ORIGINAL ARTICLE

Retinopathy of Prematurity Part II

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SUMMARY

Retinopathy of prematurity (ROP) is a disease that affects immature vasculature in the eyes of premature babies that potentially leads to blindness. Authors describe revised indications for the treatment of ROP, standard treatment – peripheral retinal ablation by laser photocoagulation and the cryotherapy using off label treatment--intravitreal anti-VEGF injection.

Key words: retinopathy of prematurity, indications, laser photocoagulation, cryotherapy, intravitreal anti-VEGF therapy

Čes. a slov. Oftal., 70, 2014, No. 2, p. 50–54

The treatment of retinopathy of prematurity has been and continues to be the subject of intensive research. To date there is no pharmacological treatment which would be capable of influencing the course of acute ROP (30). The basis of therapy remains surgical – laser coagulation and cryopexy of the avascular retina.

Indication

On the basis of the results of the multicenter trial CRYO-REP (Cryo therapy for Retinopathy of Prematurity) in 1988, the indication for treatment was set at the **threshold stage** – ROP stage 3 (Fig. 1, 2), which affects a range of 5 hours on the clock face continuously, or a cumulative range of 8 hours in zone I or II, with the presence of plus form of the disease (7, 8). With regard to the better anatomical results achieved in the case of very timely therapy, in which the incidence of adverse structural changes on the fundus was reduced during a 9-month period of observation (from 15.6% to 9.1%), changes have been brought about through indication for therapy since 2003, in accordance with the randomised controlled ETROP trial (10). A definition of the pre-threshold stage was determined (Fig. 3), and this was divided into two types: type 1 and type 2, in which timely therapy was recommended in the case of the high risk type 1. The pre-threshold stage represents any stage in zone I with plus form or ROP stage 3 without plus form and in zone II ROP stage 2 or 3 with presence of plus form (table 1). High risk type 1 ROP is indicated for timely cryotherapy or laser ablation treatment, which should be performed within 72 hours of determination of the pre-threshold stage, and low risk type 2 ROP, which does not require immediate treatment. In the case of type 2 ROP, immediate treatment is not necessary, but monitoring of the progression is required at regular intervals, applying a wait-and-watch approach, and it is necessary to consider treatment only in the case of transition of ROP type 2 to type 1. All other pre-threshold stages of ROP without plus form are considered to constitute type 2 ROP (Table 1). The state of the vasculature on the retina – presence of plus form of disease is therefore a very important factor in determining indication for treatment.

Plus form (plus disease) was defined in the ETROP trial as the presence of dilatation and tortuosity of capillaries on the posterior pole, minimally in 2 quadrants (6 and more hours) to an equal or more pronounced degree than on the standard photography CRYO-REP from 1980.

The basis of classic surgical therapy of ROP is destruction of the avascular retina by cryotherapy or laser ablation, which achieves reduction of retinal hypoxia, reduction of production of VEGF and other angiogenic mediators, and achieves regression of the disease.

Retinal cryopexy

From the 1980s onwards, cryopexy

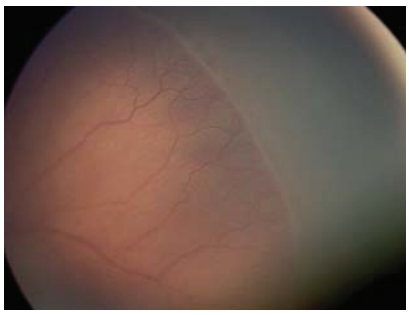

Fig. 1 ROP threshold stage (demarcation line, wall, proliferation at end of capillaries, plus form).

