(15)

Present-day conservative treatment retinopathy of prematurity

Nowoczesne kierunki leczenia zachowawczego retinopatii wcześniaczej

Modrzejewska Monika, Kubasik-Kładna Katarzyna, Kuprjanowicz Leszek

Departament of Ophthalmology, Pomeranian Medical University, Szczecin, Poland
Head: Professor Lubiński Wojciech, M.D., Ph.D.

Streszczenie: Retinopatia wcześniacza występuje u dzieci przedwcześnie urodzonych. Etiologia schorzenia jest wieloczynnikowa, a według danych epidemiologicznych częstość jego rozpoznawania w skali globalnej wzrasta. Retinopatia wcześniacza jest jedną z przyczyn znacznego niedowidzenia i ślepoty u dzieci na całym świecie. Niska skuteczność leczenia tego schorzenia powoduje konieczność poszukiwania nowych rozwiązań i stosowania nowoczesnych terapii. Dotychczas stosowane metody leczenia to laser- i krioterapia, a w przypadkach odwarstwienia siatkówki uzupełnieniem leczenia są operacje – witrektomia lub/i wpuklenie twardówki.

Celem pracy jest wnikliwy przegląd dostępnego piśmiennictwa nt. zastosowania nowych metod postępowania zachowawczego u pacjentów z retinopatią wcześniaczą. Najnowsze doniesienia o roli czynnika VEGF wydzielanego pod wpływem hipoksji wskazują, że bierze on udział w rozwoju angiogenezy i neowaskularyzacji. Dlatego obecnie w leczeniu zachowawczym retinopatii wcześniaczej znajdują zastosowanie doszklistkowo podawane inhibitory VEGF – bewacyzumab i ranibizumab. Według dostępnego piśmiennictwa podawanie tych leków wzbudza wiele kontrowersji, lecz pomimo różnych opinii na ten temat są one stosowane w monoterapii lub jako leczenie skojarzone, połączone z laseroterapią lub z leczeniem operacyjnym. W ostatnich latach wzrasta zainteresowanie doszklistkowym podawaniem triamcinolonu oraz innych eksperymentalnych substancji, które hamują rozwój włóknistonaczyniowych proliferacji w przebiegu retinopatii wcześniaczej na modelach mysich. Nadzieje wiązane są również z zastosowaniem terapii genowej, z leczeniem β-blokerami (propranololem), z suplementacją kwasami Omega-3, inhibitorami metaloproteinazy-2, nanocząsteczkami złota i letalną toksyną wąglika.

Słowa kluczowe: retinopatia wcześniacza, inhibitory VEGF, ranibizumab, bewacyzumab.

Summary: Retinopathy of prematurity occurs in prematurely born babies. Etiology of disease is multifactorial and frequency of retinopathy of prematurity diagnosis increases. Retinopathy is one of causes for major loss of vision and amaurosis in newborns around the world. Low efficacy of treatment leads to necessity for looking for new solutions and modern therapy use in treatment of this disease. So far, therapies used are: laser and cryotherapy and cases of retina detachment, the course is combined with surgical procedures of sclera and vitrectomy.

The aim of the paper was detailed observation of available literature concerning new methods of management in retinopathy of prematurity. Newest reviews on role of vascular endothelial growth factor secreted under the influence of hypoxia indicate that it takes part in angiogenesis and neovascularization. Thus, in retinopathy of prematurity management vitreous application of vascular endothelial growth factor inhibitors such as ranibizumab, bevacizumab are used as supplement or treatment combined with laser therapy or surgical procedures, however there are many controversies on this form of treatment. Recently there has been an interest in vitreous application of Triamcinolon and other experimental substances inhibiting fibro-vascular proliferations in mouse models of retinopathy of prematurity. Hopes connected with high efficacy of retinopathy of prematurity treatment are also related to use of gene therapy, β-blockers, supplementation with Omega-3 acids, matrix metalloproteinase-2 inhibitors, gold nanoparticles-GNP and anthrax lethal toxin.

Key words: retinopathy of prematurity – ROP, vascular endothelial growth factor inhibitors – VEGF, ranibizumab, bevacizumab.

