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Review article

IGF-I in the clinics: Use in retinopathy of prematurity

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ABSTRACT

Retinopathy of prematurity is a potentially blinding disease, which is associated with low neonatal IGF-I serum concentrations and poor growth. In severe cases impaired retinal vessel growth is followed by pathologic neovascularization, which may lead to retinal detachment. IGF-I may promote growth even in catabolic states. Treating preterm infants with recombinant human (rh) IGF-I to concentrations normally found during gestation has been suggested to have a preventative effect on ROP. A recent phase 2 study treating infants (gestational age between 23 weeks + 0 days and 27 weeks +6 days) with rhIGF-I/IGF binding protein-3 until 30 postmenstrual weeks showed no effect on ROP but a 53% reduction in severe bronchopulmonary dysplasia and 44% reduction in severe intraventricular hemorrhage. Oxygen is a major risk factor for ROP and during the phase 2 study oxygen saturation targets were increased to 90–95%, due to national guidelines, which might have affected ROP rate and severity making increased IGF-I a weaker preventative factor for ROP.

1. Introduction

Retinopathy of prematurity (ROP) is a potentially preventable neurovascular disorder, which is estimated to make 20.000 infants blind or severely visually impaired each year worldwide. In settings with highly developed neonatal care, ROP mainly affects extremely preterm infants born before 28 gestational weeks, while with less advanced care, more mature infants become blind from ROP [1]. Control of oxygen supplementation reduces severe ROP but optimal oxygenation targets are still unknown. Postnatal bio-energetic failure with growth retardation is a universal phenomenon in very preterm infants [2] which is associated with ROP and low circulating concentrations of IGF-I [3], an anabolic hormone with mitogenic, differentiating, anti-apoptotic and metabolic effects [4].

IGF-I exerts its actions in endocrine, paracrine and autocrine manners through binding to the IGF-I receptor and with substantially less affinity to the insulin receptor. IGF-I plays many roles, which differ depending on factors such as source [5], target cell type and developmental stage [6]. Six binding proteins (IGFBP) control IGF-I actions. Approximately 80% of circulating IGF-I is bound to IGFBP-3 which together with an acid-labile subunit (ALS), prolongs the half-life and maintains a reservoir of IGF-I in the circulation [7,8]. IGFBP-1 increases with fasting and hypoxia and restrains growth by decreasing IGF-I bioavailability [9]. Growth hormone regulates hepatic IGF-I production in children and adults but not in the fetus. During gestation, circulating fetal IGF-I concentrations are dependent on nutrient supply from the mother and increase during the third trimester [10]. At term birth, higher cord serum IGF-I concentrations are associated with increased fetal size and fat mass [11]. Circulating IGF-I is mainly derived from the liver but virtually all human fetal tissues express IGF-I from an early stage [12]. Amniotic fluid contains higher IGF-I concentrations than cord blood during gestation or at delivery and is swallowed by the fetus [13]. It is not clear whether placenta-derived IGF-I is secreted into the fetal circulation [14]. Little is known about the roles of locally synthesized versus circulating IGF-I. However, circulating IGF-I levels are thought to provide information about the state of the organism as a whole [15].

IGF-I expression in the central nervous system to which the retina belongs is highly developmentally regulated and mainly localized in large projection neurons during a brief period of late development [16]. In the maturing rat retina IGF-I mRNA is concentrated in the ganglion cell layer during the first weeks after birth when retinal vascularization takes place and then rapidly decreases [17]. In neonatal mice, IGF-I is expressed throughout the retina while the IGF-I receptor is expressed predominantly in photoreceptors and blood vessels. IGFBP-3 expression increases >5-fold in neovascular tufts in oxygen-induced retinopathy during hypoxia-driven neovascularization [18].

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After very preterm birth, IGF-I serum concentrations fall rapidly to approximately 10 ng/mL compared to >50 ng/mL in utero at postmenstrual age (PMA) 23–30 weeks (Fig. 1) [10,19–22]. Persistent low serum IGF-I levels are associated with poor general growth and poor brain growth as well as neonatal morbidities such as intraventricular hemorrhage (IVH), retinopathy of prematurity (ROP), bronchopulmonary dysplasia (BPD) and necrotizing enteritis (NEC) [23]. We will review IGF-I in relation to normal retinal development and ROP and the possible role of IGF-I supplementation in the prevention of ROP.

