Therapeutic strategies for retinopathy of prematurity

J. Liu,1 MPhil; Connie H. Y. Lai,2 MBBS, FHKAM (Ophthalmology); Amy C. Y. Lo,1,3 PhD
1Department of Ophthalmology, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong SAR, China.
2Department of Ophthalmology, Queen Mary Hospital, Hong Kong SAR, China.
3Research Centre of Heart, Brain, Hormone and Healthy Aging, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong SAR, China.

Correspondence and reprint requests:
Dr. Amy C. Y. Lo, Department of Ophthalmology, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Pokfulam, Hong Kong SAR, China.
Email: amylo@hkucc.hku.hk

Abstract

Retinopathy of prematurity is a retinal vascular disease of premature infants and the major global cause of preventable childhood blindness. The number of infants at risk from blindness due to retinopathy of prematurity has increased because of improved survival of preterm infants. We discuss the current and potentially available treatments as well as preventive strategies for retinopathy of prematurity. Peripheral retinal ablation by indirect laser photocoagulation is currently the gold standard treatment; however, newer modalities of treatment that target the vascular endothelial growth factor pathway have shown promise in certain disease stages. In the neonatal wards, oxygen saturation level monitoring has been shown to be important in the prevention of retinopathy of prematurity. Research on insulin-like growth factor 1, omega-3 polyunsaturated fatty acids, lutein, and aldose reductase is providing encouraging information about prevention of the condition. More studies are warranted on the prospective implications of these new therapeutic or interventional strategies for retinopathy of prematurity.

Key words: Retina; Retinopathy of prematurity; Vascular endothelial growth factor A

Introduction

Retinopathy of prematurity (ROP) is currently a major cause of preventable blindness in children. Over 50,000 infants worldwide are blind due to ROP.1 In the United States, the total incidence of ROP has been reported to be 0.12% overall and 7.35% for premature infants with hospital stay of longer than 14 days.2 With advancements in diagnosis and treatment, the disease can now be properly controlled; however, visual outcome for these patients varies and remains poor for some, which significantly affects their future quality of life.

The disease was first observed around 80 years ago by Dr. Terry in preterm infants 2 received supplementary oxygen treatment.3 ROP has two postnatal phases: in phase I, hyperoxia induces retinal vessel obliteration; in phase II, hypoxia induces neovascularization. Normal retinal vessel development is initiated around the gestational age of 6 weeks, and is complete shortly after birth, with choroid, hyaloid vessel and retinal vasculature developing step by step. Retinal vasculature development starts from the central optic nerve and continues towards the periphery. The driving force for normal retinal vasculature development is the physiological hypoxia in the intrauterine environment. A number of angiogenic factors are involved in the development of retinal vasculature, including vascular endothelial growth factor (VEGF), insulin-like growth factor 1 (IGF-1), basic fibroblast growth factor, transforming growth factor–beta, platelet-derived growth factor, and hepatocyte growth factor. Preterm infants (born with gestational age <37 weeks), especially extreme preterm infants (born with gestational age <26 weeks, body weight <1500 g), have an incompletely developed retinal vasculature. The normal room air environment is hyperoxic compared with the intrauterine environment, and causes cessation of retinal vessel growth, by apoptosis and capillary regression, leading to interruption of normal retinal vasculature development and later local retina ischemia. Oxygen supplementation will aggravate this process. A peripherally avascular retina can be observed, and is noted as the vaso-obliterative phase.
ROP is a multifactorial disease. The major risk factors for ROP development are low gestational age and birth weight. Both are related to the extent of retinal immaturity in neural and vascular development, thus leaving the retina vulnerable to insult. Lower gestational age and birth weight are associated with inability of the infant to take over production of the absent factors that are normally provided in the intrauterine environment. Postnatal IGF-1 level and postnatal weight gain are other risk factors for ROP development, and can be used to predict ROP occurrence. A strong association exists between early-postnatal low serum IGF-1 level and later ROP, as well as other prematurity-related morbidities in infants. The oxygen and its concentration given to preterm infants is another major risk factor for ROP. Hyperglycemia may also increase the risk. Other complications in preterm infants that are related to overall health status, such as infections, anemia, chronic lung disease and necrotizing enterocolitis, may also be risk factors for ROP.

