pathophysiology of ROP

During the first 4 months of gestation, the retina has no blood vessels, and it is nourished by the hyaloid vasculature [6].

At 16 weeks, the angioblasts near the hyaloid artery invade the nerve fiber layer, and the first retinal vessels appear at the level of the optic nerve head. They grow progressively toward the periphery, reaching the ora serrata at 36 weeks in the nasal sector and at 40 weeks in the temporal one [6].

The development of the superficial and deep layers of the retinal vasculature depends on the delicate balance between the growth factors which are secreted by the astrocytes and the microglia: vascular endothelial growth factor (VEGF) and insulin growth factor-1 (IGF-1) [6].

During the second half of pregnancy, there is relative intrauterine hypoxia. When premature birth occurs, retinal vessels are not completely developed. Altered oxygen condition is a risk factor for the development of ROP which is a biphasic disease.

The first phase (from the moment of birth to 31- to 32-week postconceptional age) is characterized by relative environmental hyperoxia which leads to the arrest of the normal retinal development [6].

During the second phase (from 32- to 36-week postconceptional age), the retina matures, and its metabolic needs increase. By consequence, it is characterized by relative hypoxia and overexpression of VEGF, IGF-1, and oxidative damage with subsequent new vessel growth and retinal detachment [6].

The association between ROP and the administration of high doses of oxygen was demonstrated for the first time by Patz et al. in 1953 [6].

3. ROP classification

ROP was classified for the first time in 1984 by an international group of experts and updated in 2005. In classifying ROP, three criteria are used: zone, stage, and presence/absence of "plus" disease [7].

Topographically, the retina is divided into three zones. Zone 1 corresponds to a circle centered on the optic disc and with the radius equal to the double distance between the optic disc and the fovea. Zone 2 corresponds to a circle centered on the optic disc with the radius equal to the distance between the optic disc and ora serrata nasally. Zone 3 corresponds to the remaining crescent of the temporal retina up to ora serrata [7].

The stage describes the retinal changes at the limit between the vascular and nonvascular retina. Stage 1 is defined by a demarcation line, stage 2 by a nonvascular (white) ridge, and stage 3 by a vascular (red) ridge. Stage 4a corresponds to

peripheral retinal detachment, stage 4b involves also the detachment of the fovea, and stage 5 represents total retinal detachment in an open or closed funnel. "Plus" disease refers to the dilation and irregularity of retinal arteries and veins in the posterior pole, as compared to a standard photograph [7].

Aggressive posterior ROP (APROP) is a subtype of ROP with a very unpredictable and aggressive behavior. It is always located posterior (zone 1 and posterior zone 2), with very severe "plus" disease and with flat neovascularization that progresses rapidly, without getting through the stages described above [7].

The Early Treatment for ROP (ETROP) study reclassified ROP according to the required attitude: type 1, ROP requiring treatment and type 2, ROP requiring closely monitoring.

4. Diagnosis and screening for ROP

Fortunately, it is estimated that less than 10% of the ROP cases require treatment worldwide. More than 90% regress spontaneously [1].

Various screening criteria apply in different countries/regions. For instance, in the USA, the screening criteria updated in 2013 include all infants with BW of 1500 g or less or GA 30 weeks or less.

Heavier and more mature babies are included in the screening at the discretion of the neonatologist, especially if other complications are present: necrotizing enterocolitis, intraventricular hemorrhage, sepsis, and bronchopulmonary dysplasia. According to our national guidelines, all premature newborns with GA of 34 weeks or less or with BW 2000 grams or less are included in the ROP screening.

The first screening should be performed at 4–6 weeks after birth or at PCA 31 weeks whichever is later. When examining a premature infant, one of three situations can be identified: mature retina, immature retinal vascularization, or ROP. ROP screening can be discontinued if retinal vascularization is present in zone 3, without previous zone 1 or zone 2 disease; there is no evidence of prethreshold disease or worse ROP by 50 weeks PCA; there is regressing ROP in zone 3 without abnormal vascular tissue that can reactivate in zone 2 or 3.

