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REVIEW ARTICLE

Retinopathy of prematurity: New developments bring concern and hope

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Abstract: Blindness from retinopathy of prematurity (ROP) in Australian and New Zealand is an uncommon event although 3% of <31 weeks gestation infants receive treatment for the disease. New world-wide estimates of the incidence of blindness from ROP are much higher than previously at 20 000 children annually. The impact of severe ROP can be reduced through good evidence-based care of very preterm infants and careful organisation of eye examinations and follow-up services. Recent oxygen saturation targeting trial results might mean the adoption of higher targets than formerly in very preterm infants and will require vigilance to ensure all eligible infants are examined appropriately. A true screening examination for acute ROP might involve non-opthalmologists obtaining photographic retinal images and remote reading of these. Although treatment with laser gives good outcomes, there is interest in intravitreal anti-vascular endothelial factor agents, but issues concerning the systemic safety and retinal results of such treatment are unresolved.

Key words: bevacizumab; childhood blindness; retinopathy of prematurity; telemedicine; vascular endothelial growth factor.

There have been recent excellent reviews of retinopathy of prematurity (ROP),[1,2] and an issue of *Clinics in Perinatology* covered many different aspects.[3] The purpose of this review is to highlight new information regarding the global burden of disease from ROP, prevention of ROP and organisation of care, and aspects of case detection and treatment.

Incidence

The most recent Australian and New Zealand Neonatal Network (ANZNN) report shows that severe ROP (stages 3 or 4) occurs in 5–6% of infants with gestation <31 weeks or birthweight <1250 g, with treatment in roughly half of these (Fig. 1), and that most severe disease is confined to infants of <27 weeks gestation (Fig. 2).[4] Fewer than five infants per annum have stage four disease, that is, at least partial retinal detachment in at least one eye. A 20-year review of severe visual impairment (vision <6/60 in the better eye) due to ROP in New Zealand reported an average of one new case per annum.[5] Cerebral (cortical) visual impairment is now the commonest cause of severe visual loss in childhood in highly developed countries and is also an important contributor in very preterm infants.[6]

Estimates of blindness from ROP on the world stage have recently been updated from an already concerning figure of 50 000 children under 15 years of age (estimated largely from reviews of schools for the blind and dubbed the 'third epidemic' of ROP[7]) to an *annual incidence* of 20 000 infants blind from ROP and a further 12 300 with mild or moderate visual impairment.[8] This estimate comes from more rigorous methodology based on the published incidence of preterm birth, mortality rates and the proportion of ROP requiring treatment, and suggests the greatest burden of disease is now in the rapidly developing economies of India, China and S. E. Asia.

A meta-analysis of 13 population-based studies over the past decade from countries with a neonatal mortality rate <5 per 1000 births reported 22% (95% CI 17–27%) of infants of <32 weeks gestation develop ROP of any stage.[8] A 1986 New Zealand national study of infants with birthweight <1500 g (83% surviving, including only two infants of 24 weeks gestation) reported 21.4% developed ROP.[9] Treatment was not yet available, and six infants became bilaterally blind.[9] By contrast, the mean gestation of the 66 infants receiving laser treatment for ROP between 1992 and 2009 in Brisbane was 24.3 weeks.[10] So, advances in neonatal intensive care have greatly improved survival for very preterm infants, but severe ROP remains a significant problem because of survival of 'micropremies'.[10,11]

Key Points

1. Recent world-wide estimates of the incidence of blindness and severe visual impairment from ROP are much higher than formerly.
2. Changing neonatal practices will mean the importance of screening for ROP in at -risk infants is greater than ever.
3. The burden of screening for ROP might be aided by a new approach involving retinal photographs taken by non-ophthalmologists and the remote reading of images.
4. Laser therapy remains the first-line treatment for acute ROP and the concerns about the safety of anti-VEGF agents both in the eye and systemically remain unresolved.