The classification of ROP was first published as International Classification of Retinopathy of Prematurity in 1984, later expanded in 1987, and further modified in 2005. The classification was based on the zone, extent and staging of the disease, whether the disease is accompanied with a plus disease or pre-plus disease, and defined aggressive-posterior ROP (AP-ROP). The retina can be divided into 3 zones: zone I is the posterior zone of the retina, which is a circle with a radius extending from the optic nerve to double the distance to the macula; zone II is an annulus with the inner border defined by zone I and the outer border defined by the radius defined as the distance from the optic nerve to the nasal ora serrata; zone III is the residual temporal crescent of the retina. The extent of the disease is recorded as hours of the clock or as 30° sectors. ROP is categorized into 5 stages that are summarized in Table 1. Plus disease refers to additional signs observed at the leading edge of abnormal retinal vasculature development and indicates the severity of active ROP that may occur. These signs include increased venous dilatation and arteriolar tortuosity of the posterior retinal vessels and may later increase in severity to include iris vascular engorgement, poor pupillary dilatation and vitreous haze. Pre-plus disease is defined as vascular abnormalities of the posterior pole with more arterial tortuosity and more venous dilatation than normal, but insufficient for the diagnosis of plus disease. AP-ROP is a severe form of ROP that occurs in the posterior retina with prominent plus disease and ill-defined nature of retinopathy. If untreated, AP-ROP usually progresses rapidly to stage 5 ROP. Most cases of ROP classified below stage 2 may regress spontaneously without treatment and with good visual prognosis. Treatment may be needed in the more severe stages of disease, however.

In the Cryotherapy for Retinopathy of Prematurity (CRYO-ROP) study, which is the largest study to date, threshold disease is defined as stage 3 disease in zone I or II, 5 contiguous clock hours of disease or 8 cumulative sectors (clock hours) in the presence of plus disease. This study was stopped prematurely as there was overwhelming evidence that treatment resulted in an approximately 50% reduction in the rate of retinal detachment and continuation of the study would have been unethical. Cryotherapy was used in this study as indirect diode laser was not available at the time.

The Early Treatment for Retinopathy of Prematurity Study revised the indications for treatment of the disease. Clock hours are no longer needed for threshold disease. Two types of diseases are defined and summarized in Table 2. Type 2 ROP needs no treatment but close monitoring. Treatment should be considered if type 2 disease progresses to type 1 disease, for which retinal ablation is recommended.

With advances in understanding of the pathogenesis of ROP, treatment strategies are constantly developing and being improved. In this paper, we will review current treatments for ROP and studies on its prevention.

### Oxygen level control

Since ROP was first described as retrolental fibroplasias by Dr. Terry in 1942, doctors and researchers have recognized the association between uncontrolled oxygen supplementation and ROP. Lowering of the oxygen saturation target has become one of the strategies to prevent ROP.

Several studies have tried to determine a feasible and optimal

---

**Table 1. Stage classification of retinopathy of prematurity in International Classification of Retinopathy of Prematurity**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Mildly abnormal blood vessel growth, and a thin demarcation line could be seen between vascularized and non-vascularized retina</td>
</tr>
<tr>
<td>2</td>
<td>Moderate abnormal blood vessels, and an elevated mesenchymal ridge could be observed</td>
</tr>
<tr>
<td>3</td>
<td>Severely abnormal blood vessels could be observed, characterized by extraretinal fibrovascular proliferation</td>
</tr>
<tr>
<td>4</td>
<td>Subtotal retinal detachment caused by the neovascularizations is observed</td>
</tr>
<tr>
<td>5</td>
<td>Total retinal detachment</td>
</tr>
</tbody>
</table>
oxygen saturation range when treating preterm babies with low gestational age and low birth body weight. Saturation of peripheral oxygen (SpO₂) is an estimation of oxygen saturation, indicating the fraction of oxygen-saturated hemoglobin relative to total hemoglobin in the blood, which can be easily monitored by a non-invasive pulse oximeter. Cole et al were the first to suggest keeping SpO₂ at 83% to 93%, and this has changed clinical practice in the neonatal wards. In a 2-year study with a sample size of 222 preterm infants, lower oxygen targeted at an early gestational age and higher oxygen targeted at an older gestational age decreased the severity and incidence of ROP. Decreasing oxygen saturation range from 87%-97% to 85%-93% decreased the incidence of ROP in preterm babies with birth weight of ≤1250 g and/or gestational age of ≤28 weeks. Clinicians have also found that a slight decrease in oxygen level to 90%-96% from the high oxygen levels (96%-99%) resulted in a small but significant reduction in ROP incidence.