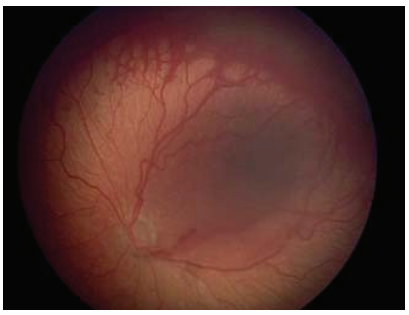

Fig. 2 ROP post-threshold stage AP--ROP, patient sent for treatment late (pronounced plus form, capillaries end in zone I, brush-like neovascular network at the ends of capillaries).

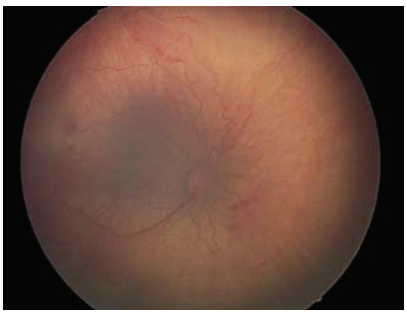

Fig 3 ROP – Post-threshold stage – ROP type I posterior form AP-ROP (fuller capillaries ending in zone I, flat neovascularisations).

Table 1 Division of the pre-threshold stage of ROP according to ETROP – access to treatment.

Type 1 ROP – indication for timely treatment		
Zone I	ROP any stage	With plus form
	ROP stage 3	With or without plus form
Zone II	ROP stage 2 or 3	With plus form
Type 2 ROP – regular monitoring of progression required – wait and watch approach		
(necessary to consider treatment only upon transition of ROP type 2 to type 1)		
Zone I	ROP stage 1 or 2	Without plus form
Zone II	ROP stage 3	Without plus form

was the main method of treatment for retinopathy of premature babies on the basis of the results of the Cryo--ROP trial. Thanks to cryotherapy, there has been a reduction of adverse anatomical results in treatment of the threshold stage of ROP from 47.9% in the untreated group to 27.2% upon treatment (9). In cryopexy, interventions are applied to the area of the avascular retina with the help of a cryo-probe at a temperature of -60° to -80°C under the control of an indirect ophthalmoscopy. The number of interventions depends on the size of the avascular zone, in which each cryo intervention is visible upon application as pronounced whitening of the retina. Treatment of the posterior pole is highly demanding and cannot be performed without opening the conjunctiva, and this is often insufficient. For coagulation of the posterior pole of the retina it is possible to use specially curved paediatric probes, which to a certain degree also enable partial treatment of this part of the retina. For this reason, some sites use the technique of treating the periphery of the retina by cryopexy in combination with laser photocoagulation of the central parts of the retina, by which the duration of the procedure is reduced. An advantage of cryopexy is that it may be used also in the case of reduced transparency of the optic media. During cryopexy, systemic (bradycardia, transient hypotension, apneusis…) as well as local complications may occur. Postoperatively it is linked to pronounced tumescence to chemosis of the conjunctiva, painfulness, elevation of intraocular pressure. Of the later complications, haemorrhage into the vitreous area, intraretinal haemorrhage, deformation of the macular region, atrophy of the optic nerve and pronounced constriction of the field of vision up to the extent of tunnel vision have been described. In comparison with laser treatment it causes greater destruction of the tissue, and in children treated with cryopexy a higher incidence of clinically significant myopia is described in comparison with eyes following laser treatment (6). Recently cryopexy has been used rather as an additional treatment in the case of progression of ROP and upon reduced transparency of the optic media.