Introduction

Retinopathy of prematurity (ROP) has incidence in premature babies. It is immature retina disease of multifactorial etiology which can lead to blindness in group of premature newborns (1, 2). Since 1960, trans-scleral cryotherapy and diode-laser panphotocoagulation have been applied in active phase of ROP. Introduction of these treatment techniques has decreased frequency of blindness incidence among infants with retinopathy of prematurity by about 25%. According to ETROP guidelines (The Treatment for Retinopathy of Prematurity Cooperative Group), laser photocoagulation has been considered as a method of choice in ROP management. In relation to current knowledge laser therapy is a more preferred method of treatment in comparison to cryotherapy because it is safer, less painful and does not cause inflammatory condition in the place of its activity. Moreover, the risk of complications is smaller than in cryoaplication. Despite beneficial effect of laser application in ROP, in some cases of active phase of disease, it does not prevent from development of retinal neovascularization and proliferation (1, 3, 4). Stages 4 and 5 ROP are considered for operational

proceeding. However, the functional outcomes of this management are not satisfactory, which leads to the necessity of searching for new therapeutic solutions. Among ROP treatment failures, significant is the presence of those risk factors which initiate the pathological process. In this group, there are various growth factors secreted by ischemic retina which in early stages of ROP are stimulated by hypoxia inducing factor-1 (HIF-1) (4). Recent scientific development in the field of inhibiting ROP advancement on the basis of experimental and clinical studies creates possibilities for searching new methods of ROP management. The authors of this paper have undergone the review of available literature in this subject.

Antiangiogenic therapies

In physiology conditions, vascular endothelial growth factor (VEGF) is needed in angiogenesis process and additionally it has neuroprotective role in retina maturing. This factor is secreted to vitreous body chamber and to subretinal liquid by endothelial cells under the influence of hypoxia. Overproduction of VEGF in the condition of clinical and experimental hypoxia causes the increase of vasopermability and proliferation of endothelial cells in retinal vessels, which results in neovascularization. Over--expression of VEGF has an important role in ROP pathogenesis. Application of VEGF inhibitors for treatment of various ophthalmic diseases is connected with administering them to the vitreous or anterior chamber of eye. In this process, blocking mechanism for VEGF-receptor is used. **Bevacizumab** (Avastin, Genentech/Roche) or **ranibizumab** (Lucentis, Novartis), monoclonal antibodies, being an off-label technique, are applied in monotherapy or as combined treatment with laser-therapy. Stage 3 ROP together with development of extra-retinal fibrovascular proliferation or rapid progression of retinal lesions with plus signs are major implications for the use of those substances. In severe ROP application of those drugs causes decrease of plus signs and limits bleeding during vitrectomy (2, 3, 5). In Med--line and Pub-Med search engines, the number of publications concerning therapeutic outcomes in ROP after bevacizumab treatment has increased. However, it should be underlined that those studies have been conducted on relatively small number of clinical cases which unable evaluation of safe application of this drug in newborns and infants (2, 4, 6–9).

BEAT-ROP examination (Bevacizumab Eliminates the Angiogenic Threat of Retinopathy of Prematurity), is a prospective, randomized, and multicentral study on a group of premature babies with 3 ROP with plus sign (67 infants in zone 1 and 83 newborns in zone 2) in which bevacizumab in a dose of 0.625 mg was administered. The control group comprised 75 babies treated with conventional laser therapy alone. Statistically higher efficacy of bevacizumab treatment was confirmed for 3 ROP with plus sign in zone 1, but not in zone 2. No systemic or local complications were confirmed in connection to the applied drug (2). Wu and colleagues have used in monotherapy the same dose of bevacizumab in 41 infants with 3 ROP stage and they obtained the comparable outcomes in comparison to the mentioned results. There has been observed regression of ROP in group of 90% of patients. However, the remaining 10% of newborns additionally needed laser therapy due to ROP reoccurrence, despite beavacizumab administration. Monotherapy was applied also in more advanced stages of the diseases: 4A ROP (6 eyes). In this stage regression of retinal lesions was observed only in 2 eyes, however in other 2 eyes progression to 5 stage of ROP appeared which required vitrectomy proceeding. Local complications after mentioned applied treatment was noted in 6 eyes (12%) including 4 eyes (8%) with haemorrhages in vitreous body or subretinal haemorrhage. In 2 eyes (4%) transitional retinal edema in inferior branch of central retinal vein was noted. Negative systemic acknowledged complications have not been pointed out (6). After intravitreous bevacizumab application, in a dose of 0.625 mg, Ahmed et al. studies observed decrease in neovascular activity in laser-treated eyes with ROP 3 (7 eyes), ROP 3 with plus sign (5 eyes), ROP 4 (2 eyes) and ROP 4 with plus sign (1 eye). The babies from this group did not require any following therapeutic management and no adverse systemic effects of drug application was observed (7).