ROP screening is made by trained ophthalmologists, using indirect ophthalmoscopy and scleral indentation in order to have access to the retinal periphery. Pupils must be dilated with a mixture of tropicamide 0.5% and phenylephrine 2.5%, and the lids are maintained open with a lid speculum throughout the examination.

5. Prevention and risk factors

The most important factor to prevent ROP is preventing premature birth [6].

The STOP-ROP multicenter study evaluated the risk for prethreshold ROP development in correlation with the oxygen saturation, and it showed no difference between maintaining an oxygen saturation level of 96–99% versus 89–94% [6].

BOOST II study showed a higher survival rate in infants younger than 28 weeks GA with 91–95% oxygen saturation levels but with an increased risk of ROP at this oxygen rate in other studies [6].

6. Treatment of ROP

Before 1980 the only treatment for ROP was vitreoretinal surgery for retinal detachment in advanced stages of the disease. Around this time cryotherapy started

to be used in order to ablate the peripheral retina and thus interrupt the pathogenic chain in ROP, but there were no guided indications in correlation with the severity of the disease [6].

CRYO-ROP elaborated a classification of ROP and defined "threshold" disease in which therapy was indicated: 5 contiguous hours or 8 non-contiguous hours of stage 3 ROP with plus disease in zone 1 or 2 [8].

A subsequent study, ETROP investigated whether treatment performed earlier than in threshold disease would further reduce the rate of anatomic unfavorable outcomes. Prethreshold disease was defined as type 1 and type 2 ROP. Clinically, type 1 ROP includes the following categories: zone 1 ROP of any stage with plus, zone 1 stage 3 ROP without plus, and zone 2 stage 2 or 3 disease with plus. In type 2 ROP, the following situations are included: zone 1 stage 1 or 2 without plus or zone 2 stage 3 without plus. ETROP recommends treatment in type 1 ROP and monitoring in type 2 ROP. At 6-year follow-up, the study proved 9% unfavorable structural outcomes in the early treated eyes, as compared to 15% unfavorable structural outcomes in the conventional treatment group. ETROP recommends peripheral laser ablation in type 1 ROP and frequent observation in type 2 ROP.

At this point, ablation of the peripheral retina was made by indirect laser photocoagulation that had replaced cryotherapy [9].

There are several advantages of laser over cryotherapy: laser requires less general anesthesia, it treats easier the posterior ROP, and it is associated with less systemic side effects: apnea, bradycardia, and cardiopulmonary arrest requiring resuscitation. However, ocular complications were reported after extensive indirect diode laser photocoagulation: vitreous hemorrhage, cataract, intraocular inflammation, choroidal effusion, and elevated intraocular pressure [9]. Theoretically, the risk of cataract is very low, given the fact that the infrared radiation that we use is absorbed deep into the choroid and not in the crystalline lens. Vitreous hemorrhage is rather a sign of ROP progression than a complication related to the laser itself.

Parvaresh et al. published the results of transscleral diode laser photocoagulation instead of transpupillary approach and concluded that it is technically easier, especially for retinal periphery and with fewer complications at the level of the anterior segment such as cataract formation [10].

During the last years, efforts have been made in order to find therapeutic methods to induce the regression of new vessels with minimal side effects [10].

Given the role of VEGF in angiogenesis, anti-VEGF administered intravitreally emerged as a promising tool for the treatment of ROP, alongside its use in ischemic retinopathies. Research conducted over the latest two decades proved that VEGF is one of the major factors involved in ROP pathogenesis [10].

VEGF inhibition with subsequent suppression of neovascular disease was proved by several experimental and clinical studies [10].

Clinical studies showed significantly higher levels of VEGF in the vitreous of patients with vasoproliferative ROP [11–13]. Sato et al. analyzed 27 cytokines in the vitreous of ROP eyes and found that VEGF was the most strongly correlated with vascularly active ROP [11]. This study also identified other factors elevated in ROP: fibroblast growth factor (FGF), granulocyte-colony stimulating factor (G-CSF), and granulocyte macrophage-colony stimulating factor (GM-CSF). This observation sustains the participation of an inflammatory response in the complex process of ROP development in addition to known vascular growth factors such as VEGF.

Animal ROP models showed the suppression of the vascular disease following intravitreal anti-VEGF injection [14, 15].