Laser photocoagulation of the retina

Today, with regard to the lower incidence of complications and the comparable effectiveness, laser photocoagulation is considered the standard treatment for ROP; mostly it is applied by a transpupillary approach, whilst a transscleral approach is also possible. With the help of a diode laser with a wavelength of 810 nm, using an indirect ophthalmoscopy and a 28 or 20 D converging lens, the avascular part of the retina is coagulated by a transpupillary approach, anteriorly from the place of fibroproliferation up to the ora serrata by a laser beam with energy from 200-400 mW, with a duration of impact from 200-400 ms. The resulting track should be greyish-white and the number of impacts varies depending on the size of the avascular zone from 200-3000. In laser therapy the method of individual impacts may be applied (with a distance of 1.0 to 1.5 of the track between the individual impacts), the method of practically confluent impacts (distance of 0.5 to 1.0 size of the track between impacts) or the method of continuous impacts, in which no free spaces are left between the individual laser tracks (Fig. 4, 5). At present the trend is towards use of denser forms of photocoagulation in the treatment of ROP (3, 4, 15). Upon the use of these forms there is less progression to the higher stages of ROP and less requirement for an additional therapy. Upon a comparison of the method of individual interventions as against practically confluent interventions, the method of denser interventions appears to be safer (28, 38). Laser photocoagulation enables treatment of the retina also in the case of aggressive posterior forms of retinopathy on the posterior pole, which could not be achieved by a cryoprobe, in which it is possible to laser treat the periphery of the retina using a scleral indentator. A problem is laser coagulation in the case of a narrow pupil, reduced transparency of media as upon the occurrence of tunica vasculosa lentis, cataracts and haemorrhages of the vitreous body. Laser therapy is more demanding in comparison with cryopexy in terms of time, but the use of new types of laser with a possible confluent – paint regime of the laser markedly reduces the duration and enables faster and better quality laser coagulation of the avascular retina with a lower burden to premature baby. In the case of use of the method of individual laser interventions, combined therapy of the posterior retina by laser photocoagulation with therapy of the peripheral retina by cryocoagulation is possible in order to reduce the duration of the procedure. The long-term results show a similar efficacy in inducing of ROP regression, whereas there is a statistically higher percentage of eyes with an anatomically good finding following photocoagulation, and better visual acuity is also stated in comparison with cryotherapy (2). In comparison with cryopexy, laser coagulation causes a smaller inflammatory reaction and less mechanical damage to the tissue. As regards postoperative complications following diode laser coagulation, in most cases they are transitory and occur in both the anterior and posterior segments of the eye. A transitional corneal oedema may be present, as well as minor haemorrhage into the anterior chamber, rupture of the iris, vitreal and intraretinal haemorrhage, which have a tendency towards spontaneous absorption. The incidence of cataract as a complication is stated in up to 1% (17), more frequently in the case of presence of tunica vasculosa lentis, owing to absorption of the laser radiation, and may be in the form of minor focal lens opacities, without a significant influence on vision, as well as concurrently with ischemia of the anterior segment and subsequent phthisis bulbi. An incidence of complications was expected mainly in the case of the confluent type of laser surgery, but no significantly higher incidence has been confirmed (15), and upon a comparison of the individual methods, the method of denser interventions is more

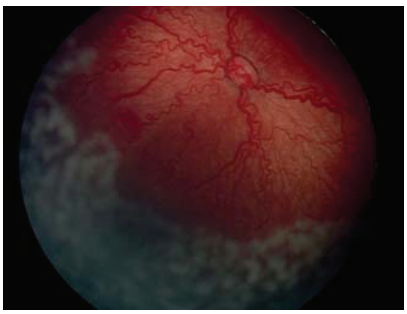

Fig. 4 Fresh traces following confluent type DLC of the retina upon AP-ROP

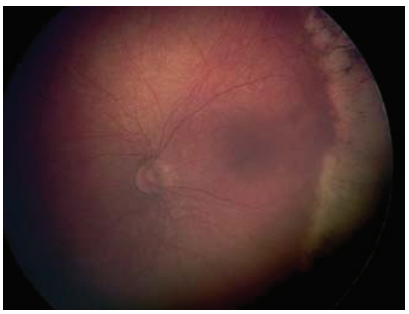

Fig. 5 Regression of ROP following DLC treatment – older pigment scars following DLC

effective (28, 38). Long-term complications are not yet sufficiently known, but include losses on the periphery of the visual field, a risk of higher incidence of later retinal detachment with regard to the presence of tears and scars on the interface of the laser treated retina and the presence of abnormal vitreoretinal tractions (4). The occurrence of high myopia and anisometropia in premature children following laser therapy is lower than following cryopexy, and is partially caused by inhibition of the growth of the anterior segment of the bulb with an anteriorly placed lens with a higher optical density.