2. Retinal vascularization and classification of ROP

Proper vascularization is essential for the supply of oxygen, nutrients and other factors to developing tissues. Since blood vessels in the eye are available for direct inspection with non-invasive methods such as indirect ophthalmoscopy and the retina may be severely affected by very preterm birth, much research has focused on retinal vascularization. Endothelial cells, which play a key role in both vasculogenesis and angiogenesis, produce IGF-I. In cultures of bovine retinal endothelial cells (BRECs), the production of IGF-I is greatly increased in a hypoxic environment [24]. IGF-I promotes glucose uptake in processes dependent on protein kinase C (PKC) and phosphatidylinositol-3 kinase (PI3K) and stimulates cell proliferation [25]. IGF-I-stimulated glucose transport in BRECs requires activation of mitogen activated protein kinase (MAPK), which is upstream of PKC but independent of PI3K in mediating the effect of IGF-I on endothelial cells [26]. However, when BRECs are exposed to high glucose concentrations they become insensitive to IGF-I at least in part due to reduced activation of the p42/44 MAPK pathway [27]. Hypoxia is a major angiogenic stimulus which increases transcription of vascular endothelial growth factor (VEGF) mRNA. IGF-I may also increase VEGF-1 synthesis [28]. Minimal levels of IGF-I are required for VEGF activation of pathways promoting retinal vascular endothelial cell proliferation and survival [29]. Impaired normal neonatal angiogenesis after preterm birth followed by tissue hypoxia and nutrient insufficiency driving proliferative angiogenesis is a hallmark of ROP but might apply to BPD [30] and encephalopathy of prematurity [31] as well.

During normal human retinal development, blood vessels grow from the optic disk at around 14 gestational weeks and reach the periphery at term. Experimental studies to elucidate mechanisms behind ROP are based on studies in oxygen induced retinopathy (OIR) in rodents i.e. mice and rats in which retinal vascularization normally takes place during the first weeks of extrauterine life. Normal vessel growth is stimulated by VEGF and other factors in response to "physiologic hypoxia" appearing in front of the vessels when the neural retina matures [32].

Retrolental fibroplasia, the end stage of ROP, was first described by Terry in 1942 in blind prematurely born infants exposed to high oxygen levels in closed incubators. Fibrovascular tissue containing the detached retina was seen behind the crystalline lens. Earlier stages of ROP were later identified and classified according to vascular changes visible with ophthalmoscopy. At very preterm birth, only the central part of the retina is vascularized and the periphery remains avascular. The first sign of ROP is a sharp demarcation line (stage 1) which may increase in volume to become a ridge (stage 2) at the border between vascularized and avascular retina. These changes often regress spontaneously, but in more severe cases, progress to stage 3 with uncontrolled neovascularization at the ridge, which in turn may regress or progress to partial (stage 4) and total (stage 5) retinal detachment (Fig. 2). Engorgement and tortuosity of central retinal vessels is an ominous sign called plus disease. In ROP classification, the retina is divided into three zones where zone I is the most central and zone III the most peripheral. In cases with central ROP and a large avascular retinal area, aggressive posterior ROP (APROP), a rapidly progressing severe form with plus disease but without distinct progression through stages, may occur [33]. Electro-physiologic studies in ROP patients have demonstrated that not only blood vessels but also neural cells such as retinal photoreceptors are affected in early stages of ROP [34].