Nonobe et al. injected bevacizumab in the vitreous of five premature infants and showed the marked decrease of aqueous humor concentration of VEGF in four of them. Law et al. injected bevacizumab in 13 eyes of seven premature infants prior

to laser or vitrectomy, and they noticed the improvement of the visualization of the retina with no systemic side effects, suggesting the role of anti-VEGF therapy prior these procedures [10].

A retrospective study carried by Lee et al. on 15 premature infants with stage 3 ROP showed the rapid regression of plus disease with more rapid development of normal vessels toward the retinal periphery, with no significant increase in systemic or ocular complications, compared with patients treated with laser photocoagulation [10].

Considerably concerns remain regarding the safety of anti-VEGF treatment in ROP, especially considering the correct dosage, timing of injection, and potential local complications such as infection, lens damage, and effect on the development of the neurosensory retina. Systemic side effects were not reported yet, but concern persists especially regarding the development of the central nervous system.

The Bevacizumab Eliminates the Angiogenic Threat of Retinopathy of Prematurity (BEATROP) study concluded that one doze of bevacizumab 0.625 mg in 0.025 ml had significantly better results in reducing the recurrence rate in zone 1 stage 3 ROP as compared to laser: 6 versus 42%, respectively. However, in posterior zone 2 ROP, the results were similar with intravitreal bevacizumab and laser. An interesting observation was that in some cases treated with intravitreal bevacizumab, late recurrence was noted: 16 ± 4.6 weeks with bevacizumab, as compared to 6.2 ± 5.7 weeks with laser. Therefore, follow-up in anti-VEGF-treated eyes should be performed for longer periods [10].

Erythropoietin (Epo) is another growth factor that was proved to promote angiogenesis in vitro and in animal models. Recombinant Epo (rhEpo) is used to treat anemia in premature infants, as it promotes red blood cell formation. Sato et al. showed significantly elevated levels of Epo in 40 eyes from 27 premature infants with stage 4 ROP [13]. Suk et al. carried out a retrospective study in which he investigated the rhEpo treatment and ROP in 265 patients. The study concluded that high dose and later starting age for rhEpo treatment are risk factors for ROP (the phase of the disease was not taken into account). However, Shah et al. in a retrospective study on 85 patients found no correlation between the rhEpo treatment and the incidence and severity of ROP [16].

Research in the field of angiogenesis led to a number of new ways to prevent ROP progression: targeting the insulin growth factor (IGF-1) pathway and dietary supplementation with omega-3 polyunsaturated fatty acids (PUFAs) [10].

Following preterm birth, serum IGF-1 is substantially reduced due to the interruption of fetal-maternal interaction. Animal models of ROP proved that IGF-1 is essential for vascular growth through interaction with VEGF signaling. Therefore, theoretically, supplementation of IGF-1 during phase 1 ROP would normalize vascular growth and subsequently prevent abnormal vascular proliferation in phase 2 ROP [10].

Omega-3 PUFAs protect against pathologic neovascularization in ROP. They lack from the diet of premature infants because there is no transfer from the mother during the last trimester. Therefore, studies are planned to investigate the potential benefit of supplementing omega-3 PUFA intake in premature infants [10].

Currently, laser photocoagulation of the nonvascular retina remains the only well-established, gold standard therapy to prevent ROP progression toward blindness. There is clinical and experimental research going on in order to add therapeutic strategies meant to improve the prognosis of this potentially blinding disease.

Despite timely treatment, it is estimated that approximately 16% of patients with type 1 ROP develop retinal detachment. The results reported by a large series of cases showed that the reattachment rate following pars plana vitrectomy is correlated with the stage of ROP: 82% for stage 4A, 70% for stage 4B, and 43% for stage

5 ROP. Scleral buckles can also be used for stage 4A ROP. A small case series showed that the association of a scleral buckle to pars plana vitrectomy did not improve the reattachment rate as compared cu PPV alone [10].

Because the therapeutic results in stage 5 ROP are extremely poor, the goal is to screen and treat type 1 ROP before the occurrence of retinal detachment.

In some circumstances, exudative retinal detachment is present, as a result of leakage from the vascular structures. This type of detachment is usually located posterior to the ridge, and it is convex in shape. Favorable results were reported in some of these cases after intravitreal administration of bevacizumab [10].