Retreatment

In the case of insufficient regression and persistence of activity of the disease, in which regression of plus form does not take place, dilatation and tortuosity of capillaries persists and "skip areas" are present with an insufficiently laser treated part of the retina, the hypoxic retina remains a reservoir for the continual production of growth factors. It is necessary to supplement the laser therapy in the skip areas, or additional cryopexy is possible upon pronounced activity and progression of retinopathy depending on the finding.

Treatment of acute retinal detachment. Scleral buckling and vitrectomy

In the case of further progression and development of adverse structural changes, with the development of amotio retinae, surgical intervention is indicated, in which the type of surgical procedure depends on the stage of ROP, the retrolental ratios, vascular activity of the disease (presence of plus form and neovascularisations) and the presence of exudative components (32). In peripherally localised and incipient retinal detachment (stage 4a ROP) it is suitable to stitch a sponge-like episcleral plombage, which is left in place for 3-6 months. In the case of a larger extent of retinal detachment, scleral buckling is possible, in which the cerclage strip is removed within one year with regard to the risk of retardation of growth of the bulb. The long-term functional results of circular scleral buckling, however, unlike stitching of an episcleral plombage, are frequently not convincing even upon anatomical reattachment of the retina. Probably induced myopisation of the bulb as a consequence of axial elongation and a shift of the lens in a forward direction potentially have an amblyogenic effect. Whereas in the past vitrectomy was the last alternative in the case of failure of scleral buckling, at present some sites prefer primary vitrectomy (35), which can be combined concurrently with scleral buckling. The advantage of vitrectomy in stage 4 ROP is the simultaneous alleviation of anterior-posterior traction, together with removal of endogenic vasodilators and angiogenic factors (VEGF) from the vitreous cavity (34). More favourable results are attained if the operation is indicated after subsidence of the activity of the disease, with regression of the plus form in stage 4a ROP. Upon retinopathy of prematurity, the applied techniques of lens sparing vitrectomy and vitrectomy with two points of entry are used as safe and effective in stage 4 and 5 ROP, and up to 25-gauge pars plicata vitrectomy has been referred (14). Vitrectomy in newborns and adults differ in several respects (39): the point of entry is more suitable for pars plicata than pars plana vitrectomy, the lens is relatively larger, it is more difficult to achieve separation of the cortical vitreous, tears are less well tolerated and successful repair of tears is rarer, a pupillary membrane occurs more frequently, iridoretinal and retino-retinal adhesions are often present, subretinal haemorrhages and exudation together with degeneration of the retinal pigment epithelium render good functional results impossible, and last but not least the maximum of functional development cannot be expected until over the course of several years. In general, however, the functional results are frequently very weak, in which the resulting vision is limited to light perception, even if the retina is anatomically reattached. In the premature retina, the photoreceptors (cones and rods) begin to degenerate shortly after retinal detachment, unlike in adults, in whom good results may be attained even several weeks after the onset of retinal detachment (11). Late indicated vitrectomy cannot ensure functional activity even if the retina is reattached, organic amblyopia is caused by the destruction of the retinal receptors, which occurs 2-3 weeks after detachment of the immature retina (20). An improvement of the results of surgical treatment has been brought about by a combination of vitrectomy with pharmacotherapy, with preoperative intravitreal administration of anti-VEGF or triamcinolone intravitreally at the end of the surgery (18) in order to reduce the vascular activity of the disease. Complete reattachment of the retina in stage 5 ROP is stated by authors in enzyme-assisted vitrectomy using autologous plasmin in order to ease the separation of the cortical vitreous and proliferative membranes from the retina (40). It is difficult to monitor the results of studies with regard to the extensive heterogeneity of patients, the findings on the retina and the activity of the disease upon the use of various surgical techniques for resolving of progressing severe forms of ROP. Effective treatment of these forms remains problematic, and even though the number of eyes in stage 4 and 5 ROP has been reduced since the implementation of the recommendations of the ETROP study into practice, it remains necessary to place heightened emphasis on the prevention of their occurrence.