The neonatal period of the very preterm newborn is characterized by problems adapting to extra-uterine life, energy deficiency, infections, hyperglycemia, low serum IGF-I and un-physiologic oxygenation with periods of hyperoxia as well as hypoxia. ROP is a two phase disease. In the first phase blood vessel growth is arrested and parts of already formed vessels regress, leaving the maturing peripheral retina avascular

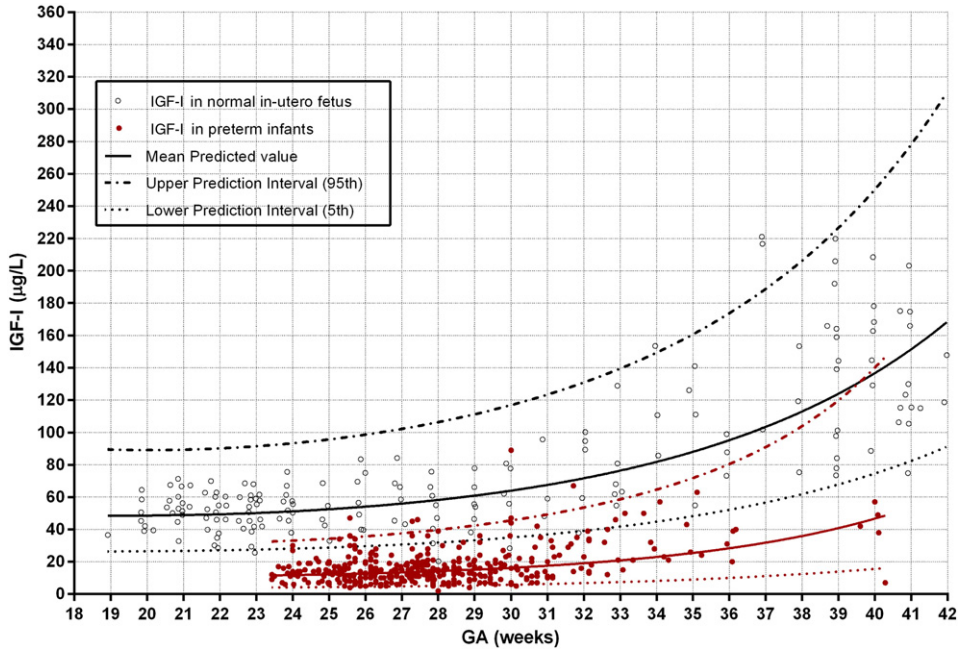

Fig. 1. Normal intrauterine IGF-I concentrations obtained from the umbilical cord with cordocentesis over 18 to 42 weeks of gestation (GA) ($n = 174$) (10,19) compared to preterm infants of matched postmenstrual ages (red dots) (20 − 22).

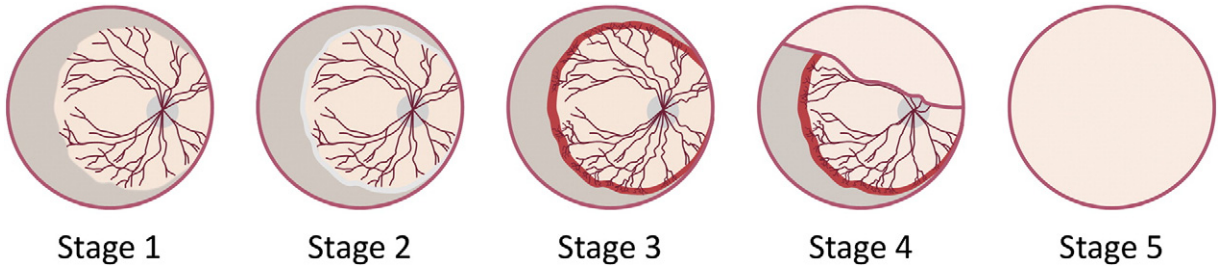

Fig. 2. Stages of ROP. Stage 1—Demarcation line between vascular and avascular retina. Stage 2—Ridge. Stage 3—Extraretinal neovascularizations at the ridge. The abnormal blood vessels grow toward the center of the eye instead of following their normal growth pattern along the surface of the retina. When infants have a certain degree of Stage 3 and "plus disease" develops, treatment is considered. "Plus disease" means that the blood vessels of the retina have become enlarged and twisted, indicating a worsening of the disease. Stage 4 —Partially detached retina. Stage 5 — Completely detached retina and the end stage of the disease. (Painting by Ann-Sofie Petersson).