7. Personal experience in the treatment of aggressive posterior ROP (APROP)

7.1 Background

APROP is a particularly severe form of ROP defined by the following characteristics: posterior location (zone I or posterior zone II), very dilated and tortuous vessels, and development of arteriovenous shunts [17]. The evolution of APROP toward retinal detachment is very rapid, without the stages described in the "classic" form of ROP.

Laser treatment of ROP became available in the Ophthalmology Department ("Iuliu Hatieganu" University of Medicine and Pharmacy from Cluj-Napoca, Romania) in 2006, whereas intravitreal bevacizumab injections started to be used in 2009 (Avastin; Genentech Inc., San Francisco, California, USA).

In this study, we aimed to establish the relative effectiveness and safety of intravitreal bevacizumab (IVB) as compared to laser photocoagulation in APROP.

7.2 Method

We analyzed retrospectively all the files of the consecutive infants with APROP that we treated either by laser photocoagulation or with IVB between January 1, 2006 and December 31, 2013 and were followed for at least 60 weeks (for the laser group) and 80 weeks (for the IVB group). The overall follow-up ranged between 60 and 144 weeks from the treatment. The study was in agreement with the declaration of Helsinki (1964), and it has the approval of the ethics committee of our university.

Main outcome measures are represented by APROP regression, and the structural outcome associated either with laser photocoagulation or with IVB.

7.2.1 Medical intervention

In APROP we perform treatment (laser or IVB) within 24 hours from diagnosis. Before the intervention, a mixture of tropicamide 0.5% and phenylephrine 2.5% was instilled four times, every 15 minutes in order to obtain pupil dilatation. All laser treatments were performed under analgesia and sedation in the neonatology unit. Laser energy was delivered transpupillary from a portable diode laser having the emission of 810 nm, through the indirect ophthalmoscope. The lids were maintained open with a lid speculum, and the light and laser energy were focalized on the retina with the help of a + 28 diopters lens. We started laser photocoagulation of the retina with a power of 150 mW which we increased gradually up to the obtaining of the desired effect (whitish burn on the retina). We did not exceed 300 mW, the exposure time was 200 ms, and the spot dimension was 200 microns in all circumstances. We applied between 4000 and

6000 burns per eye in 1 or 2 sessions, according to the amount of the nonvascularized retina. The first postlaser checkup took place at 6–7 days and continued every 6–7 days, until there was evidence of APROP regression. If APROP failed to regress, re-treatment was carried out immediately. The frequency of checkups was determined by the clinical course of the disease.

We injected bevacizumab intravitreally for APROP according to the following guidelines: topical anesthesia with 0.5% proparacaine hydrochloride administered three times, every 2 minutes, topical administration of betadine 5%, fixation of the lid speculum, and injection of 0.025 ml (0.625 mg) bevacizumab at 1.5–1.75 mm from the limbus (in the pars plicata), with a 30G needle, perpendicularly on the globe, aiming the center of the eyeball. For the next 3 days, topical tobramycin eye drops were instilled five times/day. The first checkup took place the next day (for the risk of endophthalmitis) and then 7 days following the injection. The follow-up continued every week and then according to the clinical course of the disease.

7.2.2 Follow-up

The infants treated by laser were followed for at least 60 weeks, every month, whereas the ones treated with IVB were followed for at least 80 weeks, every 2 weeks for the first 3 months and then every month. The follow-up was discontinued when full vascularization of the retina was noticed. The exams were performed by three ophthalmologists trained in ROP. In the same time, the patients were followed by pediatricians for the risk of systemic complications related to intravitreal anti-VEGF therapy.

7.2.3 Anatomical outcome

The anatomical outcome was evaluated by indirect ophthalmoscopy. The following signs were considered positive outcome: good pupil dilation and the decrease/disappearance of retinal vessel tortuosity and of the neovascularization. In the IVB group, normal development of the retinal vessels toward periphery was noted. The aggravation of APROP was defined if "plus disease" and/or neovascularization persisted/reappeared, and there were signs of retinal detachment. In these circumstances, laser photocoagulation was added if possible.