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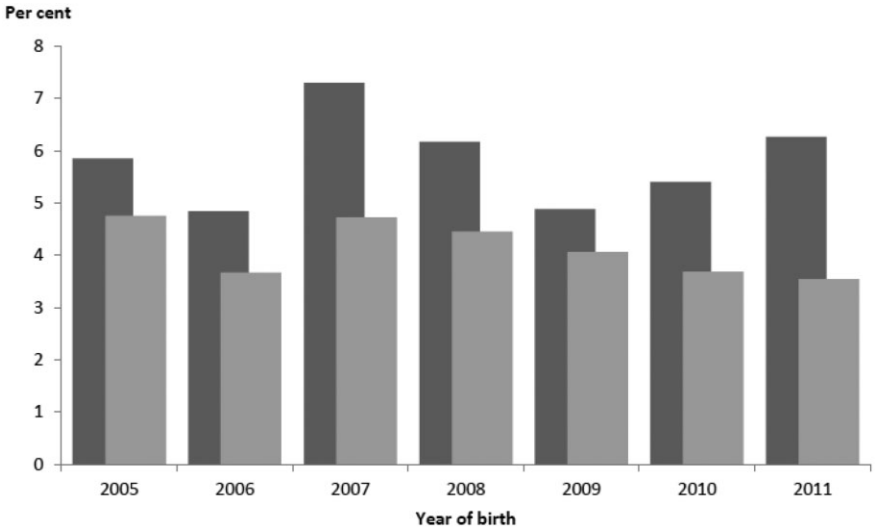

Fig. 1 Trends in severe retinopathy of prematurity (ROP) and ROP treatment in infants of <31 weeks gestation or <1250-g birthweight and registered with the Australian and New Zealand Neonatal Network (ANZNN) in 2005–2011. ■, retinopathy stages 3 or 4; ■, retinopathy treated.

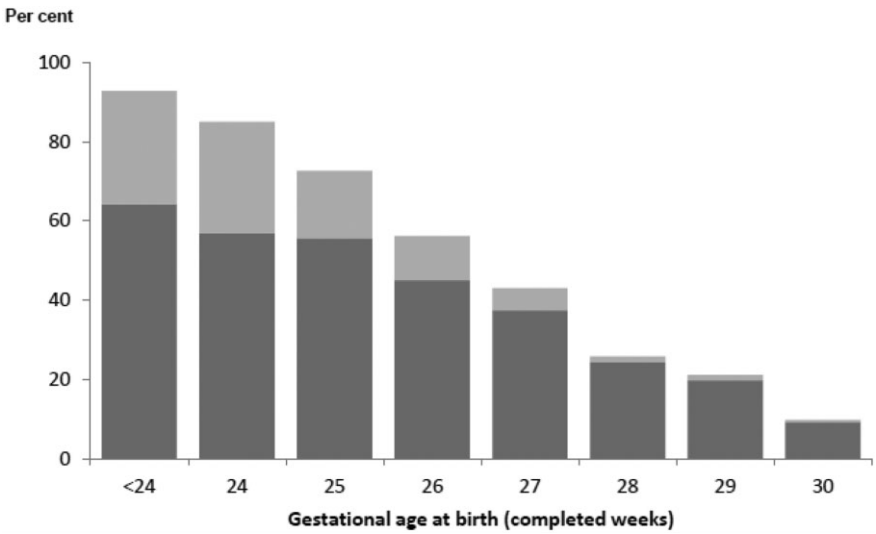

Fig. 2 Incidence of retinopathy of prematurity (ROP) of any and severe (stages 3 and 4) in infants of <31 weeks gestation registered with the Australian and New Zealand Neonatal Network (ANZNN) in 2012. ■, retinopathy stages 3 and 4; ■, retinopathy stages 1 and 2.

Importantly, there is considerable longer-term morbidity from untreated regressed ROP over and above that of extreme prematurity *per se*.[12,13]

Prevention

Much severe ROP is preventable, but to achieve this, it requires good organisation of neonatal care on a regional basis, a focus on implementing evidence-based practices and ongoing quality assurance and audit.[14,15] The incidence of severe ROP declined in units of the Vermont-Oxford Network which took part in an evidence-based quality improvement collaboration aimed at bronchopulmonary dysplasia.[16] Other quality improvement projects have focused on education about ROP as well as compliance with oxygen saturation targets.[17]

The topic of oxygen saturation (SpO_2) targets and ROP has been reviewed recently.[18,19] Five randomised controlled trials in infants with gestation <29 weeks have compared an SpO_2 target of 85–89% with 91–95% and will pool the results from all 5000 infants in an individual patient data (IPD) meta-analysis, the Neonatal Oxygenation Prospective Meta-analysis Collaboration (NeOProM).[20] Half-way through three of the trials (COT, BOOST II Australia, BOOST UK), the pulse oximeter software was upgraded to eliminate a small (2%) overestimation of SpO_2 in the 87–90% range.[21]