New methods of treatment – intravitreal administration of anti-VEGF

In the pathogenesis of ROP, vaso--obliteration takes place with subsequent neovascularisation, in which an important factor in the progression of the disease is hypoxia with other key growth mediators – VEGF and erythropoietin (37). The role of VEGF in the development of retinopathy has been demonstrated, and studies are appearing referring to the promising effect of intravitreally administered anti-growth factors in the treatment of neovascularisations in ROP. Anti-VEGF substances such as pegaptanib sodium, ranibizumab and bevacizumab have been examined off-label, but none of them has as yet been approved for use in paediatric

practice. In the literature successful results have been published following a single-shot intravitreal administration of bevacizumab (due to its large molecule of 150 D bevacizumab cannot penetrate from the intact retina and with the exception of a small quantity it cannot escape into the circulation), when 0.625 mg/0.025 ml of bevacizumab (Avastin) was applied intravitreally bilaterally to 11 children (22 eyes) with ROP in zone I and posterior zone II, without prior laser therapy, whereas no systemic or local adverse drug reactions were observed (25). In the USA the multicenter prospective trial BEAT-ROP has been conducted with 150 children – Bevacizumab Eliminates the Angiogenic Threat of Retinopathy of Prematurity (24). Recently, studies have been published with intravitreal application of ranibizumab (Lucentis 0.25 mg/0.025 ml) in monotherapy (5). With regard to a shorter half-life and a higher bonding affinity of ranibizumab in comparison with bevacizumab, the authors expect a smaller incidence of adverse drug reactions, in 6 eyes regression of the disease took place after 1 injection, and no systemic or local adverse drug reactions were observed. Use of a combined therapy of laser therapy with subsequent application of an intravitreal injection of anti-VEGF and intravitreal administration in the case of insufficient regression or failure of laser therapy was also demonstrated to be effective, whereas bevacizumab (Avastin) (22, 31), ranibizumab (Lucentis) (26) and pegaptanib (Macugen) (1) were used. Intravitreal administration of anti-VEGF however may lead to adverse contractions of the proliferative membranes and worsening of traction amotio (16), some studies describe systemic adverse drug reactions following intravitreal administration of bevacizumab, such as thromboembolic complications or hypertension, as is the case upon intravenous cancer therapy (12, 36). It has been demonstrated that bevacizumab can escape into the systemic circulation, with a subsequent reduction of serum levels of VEGF, whilst the developing vital organs (brain, lungs) are still dependent on regulatory vascular processes and require VEGF for their further development (29, 33). In comparison with conventional laser therapy in the treatment of intravitreally administered anti-growth factors, permanent destruction of the retina with constriction of the visual field does not take place, and the retinal capillaries progressively grow up to the periphery. During the normal development of retinal vasculature, the level of VEGF is altered, and as a result correct timing of administration of the VEGF inhibitor is very important. With regard to the potential recurrence of ROP in treatment with anti-VEGF, it is necessary to ensure thorough monitoring and evaluation of the finding on the retina, for a period of at least 16 weeks following application of the injection. Intravitreal administration has been demonstrated to be a promising an effective treatment, verified in small series of patients. Its regular use requires a prospective randomised multicenter clinical trial, especially with regard to the potential adverse drug reactions to the therapy (23, 25). At present it remains reserved for use in cases of weak dilatation of the pupil, opaque media with deteriorated visualisation and the impossibility of laser therapy, or in children upon insufficient regression following primary diode laser coagulation of the retina and in certain aggressive posterior forms of AP-ROP with very short capillaries, not reaching the macular area (19, 21).