In the Surfactant, Positive Pressure, and Pulse Oximetry Randomized Trial, the oxygen saturation level was controlled within 85-89% versus 91-95%. The lower oxygen level led to higher mortality; but in survivors, a lower ROP incidence was observed in the low oxygen target group. In the Supplemental Therapeutic Oxygen for Prethreshold Retinopathy Of Prematurity trial, no difference was observed between high (96-99%) and low (89-94%) oxygen saturation groups, but adverse pulmonary outcomes were observed in the group with high oxygen level. In the Benefits Of Oxygen Saturation Targeting II study, in which lower oxygen level (85-89%) and higher oxygen level (91-95%) groups were compared, a greater survival rate was observed in the 91-95% oxygen saturation group. Nonetheless, in another clinical trial with 340 preterm infants, no difference in death rate was observed between low and high oxygen target groups.

Clinical trials have shown that oxygen saturation control during oxygen supplementation would be a possible way to prevent ROP, but the target range of oxygen level remains controversial. Lowering the oxygen level did decrease ROP incidence in some studies, but it also increased the mortality and had long-term effects on development, such as the central nervous system. Finding an optimum level for the oxygen target in oxygen supplementation for preterm infants that balances the ROP incidence and mortality remains to be determined by neonatologists.

<table>
<thead>
<tr>
<th>Type</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Zone I, any stage ROP with plus disease; zone I, stage 3 ROP without plus disease; or zone II, stage 2 or 3 with plus disease.</td>
</tr>
<tr>
<td>2</td>
<td>Zone I, stage 1 or 2 ROP without plus disease; or zone II, stage 3 ROP without plus disease.</td>
</tr>
</tbody>
</table>

Ablative therapy

Ablation of the peripheral avascular retina to reduce the proliferative outcome of increased metabolic demand on the peripheral retinal cells has been developed and is now the well-established therapy for ROP. Cryotherapy, established in the late 1980s, was the first effective treatment for severe ROP prior to the advent of laser treatment, which has been proven to be a better choice between the two for ablative therapy. In the CRYO-ROP study, a lower incidence of unfavorable anatomic outcome was observed in cryotherapy-treated eyes with severe ROP when compared with untreated eyes. The structural and functional benefits of cryotherapy were found to be maintained over 15 years of follow-up. However, some ocular and systemic complications may occur with ablative therapy, such as conjunctival laceration, vitreous hemorrhage, apnea, bradycardia and arrhythmia.

Laser coagulation therapy emerged about 20 years ago, and has almost replaced cryotherapy in developed countries for severe ROP. Laser treatment had similar effectiveness in the treatment of threshold ROP. It has some practical advantage over cryotherapy, such as reduced requirement for general anesthesia, mobile equipment and its effectiveness in treating the posterior retina. In a single-center study of treatment for severe ROP, cryotherapy had a higher incidence of unfavorable structural outcome, poor visual acuity outcome and myopia, as well as systemic complications when compared with laser treatment. In another single-center study, laser-treated eyes achieved better visual acuity than cryotherapy-treated eyes after 3 years’ follow-up. Another study that aimed to compare these 2 treatments also indicated that cryotherapy had more poor visual acuity outcomes, myopia and acute systemic complications, although the poor structural outcome rates were similar in the 2 groups.

Ablative therapy, in essence, reduces VEGF production by cells in the avascular retina. Laser treatment has been shown to have better effects than cryotherapy when treating severe ROP, for its lower incidence of unfavorable structural outcome and systemic complications.