Three NeOProM trials (SUPPORT, COT, BOOST-NZ) have now reported outcomes at 18–24 months with no differences in the combined outcome of death or neurodisability.[22–24] However, both the SUPPORT,[25] and the BOOST II Australia and UK trials after the monitor upgrade,[26] reported that the lower target was associated with a small but significant increase in mortality at hospital discharge. An interim meta-analysis of mortality data (taking 18- to 24-month data for two trials and hospital discharge data for three) confirms this, being 19.3% versus 16.2%, relative risk 1.18 (95% CI 1.04–1.34).[27]

Combined data also show the lower target is associated with a lower incidence of severe ROP.[27] However, at 18- to 24-month follow-up, the rate of severe visual disability was low (around 1%) with no differences between groups, showing that treatment of ROP is largely successful.[22–24]

It is important to await the 2-year outcome data from the remaining two trials not available at the time of writing (BOOST II Australia and UK) and the IPD meta-analysis[20] before assessing the full implications of these studies, but it is clear that the recent trend to adopt lower saturation targets, to avoid consequences of oxygen toxicity, should cease because too little oxygen is accompanied by increased mortality, as in the historical data.[28] As an interim measure, most recommendations are currently to target a saturation of 90–95%[27,29,30] but with efforts to avoid hyperoxaemia (perhaps best achieved with the high target at 94% and the high alarm set at 95%[24]). One implication of this is that there must be increased efforts to ensure all infants meeting screening criteria are followed until the eyes are fully vascularised or reach treatment criteria. There is also increased interest in trials of other therapeutic options that might reduce the incidence of ROP, including intravenous insulin-like growth factor (IGF)-1/IGF-B3 complex,[2] inositol[31] and omega-3 fatty acids (ACTRN12612000503820).

Case Detection

Published screening criteria in both Australia and New Zealand are now some years old and require review. The New Zealand criteria, from the 1986 survey, are all infants of <31 weeks or <1250 g should be appropriately examined for ROP.[32] A consensus statement under development, based on contemporary data, is likely to recommend <30 weeks or <1250 g (Dr S Dai, pers. comm., 2014), and some hospitals have adopted these criteria.[33] In Australia, the NHMRC 1997 criteria of <32 weeks or <1500 g[34] have been withdrawn, and there is some support for revised criteria of <30 weeks or <1250 g.[35]

In the ANZNN dataset on high-risk infants, there are missing data on ROP, including whether ever examined, in around 8% of infants meeting screening criteria.[36] A California study reported 12.7% of eligible infants missed ROP screening in 2007.[37] A population-based study from the Netherlands documenting the reasons for failure to screen highlighted transfer to another hospital as a major factor.[38] It should be unacceptable for eligible infants to miss appropriate examinations because of organisational problems, and it is important for a country's generic guidelines to be translated into specific protocols by each unit, involving parents as partners in this process, if problems are to be avoided.[15]

An enduring issue for ROP programmes is the work load for ophthalmologists undertaking case detection. A UK survey shows that in 1 year, 8208 infants had around 20 000 examinations by 152 ophthalmologists leading to 149 infants being treated; 55 infants were examined for every one treated, and there were 134 exams for each treated infant.[39] However, we may be about to enter a new era where there is a genuine screening examination for ROP that could be undertaken by trained personnel other than ophthalmologists. The advantages of digital imaging include the ability to transfer the images remotely for evaluation and providing a permanent record of the examination.

A large National Eye Institute-funded study, involving 1257 infants, compared examinations by non-physicians using the Ret-Cam Shuttle (Clarity Medical Systems) with standard diagnostic examinations by experienced ophthalmologists.[40] Camera images were read remotely by both non-physicians and experienced ophthalmologists. Eyes were scored whether or not 'referral-warranted ROP' (RW-ROP),[41] requiring an examination by an ophthalmologist, was present. When both eyes were considered for the presence of RW-ROP (the expert observed rate being 19.4%), the telemedicine system had sensitivity of 90.0%, specificity 87.0%, a negative predictive value of 97.3% and a positive predictive value of 62.5%.[40] This study adds to earlier reports that ultimately may lead to improved access to ROP detection and treatment in both developed and developing countries.[42]