Lee and colleagues compared the efficacy of combined intravitreous bevacizumab and laser therapies in 16 eyes with ROP 3, performed in about 36 PMA (postmenstrual age) on average. The follow-up period was 1, 2, 4, 8 weeks after the applied course. Regression of plus sign and normal development of peripheral retinal vessels was observed in the eyes treated with combined therapy. Similarly to the previously cited authors, no complications were observed (4). Honda et colleagues paid attention to the fact that bevacizumab application in eyes with severe ROP and retina detachment may cause deterioration of local condition. It is probably connected with the process of angiogenesis suppression which may stimulate development of fibrous component (8).

In the literature there are single reviews on ranibizumab used for ROP treatment. Jang et al. applied the dose of 0.3 mg in a combined laser-ranibizumab treatment in newborn with ROP 3 and extraretinal fibrovascular proliferation spread in the region of over 180 degrees. After 3 months observation regression of the lesions was confirmed, however after another month retina detachment was diagnosed (9). Orozco-Gomez and colleagues conducted a study on a bigger group of patients (34 eyes) in whom a combined therapy was used achieving lesion regression in all cases (10).

In conclusion, pharmacokinetics of both bevacizumab and ranibizumab drugs in circulation of prematures is not known which substantially limits the use of abovementioned substances in ROP treatment in newborns. Due to various controversies the application of these drugs still remains an off-label procedure. There is no doubts that much more clinical studies should be conducted to established management standards in ROP. On the bases of the presented reviews, the application of the drug should depend on advanced stage of ROP. Moreover, drug dose should be appropriately chosen because too low dose might cause proliferation recurrence, too high dose might suppressed normal angiogenesis and vascularistaion not only in retina but also in different organs such as in central nervous system. What is more, the timing of the therapy is essential. Application before 31 PMA (postmenstrual age) could cause retina dystrophy and disruption of normal retinal growth. Too late administration that is after 45 PMA, just after completing of vascularistaion, can lead to rapid vasoconstriction of proliferative membrane which can result in fractional retina detachment. Review of the litera-

ISSN 0023-2157 Index 362646

ture shows that implications for the use of the mentioned substances are as follows: rubeosis iridis and narrow pupil in ROP, severe course of ROP and aggressive-posterior ROP as well as ROP recurrence after laser therapy.

Experimental therapies

Recently, **triamcinolone (Tc)** widely used steroid in ophthalmology has attracted attention of researchers in ROP therapies. The drug has anti-edemic, anti-inflammatory and antiangiogenic activity, inhibiting partly the expression of VEGF factor. Akkoyun et al. in oxygen-induced ROP in mouse model in vivo applied intravitreous Tc in a dose of 20 mg/ml and 40 mg/ml respectively in two studied groups. Decrease in the number of endothelial cells in vitro by 92% and 95% was observed when compared to the control group, which indicates that the drug inhibits retinal neovascularization. In light microscope morphological changes in the form of photoreceptors loss in outer layers of retina were confirmed (11). There was no statistically significant difference in the results between the groups. Comparable outcomes were noted by Spandau et al. who used intravitreous Tc in various doses from 0.05 mg/ml to 8 mg/ml in vivo in experimentally obtained oxygen-induced ROP in mouse model. Statistically significant decrease in number of endothelial cells in vitro by 58% was observed in comparison to controls, which may suggest suppression of retinal neovascularization. It was also confirmed that doses over 2 mg/ml may cause cytotoxic effect on endothelial cells (12). The presented results suggesting potentially toxic activity, show the necessity for additional studies before common application of this drug in ROP treatment. The review Lakhanpal et al. on a combined treatment of intravitreous Tc with vitrectomy and lensectomy applied in ROP 5 indicates the increase in frequency of recurrent retina detachment incidence with the follow-up period 6-42 months (28 months of average) (13).

Matricellular protein cysteine-rich protein 61 (CCN1/Cyr61) is essential in physiology for normal angiogenesis in the eye. Hassan and colleagues noted the lowering of concentration of this protein in the course of oxygen induced retinopathy in mouse model which may be comparable to hypoxia phase and ischemia in ROP. Intravitreous application of modified HSC (hematopoetic cells) secreting the abovementioned proteins led to normalization of retinal vascularisation (14). The results of Barnett and colleagues experimental studies on mouse and rat models of oxygen induced retinopathy noted the reduction of retinal neovascularization by the use of MMP-2 (matrix metalloproteinase-2) inhibition (15).