Anti–vascular endothelial growth factor treatment

VEGF is a potent mitogen for endothelial cells, and is responsible for angiogenesis under both physiological and pathological conditions. Seven members of the VEGF family have been identified to date — VEGF-A, VEGF-B, VEGF-C, VEGF-D, VEGF-E, VEGF-F and placenta growth factor. Until now, 3 VEGF tyrosine kinase receptors have been identified: the fms-like kinase Flt-1 (VEGFR-1/Flt-1), the kinase domain region or fetal liver kinase (VEGFR-2/KDR/Flik-1), and Flt-4 (VEGFR-3). Neuropilin-1 and neuropilin-2 are 2 co-receptors of VEGF with no kinase activity, and binding of VEGF to them enhances VEGFR-2 signaling. Binding of VEGF to their receptors triggers the RAS/RAF/MEK/ERK and PI3 kinase/AKT/mTOR pathways that are implicated in different cellular functions.
RNA splicing during the gene transcription process has enabled several isoforms of VEGF to be identified according to their amino acid length size, including VEGF-A_{165}, VEGF-A_{183}, VEGF-A_{189}, and others. The 3 most representative isoforms of VEGF are VEGF-A_{121}, VEGF-A_{165} and VEGF-A_{189} because of their role in angiogenesis under normal and pathologic conditions. VEGF-A_{165} is probably the most studied VEGF isoform for its important role in angiogenesis, embryo implantation, wound healing and tissue repair. It also mediates neovascularization in proliferative retinopathies, such as diabetic retinopathy (DR), wet age-related macular degeneration (AMD) and ROP. VEGF-A_{121} is a potent growth factor for vascular endothelial cells, promoting vascular angiogenesis and permeability; it is also correlated with angiogenesis in certain types of cancer. VEGF-A_{189} plays an important role in phases of lower angiogenic potential, supporting cell adhesion and survival. In carcinoma cells, VEGF-A_{189} level has been suggested to induce an autocrine proliferation loop, thus the existence of the VEGF-A_{189} might indicate a poor prognosis in some tumor patients. Hypoxia is the major drive for the regulation of VEGF expression. Meanwhile, hypoxia in local retinal areas occurs in most proliferative retinopathies. Thus targeting VEGF has been a popular focus in the treatment of proliferative retinopathies. Anti-VEGF treatment has already been used in some proliferative retinopathies, such as DR and AMD. Compared with laser coagulation, anti-VEGF drugs are more direct in blocking the effects of VEGF in the retina.

Currently, there are 4 anti-VEGF drugs commercially available: pegaptanib sodium (Macugen; Pfizer, USA), which partially blocks VEGF-A; and ranibizumab (Lucentis; Genentech, USA), bevacizumab (Avastin; Genentech, USA) and aflibercept (Eylea; Regeneron, USA), which are pan-VEGF-A blockers. Pegaptanib sodium, ranibizumab and aflibercept are approved by the US Food and Drug Administration (FDA) for intraocular application in treating some ocular proliferative diseases in adults. Bevacizumab is approved by the FDA only for intravenous use in the treatment of breast, colorectal, lung and renal cell cancers. The guidelines for use of anti-VEGF drugs in the treatment of ROP have not been established.

Pegaptanib is a selective VEGF-A_{165} blocker, and may provide a safer option in preterm newborns because it does not inhibit all isoforms of VEGF for physiological retinal vessel development. A clinical study using intravitreal pegaptanib injection combined with laser therapy to treat stage 3+ ROP in zone I or posterior zone II has shown a favorable anatomic outcome and stable regression of ROP, when compared with laser therapy only. More importantly, no systemic or ocular complications were found during 19.3 months’ follow-up. Ranibizumab is a monoclonal antibody fragment with a strong affinity for binding to VEGF-A, and has been approved to treat wet AMD. Two studies have reported that ranibizumab is effective as a salvage treatment for the recurrence of ROP after anti-VEGF treatment using other anti-VEGF drugs combined with laser therapy. Aflibercept is a recombinant fusion protein consisting of VEGF-binding portions from the extracellular domains of human VEGF receptors 1 and 2. It has been approved for treatment of wet AMD and colorectal cancer although no randomized clinical trials on the effects of ranibizumab or aflibercept in treating ROP have been reported so far.

Bevacizumab is a humanized monoclonal antibody against VEGF-A and inhibits angiogenesis. Although side-effects of bevacizumab include an increased risk of hemorrhage and thrombosis in adults with intravenous therapy, it has been widely used off-label at clinics for the treatment of intraocular neovascularizations at a low dose because of its controllable side-effects. It has been the most promising anti-VEGF drug for treating ROP. Quiroz-Mercado et al reported that in 13 patients with severe ROP at different stages with or without prior laser therapy, a single intravitreal dose of 1.25 mg bevacizumab led to neovascular regression in all patients. In patients with recurrence of ROP following laser treatments and AP-ROP, intravitreal injection of bevacizumab 0.625 mg resulted in neovascularization regression and favorable structural outcome in most patients, although 1 of 10 patients required further laser therapy. In a multicenter retrospective case series study, 27 patients with 49 eyes in total and stage 3+ ROP received intravitreal injection of bevacizumab 0.625 mg as initial or salvage therapy. In this study, 90% of 41 eyes with stage 3 ROP had their neovascularization regressed, one third of 6 stage 4 ROP eyes had neovascularization regressed whereas the other needed further vitrectomy. The only 2 eyes with stage 5 ROP displayed decreased vascular tortuosity after treatment. In a study on the efficacy of intravitreal bevacizumab for stage 3+ ROP, monotherapy with bevacizumab showed a significant benefit for zone I but not zone II disease, compared with conventional laser therapy. In another study that recruited 85 patients (162 eyes) with type 1 ROP, one intravitreal injection of bevacizumab 0.625 mg was given as initial therapy. In this study, 88% of the eyes exhibited ROP regression, 9% needed laser therapy and only 1% of eyes required additional injection. Moreover, only 1% of the eyes had vitreous or preretinal hemorrhage and 1 eye had cataract. Other studies applying bevacizumab 0.625 mg intravitreal injection in treating severe ROP also achieved regression of ROP with favorable anatomic outcome. Intravitreal injection of bevacizumab at different dosages (0.375 mg and 0.75 mg, respectively) also reduced neovascularization in severe ROP. Although bevacizumab showed effectiveness in treating ROP, recurrence may occur later in the course of treatment, indicating that under some circumstances its benefit may be transient.