Treatment

Knowledge of the pathogenesis of ROP, which has been advanced through the development of rodent models of oxygen-induced retinopathy, has greatly informed current approaches to treatment.[1,43] The retinal vessels grow under control of oxygen-regulated mediators including hypoxia inducible factor and vascular endothelial growth factor (VEGF), plus the non-oxygen-regulated IGF-1. IGF-1, which *in utero* is produced by the placenta, appears to be required for VEGF signalling and vessel growth and survival. In the human retina, the retinal vessels reach the *ora serrata* (periphery) on the nasal side around 36 weeks and the temporal side around 38 weeks postmenstrual age (PMA). In phase 1 ROP, following preterm birth, there are low concentrations of IGF-1, and the relative hyperoxia of the *ex utero* environment, exacerbated by supplementary oxygen, may result in arrest of vessel growth and vasoconstriction. As the neural retina develops, the increased oxygen demand means there is relative hypoxia and hence increased secretion of VEGF from the anterior avascular retina. If there is sufficient IGF-1, normal vessel growth may continue, but if there is excess VEGF, then proliferative ROP will result. This phase 2 ROP commences around 30 weeks PMA.[2] This basic model has been extended to incorporate newer data, including identifying that erythropoietin is a second hypoxia-induced factor that acts in a similar way to VEGF, although independently.[43]

Standard treatment of acute ROP, which has reached the criteria of so-called type 1 disease, is with laser ablation of the peripheral retina with generally excellent results.[44] However, a proportion of cases continue to progress despite laser treatment, and even a favourable early outcome may not mean normal vision. Hence, it is natural that ophthalmologists, who are familiar with anti-VEGF treatment in adult eyes with proliferative retinopathy, should consider using this therapy for ROP. Intravitreal injections might provide a simpler and cheaper approach compared with laser therapy.

After publication of case reports and series of bevacizumab or ranibizumab, either in combination with laser or as monotherapy,[45] there is now one randomised controlled trial of intravascular bevacizumab treatment of acute ROP. The

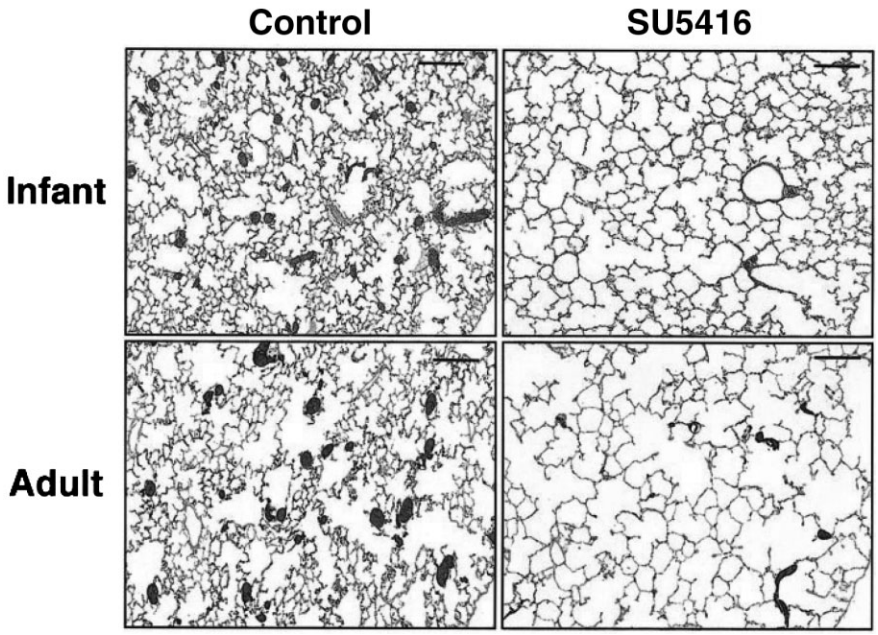

Fig. 3 Histology of newborn rat lungs after treatment with a vascular endothelial growth factor (VEGF) receptor inhibitor. Histology of newborn rat lungs at 3 weeks ('infant') and 3–4 months ('adult') both for non-treated controls and after treatment with one systemic dose of the VEGF receptor inhibitor, Su-5416 (see text; reproduced from Le Cras *et al*., with permission).[63]

Bevacizumab Eliminates the Angiogenic Threat for ROP (BEAT-ROP) trial randomised 150 infants with severe Zone 1 or posterior Zone II ROP to receive either laser therapy or an intravitreal injection of 0.625 mg bevacizumab (both eyes receiving the same treatment).[46] Bevacizumab treatment was associated with fewer infants requiring retreatment before 54 weeks PMA, 4/70 (6%) bevacizumab versus 19/73 (26%) laser (OR 0.17 (95% CI 0.05 to 0.53) $P = 0.002$), but benefit was confined to infants with Zone I disease.[46]

Several authors have drawn attention to design and other problems with this trial, including the relatively high dose of bevacizumab used, treatment was not always given at standard type 1 ROP staging, the poor outcomes for laser-treated eyes compared with the literature, the primary outcome of recurrence of ROP requiring treatment was assessed at the early age of 54 weeks PMA and by non-impartial observers, and the lack of power to assess important adverse outcomes.[47–49]