CONCLUSION

It is necessary to emphasise the importance of co-operation of the ophthalmologist with the neonatologist, not only in screening but also in the diagnostic-therapeutic process of ROP. Thanks to considerable advances in neonatal care, balanced and controlled application of oxygen, new procedures in ventilation, application of surfactants, antenatal administration of corticoids, the overall incidence, as well as the incidence of severe forms of ROP, has remained stabilised in this country in recent years. The introduction of an adequate screening programme of threshold or pre-threshold stages of retinopathy of premature babies and timely treatment with complete ablation of the periphery of the avascular retina have brought a marked improvement of the anatomical and functional results in premature babies. Although telemedicine with the possibility of documenting and transmitting of images via a RetCam can help bring a further improvement in the diagnosis and treatment of retinopathy of prematurity, examination of the retina by indirect ophthalmoscopy with the use of indentation remains the key examination in its diagnostics. Technological progress and new techniques of confluent diode laser coagulation now enable swift and safe treatment of the retina. In future it is possible to expect development in pharmacological therapy and prevention of ROP. The most recent results from multicenter prospective trials with the use of intravitreally applied anti-growth factors are very promising, above all in aggressive posterior forms of AP-ROP, though it is necessary to wait for the long-term results on larger groups of patients before the standard implementation of this therapy. A renaissance is under way in the application of vitamins E and C as antioxidants, sustaining the integrity of the cell membranes. The use of unsaturated omega fatty acids, erythropoietin, IGF-1 (insulin-like growth factor-1), GSFT (granulocyte colony stimulating factor) as well as new antioxidants, anti-inflammatory factors, stem cells or gene therapy may prospectively bring successes in the prevention or treatment of ROP (27). Worldwide a large amount of attention is being focused on this still potentially blinding disease, and studies organised with the help of the WHO Vision 2020 Programme (13) envisage that ROP may in future be a preventively treatable disease. At present it is necessary to keep in mind that the monitoring of premature infants does not end with the completion of screening and adequate treatment of acute ROP, but that it is essential to ensure their long-term monitoring up to adolescence, with regard to a risk of other ocular complications of prematurity.

LITERATURE

1. **Autrata, R., Krejãírová, I., Šenková, K.,et al.:** Intravitreal pegaptanib combined with diode laser therapy for stage 3+ retinopathy of prematurity in zone I and posterior zone II. Eur J Ophthalmol, 22(5); 2012: 687–94.
2. **Autrata, R., Šenková, K., Holousová, M, et al.:** Retinopatie nedonošených a možnosti chirurgické léčby. Folia Strabol Neuroophthalmol, X; 2009: 40–45.
3. **Banach, M.J., Ferrone, P.J., Trese, M.T.:** A comparison of dense versus less dense diod laser photocoagulation patterns for threshold retinopathy of prematurity. Ophthalmology, 107; 2000: 324–328.
4. **Banach, M.J.,Berinstein, D.M.:** Laser therapy for retinopathy of prematurity. Current Opinion in Ophthalmology, 12; 2001: 164–170.
5. **Castellanos, M. A. M., Schwartz, S.,**