and devoid of oxygen and nutrients. The onset of the second phase has not been properly defined and one may consider the appearance of any ROP stage as the beginning of phase II, (which we will do in this review) or the onset of the neovascularization of stage 3 exclusively. Phase I extends from birth to around 30–34 weeks when the ocular characteristics of ROP are first seen. Efforts to reduce ROP include *prevention* of blood vessel loss and promotion of normal retinal vessel growth in the first phase of the disease and *treatment* i.e. measures to make neovascularization regress in phase II to prevent retinal detachment. Thus, intervention approaches are diametrically different in the two phases. In addition, prevention of progression from mild to severe ROP using oral propranolol has the potential to reduce severe ROP but safety is a serious concern [35].

3. Current ROP treatment

Current treatment addresses neovascularization in advanced ROP to prevent retinal detachment and blindness. Ablation of the avascular and hypoxic retina (which produces many angiogenic factors such as VEGF) peripheral to the ridge by laser or cryotherapy constitutes the only evidence-based treatment. However, intra-vitreal injection of *anti*-VEGF antibodies is gaining popularity despite being poorly investigated regarding dosage and long-term safety. Compared to treatment of neovascular retinal disease in mature adults, suppressing vascular growth in the vasoproliferative phase must take into account the need for allowing normal angiogenesis in the retina but also in other organs in a fast growing immature preterm infant. Anti-VEGF-antibodies escape the eye and stay in the circulation for weeks to months and reduce circulating VEGF with unknown effects on brain, kidneys, lungs and other organs [36].

4. Current ROP prevention

When unrestricted oxygen supplementation was initially identified as a cause of retinopathy in preterm infants in the mid-1900s, oxygen supply was severely curtailed and the incidence of retrolental fibroplasia decreased but at the cost of increased mortality and cerebral palsy [37]. The optimal oxygenation of preterm infants is still unknown. Oxygen toxicity may also vary by postnatal age, which has not been addressed in clinical trials. Lately five randomized controlled trials report that a higher oxygen saturation (91–95%) target range for babies regardless of gestational age at birth is associated with less mortality than a lower (85–89%) [38]. However, the quality of evidence for this estimate of effect was later found to be low [39]. Based on these studies, an oxygen saturation target range of 91–95% is now used in many neonatal intensive care units. Aggressive parenteral nutrition may decrease the incidence of total ROP but not severe ROP, and supplementation of vitamin A, E, and breast milk feeding have been shown to be beneficial but only in observational studies [40]. Interestingly, serum IGF-I concentrations correlate with growth (change in weight standard deviation score) but not with nutrient intake until 30 weeks PMA, Fig. 3 [41].

5. IGF-I in the two phases of ROP

IGF-I is essential for normal neurovascular development and low serum concentrations in the first phase of ROP, concomitant with the growth retardation phase in very preterm infants, correlate with later severe disease. From around 30 weeks PMA, catch up growth commonly occurs and uncontrolled neovascularization may ensue when IGF-I concentrations increase, since IGF-I also plays a key role in pathologic neovascularization [42]. Pharmacologic inhibition or genetic deletion of the

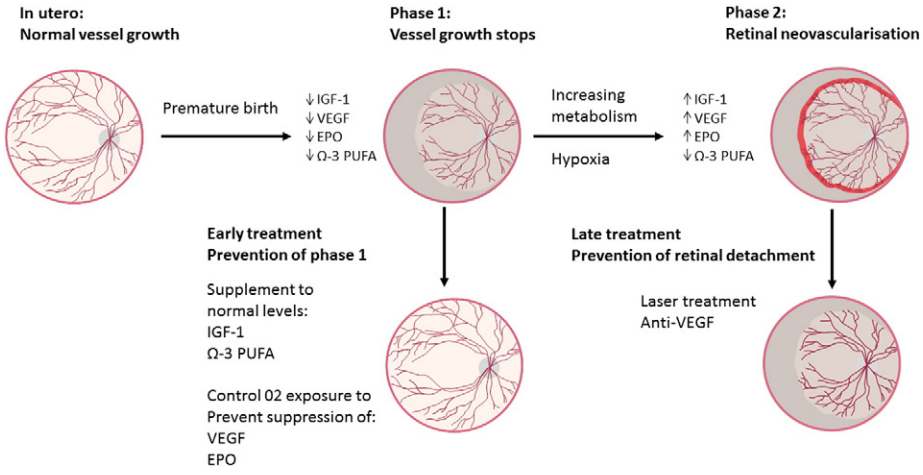

Fig. 3. Major pathways of ROP.