Kim et al. assessed the influence of intravitreaously applied **gold nanoparticles-GNP** on development of oxygen-induced ROP in mouse model and they confirmed inhibiting abilities of this substance on neovascularization of ROP. In this study toxic activity of GNP on retina was not confirmed. The action of GNP is based on blocking autofosforilation induced by VEGF in VEGFR-2 receptor (16). The research indirectly proves the role of VEGF in ROP pathogenesis and its regulation on different levels. Confirmation of this theory is the paper of Wilkinson-Berk and colleagues in which they described the decrease of pathological neovascularization even by 50% lowering of VEGF activity and its receptor VEGFR-2 observing no influence on physiological vascularization (17). Bromberg-White and colleagues presented a paper in which decrease of oxygen reduced retinopathy was received in mouse model, independently from VEGF action. In the study the authors used **anthrax lethal toxin (LeTx)** which is an inhibitor of kinase activated by mitogen – protein kinase and takes part in pathogenesis of ROP (18). Currently there are studies being conducted on animals with the use of gene therapy which via gene vector applied intravireously might implement the substance suppressing overproduction of growth factors taking part in premature neovascularization (anti-VEGF) (1). In the literature there are reviews on application of **propranolol** and statin in beneficial ROP treatment. There are studies that are known to confirm the disease regression on mouse model with oxygen induced ROP (19, 20). Nowadays, there are clinical studies PROP-ROP (safety and efficacy of propranolol in newborns with Retinopathy of Prematurity), which aims at comparison of ROP treatment effects with conservative therapy (according to ETROP) with a combined therapy with beta-blocker application (19). It should be mentioned that the studies are being conducted on other substances such as insulin like **growth factor IGF-1** and **OMEGA -3 acids** as supplements in the treatment of the ROP (21).

Summing up, it needs to be underlined that despite immense advancement in the medicine that diagnosing and treatment of retinopathy of prematurity, effective scheme of action which could give full success in this vaso-proliferative disease management still has not been found. The studies on the subject continue.

References:

1. Clark D., Mandal K.: *Treatment of retinopathy of prematurity*. Early Hum. Dev. 2008 Feb; Vol. 84 (2), 95–99.
2. Mintz-Hittner H.A., Kennedy K.A., Chuang A.Z.: *Efficacy of intravitreal bevacizumab for stage 3+ retinopathy of prematurity.* BEAT-ROP Cooperative Group. N. Engl. J. Med. 2011 Feb 17; Vol. 364 (7), 603–615.
3. Repka M.X., Tung B., Good W.V., Capone A. Jr., Shapiro M.J.: *Outcome of eyes developing retinal detachment during the Early Treatment for Retinopathy of Prematurity study.* Arch. Ophthalmol. 2011 Sep; Vol. 129 (9), 1175–1179.
4. Lee J.Y., Chae J.B., Yang S.J., Yoon Y.H., Kim J.G.: *Effects of intravitreal bevacizumab and laser in retinopathy of prematurity therapy on the development of peripheral retinal vessels.* Graefes Arch. Clin. Exp. Ophthalmol. 2010 Sep; Vol. 248 (9), 1257––1262.
5. Kimoto K., Kubota T.: *Anti-VEGF Agents for Ocular Angiogenesis and Vascular Permeability.* J. Ophthalmol. 2012; Vol. 2012, 852183.
6. Wu W.C., Yeh P.T., Chen S.N., Yang C.M., Lai C.C., Kuo H.K.: *Effects and complications of bevacizumab use in patients with retinopathy of prematurity: a multicenter study in Taiwan.* Ophthalmology 2011 Jan; Vol. 118 (1), 176–183.
7. Ahmed A.E., Channa R., Durrani J., Ali A., Ahmad K.: *Early experience with intravitreal bevacizumab combined with laser treatment for retinopathy of prematurity.* Middle East Afr. J. Ophthalmol. 2010 Jul; Vol. 17 (3), 264–267.
8. 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.* Grae-