7.2.4 Statistical analysis

Statistical analysis was performed using Microsoft Excel and IBM SPSS (version 23.0).

7.3 Results

Between January 1, 2006 and December 31, 2013, we treated 23 infants with APROP. The laser group includes 6 APROP infants and the intravitreal bevacizumab (IVB group) and 17 APROP infants. In both groups, the treatment was bilateral.

7.3.1 Evolution following treatment

APROP treated by laser totalized 24 eyes and by bevacizumab, 34 eyes. Among the laser-treated eyes, the outcome was favorable in 18 eyes (75%), and within the IVB-treated eyes, result was favorable in 29 eyes (85.29%). Chi-square test and Fisher exact test prove no statistically significant difference: $p = 0.419$ and $p = 0.412$, respectively.

We needed to repeat laser treatment in 10 of the 24 eyes with APROP (41.66%) with good outcome in 8 of them. Supplementary laser spots were applied on the skipped areas toward the macula.

APROP regressed in 29 eyes (85.29%) from the IVB-treated group and failed to regress in five eyes (14.71%). In three of the five eyes, laser photocoagulation was carried out, with favorable outcome in all of them. In the remaining two eyes, laser treatment could not be performed due to the lack of visualization.

7.3.2 Comparative evolution after treatment between the two groups

The observed differences between the two groups are statistically significant, as proved by McNemar's test (p < 0.001). Global success rate (bilateral or unilateral regression) versus unsuccessful treatment was higher for IVB (94, 12% of cases) against laser photocoagulation (66, 66%), but no statistically significance higher (Chi-square test p = 0.420, Fisher exact test p = 0.462).

After excluding the infants with bad outcome, who came from the same NICU, the difference between the two groups regarding regression rate is no longer significant: 85.29% in the IVB group and 81.25% in the laser photocoagulation group (p > 0.05).

Treatment worked quicker within the IVB group, as compared to the laser photocoagulation group.

The bad outcome was identified 1 week after treatment, in all the 16 eyes within this series (11 from the laser photocoagulation group and 5 from the IVB group). We had no late recurrence in this series.

7.4 Discussion

7.4.1 Indirect diode laser photocoagulation for APROP

Laser photocoagulation of the retina is the gold standard in the treatment of ROP, and it proved its efficacy in more than 90% of ROP cases [18]. On the other hand, laser destroys the retina, and complications were cited in relation to it: cornea, iris and lens burns, hyphema, uveitis, retinal hemorrhages, and choroidal ruptures [19]. In our series, we report two cases of mild anterior uveitis following laser photocoagulation for APROP, with prompt resolution following mydriatic and anti-inflammatory eye drops.

Laser photocoagulation does not address the underlying cause of the disease [18]. Zone 1 APROP is known to have worse prognosis following laser photocoagulation, as compared to the classical form of the disease [20].

Because of the lack of landmarks in APROP, laser photocoagulation of the retina toward the posterior pole is difficult, and sometimes untreated areas of the avascular retina remain as a source of VEGF explaining the progression of the disease. By consequence, one single session of laser treatment is often insufficient in APROP.

Within the laser photocoagulation group, APROP final failure rate was 45.83%, represented by 11 eyes from 7 infants (four, bilaterally and three, unilaterally). From these seven cases, five came from the same neonatal unit and totalize eight eyes with bad outcome (three, bilaterally and two, unilaterally). This observation can lead us to the supposition that the inadequate neonatal care and oxygen administration might be at the origin of the severity and unresponsiveness to the laser treatment in these cases.

If we exclude these eight eyes from our analysis, the success rate following laser photocoagulation for APROP becomes 81.25% (in 13 of the remaining 16 cases, APROP could be stopped by laser treatment).

7.4.2 IVB for APROP in our series

APROP regression rate following IVB was 85.29% in our series (29 of the 34 eyes). We added laser photocoagulation in all the five eyes with lack of regression following IVB, with good outcome in three of them. The two eyes with final poor outcome belonged to different infants.

We did not identify any local complication subsequent to IVB in our group. No late reactivation of the disease was present.