García-Aguirre, G., et al.: Short-term Outcome After Intravitreal Ranibizumab Injections for the Treatment of Retinopathy of Prematurity. Br J Ophthalmol. 97(7); 2013: 816–819.
6. **Cook, Anne, White, S., Batterbury, M., Clark, D.:** Ocular growth and refractive error development in premature infants without retinopathy of prematurity. Invest Ophthalmol Vis Sci, 44(3), 2003: 953-960.
7. Cryotherapy for Retinopathy of Prematurity Cooperative Group. Multicenter trial of cryotherapy for retinopathy of prematurity. 3 1/2 year outcome-structure and function. Arch Ophthalmol. 111;1993: 339–44.
8. **Cryotherapy for Retinopathy of Prematurity Cooperative Group:** Multicenter trial of cryotherapy for retinopathy of prematurity. Preliminary results. Arch Ophthalmol. 106; 1988: 471–9.
9. **Cryotherapy for Retinopathy of Prematurity Cooperative Group:** Multicenter trial of cryotherapy for retinopathy of prematurity: Ophthalmological outcomes at 10 years. Arch Ophthalmol, 119; 2001: 1110–1118.
10. **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, 121(12), 2003: 1684–1694.
11. **Fisher, S.K.:** Cellular effects of detachment on the neural retina and retinal pigment epithelium. In: Ryan,S.J.: Retina(ed 2), St Louis, Mosby, 1994, s. 2035–2061.
12. **Fung, A.E., Rosenfeld, P.J., Reichel, E.:** The international intravitreal bevacizumab safety survey: using the internet to assess drug safety worldwide. Br J Ophthalmol, 90(11), 2006: 1344–1349.
13. **Gilbert, C., Foster, A.:** Childhood blindness in the context of VISION 2020: the right to sight. Bulletin of the World Health Organization, 79(3); 2001: 227–232.
14. **Gonzales, C. R., Boshra, J., Schwartz, S. D.:** 25-Gauge pars plicata vitrectomy for stage 4 and 5 retinopathy of prematurity. Retina, 26(7); 2006: S42–S46.
15. **Gonzales, V.H., Giuliari, G.P., Banda, R.M et al.:** Confluent Laser Photocoagulation for the Treatment of Retinopathy of Prematurity, J Pediatr Ophthalmol Strabismus, 47(2), 2010: 81–85.
16. **Honda, S., Hirabayashi, H., Tsukahara, Y., Negi, A.:** Acute contraction of the proliferative membrane after an intravitreal injection of bevacizumab for advanced retinopathy of prematurity. Graefes Arch Clin Exp Ophthalmol, 246(7); 2008: 1061–3.
17. **Christiansen, S.P., Bradford, J.D.:** Cataract in infants treated with argon laser photocoagulation for threshold retinopathy of prematurity, Am J Ophthalmol, 119(2); 1995: 175–80.
18. **Lakhanpal, R. R., Fortun, J. A., Chan-Kai, B., et al.:** Lensectomy and vitrectomy with and without intravitreal triamcinolone acetonide for vascularly active stage 5 retinal detachments in retinopathy of prematurity. Retina, 26(7); 2006: 736–740.
19. **Lalwani, G.A., Berrocal, A.M., Murray, T.G. et al.:** Off-label use of intravitreal bevacizumab (Avastin) for salvage treatment in progressive threshold retinopathy of prematurity, Retina, 28; 2008: 13–18.
20. **Lashkari, K., Hirose, T., Yazdany, J., et al.:** Vascular endothelial growth factor and hepatocyte growth factor levels are differentially elevated in patients with advanced retinopathy of prematurity. Am J Pathol, 156(4); 2000: 1337–1344.
21. **Law, J.C., Recchia, F.M., Morrison, D.G. et al.:** Intravitreal bevacizumab as adjunctive treatment for retinopathy of prematurity. J AAPOS, 14(1); 2010: 6–10.
22. **Lee, J.Y., Chae, J.B., Yang, S.J. et al.:** Effects of intravitreal bevacizumab and laser in retinopathy of prematurity therapy on the development of peripheral retinal vessels. Graefes Arch Clin Exp Ophthalmol, 248(9); 2010: 1257–1262.