IGF-I receptor in the retinal vasculature of rodents prevents neovascularization [43,44].

6. Serum IGF-I levels in prediction of ROP

In preterm infants a strong correlation between low serum IGF-I levels during the first weeks of life and later ROP development was found and it was suggested that neonatal serum IGF-I levels might be used to predict which infants were at increased risk of developing severe ROP [29]. If such predictions were possible, those at low risk could be spared some eye examinations and those at high risk could get extra attention. ROP screening programs generally include infants based on gestational age (GA) at birth and/or birth weight (BW). Only a small fraction of these infants, who are subjected to repeat painful and stressful eye examinations, need treatment. In Sweden, infants born before 32 gestational weeks had on average 5.2 eye examinations and only 4.4% of the infants were treated for severe ROP [45]. Based on longitudinal weight and IGF-I development after birth the algorithm Weight IGF-I Neonatal ROP (WINROP) was developed [46]. At validation in Sweden, WINROP identified all infants needing treatment weeks to months before they were diagnosed with proliferative ROP [47]. The strong correlation between serum IGF-I and weight gain made it possible to use WINROP based on weight development only, thus avoiding blood sampling [48]. WINROP has now been validated in thousands of infants in many different countries with high sensitivity in settings with advanced neonatal care [49] but lower sensitivity when care is less developed [50]. We find it valuable as an adjunct to general screening.

7. IGF-I intervention in prevention of ROP

An old report on the regression of diabetic retinopathy in a patient with pituitary infarction [51] prompted an investigation of the role of the GH-IGF-I axis in a mouse model of ischemic retinopathy. Neovascularization was suppressed with inhibition of the GH-IGF-I axis and it was concluded that systemic inhibition or GH or IGF-I might prevent ROP [52]. However, inhibition of the GH-IGF-I axis results in a dwarf phenotype. Since the neovascular phase of ROP is preceded by a first phase of impaired retinal vessel growth, it was speculated and confirmed that severe ROP is associated with low circulating IGF-I concentrations during this phase. It was further suggested that early postnatal supplementation with IGF-I to normal fetal levels might prevent ROP [23,29].

In a commonly used OIR mouse model, mice pups are exposed to 75% oxygen from postnatal day (P) 7 to P12 and thereafter kept in room air. At P17 extensive neovascularization occurs in all mice [53]. Using this model, IGF-I knockout mice have retarded retinal vessel growth and low IGF-I suppresses VEGF-induced survival and proliferation signaling in retinal endothelial cells [29].

In an experimental study of IGF-I supplementation in OIR, neonatal mice in normal and larger litters were exposed to hyperoxia. Neonatal mice in larger litters weigh less, have lower levels of circulating IGF-I and develop more proliferative retinopathy than mice pups in normal litters. Treatment with a single intraperitoneal dose of rhIGF-I as well as of placebo (saline) is associated with >90% mortality in mice pups of larger litters precluding the study of IGF-I supplementation effects in that group. Pups of normal litters that received recombinant human (rh) IGF-I on day 4 weighed more, had higher endogenous IGF-I levels, matured faster and had less retinopathy than those who received placebo [54].