7.4.3 IVB versus laser photocoagulation in the treatment of APROP

The main reason that determined us to replace laser photocoagulation with IVB in APROP was the high failure rate in this form of ROP, following laser treatment, in our practice, which is in agreement with data in the literature (45.83%) [21]. Besides, there are other disadvantages of laser treatment for APROP: the need to apply many laser spots during long and laborious sessions and the need to repeat laser because often at the moment of treatment there are no well-defined landmarks between the vascularized and the nonvascularized retina (typical feature of APROP). Often pupils do not dilate well in these severe cases, and vitreous hemorrhage can be associated, making laser treatment inadequate. The general status of the infant is often severe in APROP cases, making laser treatment risky for the patient's life. Finally, IVB does not destroy the retina as opposed to laser which ablates the nonvascularized retina in order to keep alive its vascular part. [21].

APROP regression rate was significantly better following IVB as compared with laser photocoagulation in our series. However, when we remove from the laser photocoagulation group, the infants with bad outcome, who came from the same NICU, the difference is no longer significant.

Another major advantage of IVB over laser is the continuation of retinal vascularization following treatment up to the periphery [20]. This observation was verified in our series. Anti-VEGF and laser act by different mechanisms in stopping the progression of ROP toward retinal detachment. Whereas laser photocoagulation destroys the source of VEGF (ischemic retina), anti-VEGF annihilates also the VEGF already present in the vitreous. This explains the quicker response and higher efficacy of IVB as compared to laser in APROP.

According to our experience, all bad outcomes were identified 1 week after treatment. Therefore, we consider them as unresponsiveness to treatment, not late recurrences [21].

7.4.4 Asymmetric response to treatment

We identified asymmetric response to treatment in six cases: three from the laser group and three from the IVB group. The possible explanation of this outcome might be the unequal development of the eyes which also explains the rare situation of unilateral ROP.

7.4.5 Safety issues related to anti-VEGF therapy

The main issue related to IVB treatment is its safety. There is proof that following IVB injections the serum VEGF levels decrease and anti-VEGF was found in the systemic circulation [21]. It is known that in ROP the blood-retinal barrier is broken down, allowing the exit of anti-VEGF in the systemic circulation, while the infant is still during the process of organogenesis. Concern comes from the fact that VEGF is necessary for the development of the lungs, brain, kidneys, and skeleton. VEGF also

acts as a neural survivor factor inside the eye, and its suppression might prevent the development of neural components in the retina [21].

7.4.6 Comparison between laser and IVB in the treatment of ROP

The advantages of IVB over laser photocoagulation in the treatment of ROP are related to its simplicity; short duration; lack of retinal destruction, conducting under topical anesthesia; lower price; and possibility to be performed in the eyes with small pupils and hazy media and in infants with poor general condition in which laser treatment under general anesthesia would be risky [21]. As proved by our series, IVB allows further development of retinal normal vascularization up to periphery, as opposed to laser. However, IVB is not risk free as far as local complications are considered. Lens injury, intraocular hemorrhage, retinal detachment, and endophthalmitis are possible, but they were not reported in the literature so far.

According to our experience, the most important advantage of IVB as compared to laser treatment is the better outcome in APROP, as published by other authors [21]. In this context, IVB represents our first therapeutic indication for APROP, even if the systemic safety issues were not fully addressed [21].

In a study that compared laser with bevacizumab in ROP and published in 2015, similar results were reported in the two groups, but it included all ROP cases, not just the severe ones (APROP) [22].

Other authors found higher recurrence rate of ROP following IVB as compared to laser, but within the laser group, macular ectopia had a higher incidence [23]. This observation is in agreement with our study that identified macular ectopia only in one case from the laser treated group.

In a previously published study, we showed that in the IVB-treated eyes, the retinal vascularization continued up to the periphery, unlike with laser [24].

Another observation of this comparative study is that the response to IVB was quicker than following laser. The explanation is represented by the fact that anti-VEGF suppresses not only the VEGF in the retina (such as laser does) but also the VEGF which is already released in the vitreous.

8. Conclusion

8.1 Personal experience

Intravitreal bevacizumab has emerged as a very useful tool in the treatment of ROP. We found a statistically significant higher APROP regression rate after IVB, as compared to laser photocoagulation in our series. IVB is much shorter, easier, accessible, and less expensive than laser photocoagulation. We could perform IVB in the eyes with small pupils and hazy media. By consequence, bevacizumab given intravitreally replaced laser in APROP, becoming the standard of care in this severe form of ROP, in our practice.