23. **Kong, L., Mintz-Hintzer, A.H.:** Intravitreal Bevacizumab as Anti-Vascular Endothelial Growth FactorTherapy for Retinopathy of Prematurity: A Morfologic Study. Arch. Ophthalmol, 126(8); 2008: 1161–1163.
24. **Mintz-Hittner, H.A., Kennedy, K.A., Chuang, A.Z.:** BEAT-ROP cooperative group: efficacy of intravitreal bevacizumab for stage 3+ retinopathy of prematurity. N Engl J Med, 364(7); 2011: 603–615.
25. **Mintz-Hittner, H.A., Kuffel, R.R.:** Intravitreal injection of bevacizumab (Avastin) for treatment of stage 3 retinopathy of prematurity in zone I or posterior zone II. Retina, 28(6); 2008: 831–838.
26. **Mota, Á., Carneiro, Á., Breda, J., et al.:** Combination of Intravitreal Ranibizumab and Laser Photocoagulation for Aggressive Posterior Retinopathy of Prematurity. Case Rep Ophthalmol, 3(1); 2012: 136–141.
27. **Mutlu, F.M., Sarici, S.U.:** Treatment of retinopathy of prematurity: a review of conventional and promising new therapeutic options. Int J Ophthalmol, 6(2); 2013: 228–236.
28. **Paysse, E.A., Hussein, M.A., Miller, A.M. et al.:** Pulsed mode versus near continous mode delivery of diode laser photocoagulation for high– risk retinopathy of prematurity. JAAPOS, 11; 2007: 388–392.
29. **Pieh, C., Agostini, H., Buschbeck, C. et al.:** VEGF-A,VEGF-1, VEGFR-2 und Tie2 levels in plasma of premature infants: relationship to retinopathy of prematurity. Br J Ophthalmol, 92(5); 2008: 689–693.
30. **Repka, M.X.:** Ophthalmological problems of the premature infant. Ment Retard Dev Disabil Res Rev, 8; 2002: 249-57.
31. **Roohipoor, R., Ghasemi, H., Ghassemi, F. et al.:** Intravitreal bevacizumab in retinopathy of prematurity: an interventional case series. Graefes Arch Clin Exp Ophthalmol, 249(9); 2011: 1295–1301.
32. **Roohipoor, R., Karkhaneh, R., Riazi-Esfahani, M. et al.:** Surgical management in advanced stages of retinopathy of prematurity; our experience. Journal of ophthalmic & vision research, 4(3); 2009: 185–190.
33. **Sato, T., Wada, K., Arahori, H. et al.:** Serum concentrations of bevacizumab (avastin) and vascular endothelial growth factor in infants with retinopathy of prematurity. Am J Ophthalmol, 153(2); 2012: 327–333.
34. **Sears, J. E., Sonnie, C.:** Anatomic success of lens-sparing vitrectomy with and without scleral buckle for stage 4 retinopathy of prematurity. Am J Ophthalmol, 143(5); 2007: 810–813.
35. **Shah, P. K., Narendran, V., Kalpana, N. et al.:** Anatomical and visual outcome of stages 4 and 5 retinopathy of prematurity. Eye, 23(1); 2009: 176–180.
36. **Shima, C., Sakaguchi, H., Gomi, F. et al.:** Complications in patient after intravitreal injection of bevacizumab. Acta Ophthalmol, 86(4); 2008: 372–376.
37. **Smith, L. E.: Through the eyes of a child:** understanding retinopathy through ROP the Friedenwald lecture. Invest Ophthalmol Vis Sci, 49(12); 2008: 5177–5182.
38. **Tomšíková, D., Prepiaková, Z., Kostolná, B. et al.:** Prínos konfluujúcej (paint) – diódlaserkoagulácie v liečbe retinopatie nezrelých detí. Čes a Slov Oftal, 67; 2011: 115–118.
39. **Tawansy, K. A., Samuel, M. A.:** Retinopathy of prematurity: practical surgical management in the new millennium. Tech Ophthalmol, 2; 2004: 60–67.
40. **Tsukahara, Y., Honda, S., Imai, H. et al.:** Autologous plasmin-assisted vitrectomy for stage 5 retinopathy of prematurity: a preliminary trial. Am J Ophthalmol, 144(1); 2007: 139–141.