Adult fresh frozen plasma contains varying amounts of IGF-I. For a better understanding of the pharmacokinetics of IGF-I and IGFBP3 in preterm infants two studies were performed. One evaluated the effects of transfusing fresh frozen plasma and the other of infusing rhIGF-I/IGFBP-3 over a period of three hours on serum IGF-I and IGFBP-3 levels. Fresh frozen plasma increased serum concentrations of IGF-I and IGFBP-3 but the half-life of IGF-I in serum after plasma infusion was short ($\approx$3 h compared to $\approx$17 h in adults [55,56]). After intravenous infusion for 3 h of the drug mecasermin rinfabate, an equimolar preparation of a recombinant protein complex of rhIGF-I and IGFBP-3, the IGF-I half-life was even shorter (<1 h) suggesting that administration of IGF-I to preterm children should be performed via continuous intravenous infusion [57].

In a later study, infusion of an equimolar preparation of rhIGF-I/rh IGFBP-3 (Premiplex) in doses ranging between 21 and 111 μg/kg/24 h during the first week of life increased serum IGF-I concentration to the lower range of the normal intrauterine range without any evident adverse effects [58].

A multicenter phase 2 study (IGF-I IGFBP3 prevention of Retinopathy of Prematurity, ClinicalTrials.gov Identifier: NCT01096784) has recently been completed by Shire et al. One-hundred-twenty-one infants with GA between 23 weeks + 0 days and 27 weeks +6 days were treated with mecasermin rinfabate until post-menstrual age 30 weeks. Results have not been published yet, but in a press release by the company, no effect was reported on ROP. However, treated infants had a 53% reduction in incidence of severe BPD compared to untreated infants. In addition, an 89% reduction was found in those who achieved target serum IGF-I concentrations compared to untreated infants. Data also showed a 44% reduction in the incidence of severe IVH (grade III and IV) in treated patients and a 64% reduction in those with serum IGF-I within target range.

Are there any plausible explanations for the lack of effect of IGF-I supplementation on ROP in this study?

One explanation may involve oxygen, the best known risk factor for ROP. During this phase 2 study, the oxygen saturation (SpO_2) target level was 91–95%. To our knowledge, compliance with this target range was not investigated. The neonatal intensive care unit of our hospital, Sahlgrenska University Hospital in Gothenburg Sweden, did not participate in this study, but in 2014 the new higher SpO_2 target range of 91–95% was implemented. After that change, the number of infants who needed treatment for ROP doubled. In addition, WINROP, which prior to the increase identified close to 100% of infants who would later develop ROP now failed to identify approximately half of the infants that were later treated for ROP (manuscript in preparation) indicating that perhaps factors related to growth may be less important with this new oxygenation saturation target of SpO_2 within 91–95%. Manley et al. have also reported increased rates and severity of ROP after implementation of this higher SpO_2 target range [59]. They speculated that a higher target range increases the tolerance by clinical staff to saturations above this range. In addition, low compliance with oxygen targeting with upper alarm limits inappropriately set too high and difficulties in maintaining saturation below the upper limit are common [60–63]. However, other explanations for the outcome of the study are possible.

This implies that in studies concerning risk factors for ROP, treatment with oxygen and monitoring thereof has to be optimized. A very important factor is compliance with saturation targets. It is crucial that alarm limits are set close to target limits and that the staff is well trained and sufficient in number, and that there are well documented strategies for oxygen titration. Automated adjustment of the fraction of inspired oxygen may improve SpO_2 targeting across different SpO_2 ranges [61,64]. A reduced incidence of ROP has been reported after implementation of meticulous oxygen control [60,65].

8. In conclusion

There is at present no evidence supporting an effect of IGF-I supplementation in very preterm infants for the prevention of ROP, although a preventive effect has been found for severe BPD and IVH. Oxygen treatment is a strong risk factor for ROP, and oxygen saturation is often poorly controlled. If this was the case in the phase 2 study evaluating effects of IGF-I supplementation on ROP, it is possible that future studies with strict oxygen control may generate different results.

Conflict of interest

Prevention of ROP by administering IGF-I are covered by patent owned by or licensed to Premacure AB, Uppsala, Sweden. AH, DL, IHP, CL and ALH owns shares in a company with financial interest in Premacure AB. AH, DL, IHP, BH and LEHS work as consultants for Shire pharmaceuticals. All funding for the review is stated in acknowledgement.

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