8.2 General

Progress in neonatal care was associated with higher survival rates of low birth weight and low gestational age newborns.

ROP is a biphasic disease: the first phase (from the moment of birth to 31–32 weeks postconceptional age) is called hyperoxic and it leads to the arrest of the normal retinal development, and the second phase (from 32- to 36-week

postconceptional age) is called hypoxic with overexpression of VEGF, IGF-1, and oxidative damage with subsequent new vessel growth and retinal detachment.

The Early Treatment for ROP study (ETROP) reclassified ROP according to the required attitude: type 1, ROP requiring treatment and type 2, ROP requiring closely monitoring. APROP is a very severe type 1 ROP characterized by rapid evolution toward retinal detachment if not addressed accordingly.

ROP screening should be made by trained ophthalmologists and started at 4–6 weeks after birth or at PCA 31 weeks whichever is later and continued up to the complete vascularization of the retina.

The most important factor to prevent ROP is preventing premature birth.

The gold standard for the treatment of ROP is indirect laser photocoagulation of the nonvascularized retina. Clinical studies conducted during the last years proved the superior efficacy of IVB over laser in APROP as well as its other advantages.

Research in the field of angiogenesis led to a number of new ways to prevent ROP progression: targeting the insulin growth factor (IGF-1) pathway and dietary supplementation with omega-3 polyunsaturated fatty acids (PUFA).

Acknowledgements

Conflict of interest

The author declares no conflict of interest related to the publication of this chapter.

Author details

Simona Delia Nicoară
Department of Ophthalmology, "Iuliu Hațieganu" University of Medicine and Pharmacy, Cluj-Napoca, Romania

*Address all correspondence to: simonanicoara1@gmail.com

IntechOpen

References

[1] Good WV, Carden SM. Retinopathy of prematurity. British Journal of Ophthalmology. 2006;**90**(3):254-255. DOI: 10.1136/bjo.2005.081166

[2] Salgado CM, Celik Y, Vanderveen DK. Anterior segment complications after diode laser photocoagulation for prethreshold retinopathy of prematurity. American Journal of Ophthalmology. 2010;**150**(1):6-9. DOI: 10.1016/j.ajo.2009.12.017

[3] Wilkinson AR, Haines L, Head K, Fielder AR. UK retinopathy of prematurity guideline. Early Human Development. 2008;**84**(2):71-74. DOI: 10.1016/j.earlhumdev.2007.12.004

[4] Jalali S, Matalia J, Hussain A, Anand R. Modification of screening criteria for retinopathy of prematurity in India and other middle-income countries. American Journal of Ophthalmology. 2006;**141**(5):966-968. DOI: 10.1016/j.ajo.2005.12.016

[5] Gilbert C, Rahi J, Eckstein M, O'Sullivan J, Foster A. Retinopathy of prematurity in middle-income countries. Lancet. 1997;**350**(9070):12-14. DOI: 10.1016/S0140-6736(97)01107-0

[6] Suelves AM, Shulman JP. Current screening and treatments in retinopathy of prematurity in the US. Eye and Brain. 2016;**8**(1):37-43. DOI: 10.2147/EB.S94439

[7] International Committee for the Classification of Retinopathy of Prematurity. The International Classification of Retinopathy of Prematurity revisited. Archives of Ophthalmology. 2005;**123**(7):991-999. DOI: 10.1001/archopht.123.7.991

[8] Cryotherapy for Retinopathy of Prematurity Cooperative Group. Multicenter trial of cryotherapy for retinopathy of prematurity: Preliminary results. Archives of Ophthalmology. 1988;**106**(4):471-479. DOI: 10.1001/archopht.1988.01060130517027

[9] Kieselbach GF, Ramharter A, Baldissera I, Kralinger MT. Laser photocoagulation for retinopathy of prematurity: Structural and functional outcome. Acta Ophthalmologica Scandinavica. 2006;**84**(1):21-26. DOI: 10.1111/j.1600-0420.2005.00548.x