fes Arch Clin. Exp. Ophthalmol. 2008 Jul; Vol. 246 (7), 1061––1063.
9. Jang S.Y., Choi K.S., Lee S.J.: *Delayed-onset retinal detachment after an intravitreal injection of ranibizumab for zone 1 plus retinopathy of prematurity.* J. AAPOS 2010 Oct; Vol. 14 (5), 457––459.
10. Orozco-Gómez L.P., Hernández-Salazar L., Moguel-Ancheita S., Ramírez-Moreno M.A., Morales-Cruz M.V.: *Laser-ranibizumab treatment for retinopathy of prematurity in umbral-preumbral disease. Three years of experience.* Cir. 2011 May-Jun; Vol. 79 (3), 207–214, 225–232.
11. Akkoyun I., Yilmaz G., Oto S., Kahraman B., Haberal N., Akova Y.A.: *Impact of triamcinolone acetonide on retinal endothelial cells in a retinopathy of prematurity mouse model.* Acta Ophthalmol. Scand. 2007 Nov; Vol. 85 (7), 791–794.
12. Spandau U.H., Sauder G., Schubert U., Hammes H.P., Jonas J.B.: *Effect of triamcinolone acetonide on proliferation of retinal endothelial cells in vitro and in vivo.* Br. J. Ophthalmol. 2005 Jun; Vol. 89 (6), 745–747.
13. Lakhanpal R.R., Fortun J.A., Chan-Kai B., Holz E.R.: *Lensectomy and vitrectomy with and without intravitreal triamcinolone acetonide for vascularly active stage 5 retinal detachments in retinopathy of prematurity.* Retina 2006 Sep; Vol. 26 (7), 736–740.
14. Hasan A., Pokeza N., Shaw L., Lee H.S., Lazzaro D., Chintala H. i wsp.: *The matricellular* protein *cysteine-rich protein 61 (CCN1/ Cyr61) enhances physiological adaptation of retinal vessels and reduces pathological neovascularization associated with ischemic e retinopathy*. J. Biol. Chem. 2011 Mar 18; Vol. 286 (11), 9542–9554.
15. Barnett J.M., McCollum G.W., Fowler J.A., Duan J.J., Kay J.D., Liu R.Q. i wsp.: *Pharmacologic and genetic manipulation of MMP-2 and -9 affects retinal neovascularization in rodent models of OIR*. Invest. Ophthalmol. Vis. Sci. 2007 Feb; Vol. 48 (2), 907–915.
16. Kim J.H., Kim M.H., Jo D.H., Yu Y.S., Lee T.G., Kim J.H.: *The inhibition of retinal neovascularization by gold nanoparticles via suppression of VEGFR-2 activation.* Biomaterials 2011 Mar; Vol. 32 (7), 1865–1871.
17. Wilkinson-Berka J.L., Jones D., Taylor G., Jaworski K., Kelly D.J., Ludbrook S.B. i wsp.: *SB-267268, a nonpeptidic antagonist of alpha(v)beta3 and alpha(v)beta5 integrins, reduces angiogenesis and VEGF expression in a mouse model of retinopathy of prematurity.* Invest. Ophthalmol. Vis. Sci. 2006 Apr; Vol. 47 (4), 1600–1605.
18. Bromberg-White J.L., Boguslawski E., Hekman D., Kort E., Duesbery N.S.: *Persistent inhibition of oxygen-induced retinal neovascularization by anthrax lethal toxin.* Invest. Ophthalmol. Vis. Sci. 2011 Nov 21; Vol. 52 (12), 8979–8992.
19. Filippi L., Cavallaro G., Fiorini P., et al.: *Study protocol: safety and efficacy of propranolol in newborns with Retinopathy of Prematurity (PROP-ROP)*. BMC Pediatr. 2010 Nov 18; Vol. 10: 83.
20. Bartoli M., Al-Shabrawey M., Labazi M., Behzadian M.A., Istanboli M., El-Remessy A.B. i wsp.: *HMG-CoA reductase inhibitors (statin) prevents retinal neovascularization in a model of oxygen-induced retinopathy.* Invest. Ophthalmol. Vis. Sci. 2009 Oct; Vol. 50 (10), 4934–4940.
21. Mantagos I.S., Vanderveen D.K., Smith L.E.: *Emerging treatments for retinopathy of prematurity.* Semin. Ophthalmol. 2009 Mar-Apr; Vol. 24 (2), 82–86.

The study was originally received 31.07.2012 (1405)/
Praca wpłynęła do Redakcji 31.07.2012 r. (1405)
Accepted for publication 09.11.2012/
Zakwalifikowano do druku 09.11.2012 r.

Reprint requests to (Adres do korespondencji):
dr hab. n. med. Monika Modrzejewska
Katedra i Klinika Okulistyki PUM
al. Powstańców Wielkopolskich 72
70-111 Szczecin
e-mail: monika_modrzej@op.pl

ISSN 0023-2157 Index 362646