Laser therapy is somewhat destructive of the peripheral retina; however, 6-year follow-up data from the ET-ROP trial showed only small differences in visual fields between laser-treated and non-treated eyes with regressed ROP.[50] As yet, we do not know what the long-term outcomes for eyes treated with bevacizumab will be. The BEAT-ROP study group has now reported refractive outcomes at a mean 2½ years and noted more very high myopia in eyes treated by laser compared with eyes treated by bevacizumab.[51] Given the poorer than expected initial results associated with laser in this trial, it is unclear how much weight should be given to these findings. A small study of fluorescein angiography 9 months after treatment of Zone I ROP reported both posterior pole and peripheral abnormalities were more likely following treatment with bevacizumab than with laser.[52]

There are also increasing reports of complications in eyes treated with bevacizumab. These include late recurrence of proliferative vascular changes that can progress to retinal detachment, sometimes despite a dramatic initial response[53,54] and which mandate that eyes treated with anti-VEGF agents must have regular ongoing ophthalmic follow-up, although for how long is unclear. Similar findings have also been reported after ranibizumab injection.[55] Also, as noted by Mintz-Hittner *et al*.,[46] if the timing of injection is too late, then worsening of the fibrovascular changes may eventuate.[56]

Although the BEAT-ROP authors suggested bevacizumab was unlikely to escape the eye into the systemic circulation,[46] that is demonstrably not the case.[57] Evidence from animal models and adults shows that bevacizumab reaches higher systemic concentrations and with a much longer half-life (around 20 days) than other anti-VEGF agents, although these also do reach the systemic circulation.[57] An intravitreal injection of 1.25 mg in adult macaques resulted in peak bevacizumab concentrations at 1 week and concentrations still at half of this at 8 weeks.[58] Intravitreal bevacizumab treatment to one or two eyes in 11 infants previously treated with laser was followed by a continuing rise in systemic concentrations over 2 weeks and a rapid fall in serum VEGF concentrations by 1 day and which remained low at 2 weeks.[59] When intravitreal bevacizumab, 0.62 mg per eye, was given as monotherapy for ROP in 11 eyes, there was a dramatic fall in serum bevacizumab concentrations 1 week later, and these remained low for at least 7 weeks.[60] It has been estimated that with the doses currently in use, the concentration of intravitreal bevacizumab is 10 000 times that needed to neutralise VEGF in the vitreous in eyes with ROP, and is associated with systemic concentrations 1000-fold higher than serum VEGF-A on a molar basis.[61]

VEGF has multiple important roles in both normal and abnormal angiogenesis and in the development of major organs outside of the eye, including the lungs, kidneys and central nervous system.[47–49,62] Hence, there are well-founded concerns

that intravitreal treatment of ROP with anti-VEGF agents may have significant systemic side effects.[47,48] A dramatic example of the potential for anti-VEGF agents to impair organogenesis comes from animal data. Le Cras and colleagues injected a single dose of the systemic VEGF receptor inhibitor, Su-5416, into 1-day-old rat pups.[63] Histology of the lungs performed at 3 weeks of age showed evidence of pulmonary hypertension, alveolar simplification with reduced septation and enlarged distal air spaces (Fig. 3). This pattern persisted into adulthood (3–4 months) and resembles the changes seen with bronchopulmonary dysplasia (Fig. 3).[63] While this does not prove that similar effects could occur with anti-VEGF agents reaching the systemic circulation following intravitreal injections in infants, it does demonstrate how difficult it might be to determine harm from the latter procedure given the similarities of potential problems to known morbidities in very preterm infants.

Given these concerns, there is a need for further studies of the pharmacokinetics of bevacizumab and other anti-VEGF agents in preterm infants and ideally for well-designed randomised controlled trials to compare these agents with laser treatment. The latter should be adequately powered to detect both short- and long-term visual and systemic outcomes.[43,44,48,49,64] Given the relative ease of administration of anti-VEGF agents, they are being widely used around the world to treat acute ROP, and other approaches to determine efficacy and safety, including further basic science and animal studies, are urgently required.[65] Most major neonatal networks now keep a register of cases receiving such treatment. Anti-VEGF agents are not licensed for intravitreal use in children but might be considered 'off label' when conventional laser has failed, the disease is very posterior or there is a poor view of the posterior pole, or if the infant is too unstable to tolerate laser therapy.

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