[10] Jing C, Stahl A, Hellstrom A, Smith LS. Current update on retinopathy of prematurity: Screening and treatment. Current Opinion in Pediatrics. 2011;**23**(2):173-178. DOI: 10.1097/mop.0b013e3283423f35

[11] Sato T, Kusaka S, Shimojo H, Fujikado T. Simultaneous analyses of vitreous levels of 27 cytokines in eyes with retinopathy of prematurity. Ophthalmology. 2009;**116**(11):2165-2169. DOI: 10.1016/j.ophtha.2009.04.026

[12] Sonmez K, Drenser KA, Capone A Jr, Trese MT. Vitreous levels of stromal cell-derived factor 1 and vascular endothelial growth factor in patients with retinopathy of prematurity. Ophthalmology. 2008;**115**(6):1065-1070. DOI: 10.1016/j.ophtha.2007.08.050

[13] Sato T, Kusaka S, Shimojo H, Fujikado T. Vitreous levels of erythropoietin and vascular endothelial growth factor in eyes with retinopathy of prematurity. Ophthalmology. 2009;**116**(9):1599-1603. DOI: 10.1016/j.ophtha.2008.12.023

[14] Aiello LP, Pierce EA, Foley ED, et al. Suppression of retinal neovascularization in vivo by inhibition of vascular endothelial growth factor (VEGF) using soluble VEGF-receptor chimeric proteins. Proceedings of

the National Academy of Sciences of the United States of America. 1995;**92**(23):10457-10461

[15] Smith LE, Shen W, Perruzzi C, et al. Regulation of vascular endothelial growth factor-dependent retinal neovascularization by insulin-like growth factor-1 receptor. Nature Medicine. 1999;**5**(12):1390-1395. DOI: 10.1038/70963

[16] Shah N, Jadav P, Jean-Baptiste D, Weedon J, Cohen LM, Kim MR. The effect of recombinant human erythropoietin on the development of retinopathy of prematurity. American Journal of Perinatology. 2010;**27**(1):67-71. DOI: 10.1055/s-0029-1224872

[17] Drenser KA, Trese MT, Capone A Jr. Aggressive posterior retinopathy of prematurity. Retina. 2010;**30**(suppl):S37-S40. DOI: 10.1097/IAE.0b013e3181cb6151

[18] Hellström A, Smith LEH, Dammann O. Retinopathy of prematurity. Lancet. 2013;**382**(9902):1445-1457. DOI: 10.1016/S0140-6736(13)60178-6

[19] Laser ROP Study Group. Laser therapy for retinopathy of prematurity. Archives of Ophthalmology. 1994;**112**(2):154-156

[20] Nicoara SD, Nascutzy C, Cristian C, et al. Outcomes and prognostic factors of intravitreal bevacizumab monotherapy in zone I stage 3+ and aggressive posterior retinopathy of prematurity. Journal of Ophthalmology. 2015;**2015**:1-8. DOI: 10.1155/2015/102582

[21] Nicoara SD, Stefanut AC, Nascutzy C, Zaharie G, Toader LE, Drugan T. Regression rates following the treatment of aggressive posterior retinopathy of prematurity with bevacizumab versus laser: 8 year retrospective analysis. Medical Science Monitor. 2016;**22**:1192-1209. DOI: 10.12659/MSM.897095

[22] Maram I, Kamiar M, Nasrin T. Treatment of type 1 retinopathy of prematurity with bevacizumab versus laser. JAAPOS. 2015;**19**:140-144. DOI: 10.12659/MSM.897095

[23] Hwang KC, Hubbard GB, Hutchinson AK, Lambert SR. Outcomes after intravitreal bevacizumab versus laser photocoagulation for retinopathy of prematurity: A 5-year retrospective analysis. Ophthalmology. 2015;**122**:1008-1015. DOI: 10.12659/MSM.897095

[24] Nicoară SD, Nascutzy C, Cristian C, et al. Outcomes and prognostic factors of intravitreal bevacizumab monotherapy in zone I stage 3+ and aggressive posterior retinopathy of prematurity. Journal of Ophthalmology. 2015;**2015**:102582. DOI: 10.1155/2015/102582