In previous studies and case reports, anti-VEGF was applied after the diagnosis of stage 3+ ROP. Combined use of anti-VEGF and laser treatments achieved the most ideal clinical outcome, with less reocurrence and better structural outcome.
monotherapy with anti-VEGF or laser treatment. Anti-VEGF could be used as a salvage strategy when standard ablative therapy did not work well.

Anti-VEGF may also have some disadvantages as with other therapeutic strategies, including endophthalmitis following intravitreal injection, damage to the lens causing cataract, possible effects on organ development, possibly higher death rate, and extended follow-up due to late reoccurrence of severe ROP. Controversy regarding the use of this drug is still evident and no clear guideline regarding the dosage, number of injections, monitoring and cessation of screening of disease is available.

Supplemental therapies

Insulin-like growth factor 1

IGF-1 plays an important role in fetal growth and development throughout pregnancy. IGF-1 levels rise significantly in the third trimester. It has been reported as a permissive factor for normal retinal vascular development via regulation of VEGF signaling. IGF-1 is synthesized in the placenta and fetal liver in nutrient-dependent processes, and its levels in preterm newborns decrease because of the loss of maternal-fetal interaction. Thus preterm birth leads to early decreasing IGF-1 levels and suppression of VEGF, and this hinders normal retinal vessel development. Lack of IGF-1 has been noted to be a risk factor for phase I ROP. The decreased serum IGF-1 level has been reported to be associated with ROP incidence, and the IGF-1 level has been suggested to be predictive of severe ROP. If IGF-1 supplementation is performed in phase I ROP matching the levels of VEGF for normal retinal vessel growth, then the abnormal neovascularization in phase II might be reduced. In laboratory animals, administration of recombinant human IGF-1 promoted body weight gain in newborn mouse pups and reduced retinal neovascularization in an oxygen-induced retinopathy (OIR) model. In human subjects, although no reports on treatment of ROP by IGF-1 supplementation have been published, a study on parenteral nutrition in preterm infants indicated that low IGF-1 level was negatively correlated with development of ROP. The safety and pharmacokinetics of recombinant human IGF-1 have been described recently. A clinical trial aiming to prevent ROP by restoring IGF-1 level to uterine levels in preterm infants is now at the recruitment stage.

Omega-3 polyunsaturated fatty acids

The polyunsaturated fatty acids (PUFAs) contain more than one double bond between carbon atoms in their backbone. The nomination of PUFAs depends on the location of the first double bond from the methyl end, that is, the omega- or the n- end. The major PUFAs in the retina are docosahexaenoic acid and arachidonic acid that belong to omega-3 and omega-6 PUFAs, respectively, and are found in the cell membrane phospholipids of neural and vascular cells. Omega-3 and omega-6 PUFAs are essential fatty acids for normal growth in young children; in other words, they cannot be synthesized by the human body, but must be obtained from daily diet. Omega-3 PUFAs display some beneficial effects in cardiovascular disease and reduce cardiac death. Omega-6 PUFAs, unlike omega-3 PUFAs, are linked to some negative health effects when taken in excess. The metabolites of omega-6 PUFAs, omega-6 eicosanoids, are associated with arthritis, inflammation and cancer. Similar to IGF-1, the fetal omega-3 and omega-6 PUFAs depend on transfer from mother to fetus during the third trimester of pregnancy. Preterm infants lack these PUFAs because of the lost supply source. The role of omega-3-PUFAs and omega-6-PUFAs in the pathogenesis of ROP is being evaluated. It has been shown that decreased omega-6/omega-3 PUFA ratio has a protective effect against pathologic angiogenesis due to increased regrowth of vessels after vessel loss in a mouse ROP model. The derived bioactive mediators of omega-3 PUFA also have similar effects. The protective effects may be related to suppression of pro-inflammatory cytokine tumor necrosis factor–alpha (TNF-α) in a subset of microglia that is closely associated with retinal vessels. It has been shown that peroxisome proliferator-activated receptor gamma mediates the suppressive effects on TNF-α by omega-3 PUFA. A recent study has shown that low serum level of omega-3 PUFAs was present in preterm infants. In a mouse OIR model, supplementation with omega-3 PUFAs ameliorated neovascularization through adiponectin by suppressing endoplasmic reticulum stress.

In premature infants, the essential fatty acid loss due to preterm birth must be supplemented by total parenteral nutrition. Nonetheless the total parenteral nutrition currently given to premature infants contains only omega-6 PUFA, but no omega-3 PUFA. Supplementary omega-3-PUFAs intake in preterm infants may be beneficial in preventing ROP. Clinical trials on the benefits and safety of omega-3 PUFA supplementation in preventing ROP are needed.

Lutein

Lutein is a naturally occurring carotenoid. In the retina, lutein acts as an antioxidant and protects the retina from blue light damage. It has already been used in AMD patients to improve their vision. It also plays a protective role in a retina ischemic/hypoxic model in vivo and in vitro. The risk profile of lutein was also reviewed in 2006 by the Council for Responsible Nutrition in Washington D.C. It was concluded that apart from the reversible skin discoloration, no other adverse effects were observed. Studies on supplementing lutein to prevent ROP have been performed and several clinical trials have demonstrated that lutein is well tolerated in preterm infants. Nonetheless, although a trend of decrease in ROP incidence was observed in a lutein-treated group, the change was not significant on statistical analysis, possibly due to the small study sample. More clinical trials on the effects of lutein for treating ROP with a large sample size are needed in the future.

Aldose reductase inhibition

Aldose reductase (AR) is the key enzyme in the polyol pathway of glucose metabolism. It catalyzes the conversion
of glucose to sorbitol in a nicotinamide adenine dinucleotide phosphate–dependent manner. Excess activated AR contributes to oxidative stress to which the retina is susceptible. In an ischemic retinopathy animal model, genetic AR deficiency or pharmacological inhibition of AR activity by fiaxistat (an AR inhibitor) could protect the retina from ischemia/hypoxia injury. AR deficiency and inhibition also protected the retina from diabetes-induced blood retinal barrier breakdown in a type 2 diabetes mouse model. Recently, using the murine OIR model, it has been demonstrated that AR-deficient mice and mice treated with fiaxistat display reduced neovascularization development and less inflammatory reaction. The neuronal function of the retina may also be protected by AR deficiency in a mouse OIR model. AR inhibition might be an option for treating or preventing ROP, but more studies are needed.

It is clear that IGF-1 and omega-3 PUFAs in the fetus can only be obtained from maternal milk. As preterm infants lack these 2 factors, supplemental administration of IGF-1 or omega-3 PUFAs can be implemented before the onset of ROP, so as to promote normal retinal vessel development, thereby reducing the hypoxia level of local retinal microenvironment. Lutein supplementation can also be applied at an early stage of ROP or even before the onset of ROP, for its antioxidant effects and absence of reported side-effects. Nonetheless the appropriate timing of potential supplement therapies against ROP needs to be tested by more clinical trials.

Conclusion

Current advances in neonatal intensive care have increased the survival rate of very premature infants. Meanwhile, the improved survival rate has resulted in an increased incidence of ROP that remains a challenge to neonatologists. Prevention of the development of severe ROP should be the best strategy to avoid ROP-initiated visual impairment and blindness. Reducing the risk factors of ROP, such as oxygen control and nutrition improvement, is important. The current standard treatment for ROP is retinal ablative therapy by laser photocoagulation. Although it usually works well, ablative therapy also has limitations and may have long-term effects. ROP is now under intense investigation and numerous findings have been obtained in recent years with promising therapeutic implications. Therapies that target the VEGF pathway are currently considered the most promising treatment of ROP. Although a few clinical studies have reported their beneficial effects on ROP, more clinical trials are warranted. Other studies of IGF-1, omega-3 PUFAs, lutein and antioxidative drugs also provide valuable and encouraging information for the future treatment of ROP.

References

19. SUPPORT Study Group of the Eunice Kennedy Shriver NICHD Neonatal Research Network, Carlo WA, Finer NN,
14

**REVIEW ARTICLE**


