Retinopathy of Prematurity: Transforming Treatment Paradigms

Prof. Andreas Stahl
University Medical Center
Greifswald, Germany

Prof. Neil Marlow
University College London
London, United Kingdom

Prof. Maria Ana Martinez-Castellanos
Association to Prevent Blindness in Mexico
Hospital “Luis Sánchez Bulnes,” I.A.P
Mexico City, Mexico

This supplement is intended for non-promotional scientific purposes only and may contain information on products or indications currently under investigation and/or that have not been approved by the regulatory authorities. The opinions and views expressed in this supplement are those of the faculty members and do not necessarily constitute the opinions or recommendations of Novartis. The presentations were accurate at the time of presentation. Any data on competitor product(s) are based on publicly available information at the time of presentation. Prescribing information may vary depending on local health authority approval in each country. Before prescribing any product, always refer to the SmPC or product information approved in your local country. Permissions for all content within have been received from each copyright holder for the presentations. Separate use, adaptation, and/or translation requires application for specific use permissions from each copyright holder. All product names, trademarks and registered trademarks are property of their respective owners.
Retinopathy of Prematurity: Transforming Treatment Paradigms

This supplement features a summary of a Novartis-sponsored webcast which took place in April 2020 entitled, “Retinopathy of Prematurity: Transforming Treatment Paradigms,” presented by Prof. Andreas Stahl, Prof. Neil Marlow, and Prof. Maria Ana Martinez-Castellanos.

Introduction

Andreas Stahl

Retinopathy of prematurity (ROP) is one of the most common avoidable causes of blindness in children.1 Of the 15 million babies born preterm (i.e., before 37 completed weeks of gestation) every year,2 approximately 15 to 20% are affected with ROP.3 This frequency increases to 30% in babies with a birth weight of 750 to 999 g.3 “Annually, an estimated 32,300 infants worldwide are diagnosed with irreversible visual impairment from ROP, of whom an estimated 20,000 become blind or severely visually impaired,”4 said Prof. Andreas Stahl.

The key risk factors for the development of ROP are low gestational age, low birth weight, and postnatal oxygen supply. Other factors contributing to the risk of ROP are hypoxemia, low postnatal weight gain, postnatal hyperglycemia, neonatal infections, and hypercarbia.5-7 These risk factors are often connected with undernutrition and other comorbidities such as neurological dysfunction, poor brain growth, necrotising enterocolitis, intraventricular haemorrhage, and bronchopulmonary dysplasia.5

A Neonatal Perspective on Preterm Morbidity and Retinopathy

Neil Marlow

The duration of a normal pregnancy is around 38 to 42 weeks of gestation, and full-term infants weigh between 2,500 and 4,000 g at birth.6 The definition of a preterm baby is one born alive at less than 37 weeks,6 with ‘very preterm’ infants born at less than 32 weeks of pregnancy and ‘extremely preterm’ infants born at or before 28 weeks.7 Since gestational age is only accurate if based on an early first trimester scan, birth weight is also used to classify preterm babies into low birth weight (< 2,500 g; generally equivalent to all preterm babies), very low birth weight (< 1,500 g; generally equivalent to < 31 weeks’ gestation) and extremely low birth...
while the proportion of babies surviving has increased, the rate of disability in the overall population has remained relatively unchanged (Figure 3).16 “We have now come from trying to save more lives to looking at the quality of those lives that we’re saving,” said Prof. Marlow. “We also have to think about our care with respect to what happens after the neonatal period as the child grows up, because we know that this has a strong relationship to the perinatal period.” A direct relationship has been noted between gestational age at birth and the risk of special educational needs later in childhood.17 Other outcomes of prematurity that can continue to impact individuals through to adulthood include neurocognitive issues (e.g. educational and behavioral problems), respiratory problems (e.g. asthma), and ocular problems (e.g. strabismus, low visual acuity, and myopia).5,9

ROP is an important morbidity associated with prematurity, but its prevention is challenging. Strategies include the use of antenatal steroids to reduce the rate of respiratory disease and the need for oxygen, as well as ensuring that oxygen saturation targets are maintained.18 However, these approaches are not necessarily simple. The Neonatal Oxygenation Prospective Meta-analysis (NeOProM) collaboration, which investigated the use of different oxygen saturation targets in extremely preterm infants, reported that lower oxygen saturation targets were associated with a higher risk of death and necrotizing enterocolitis, but a lower risk of ROP.19 “We’ve known since the late 1940s about the danger of giving excess amounts of oxygen to premature babies, but this must be balanced against the risk of giving insufficient oxygen and causing excess mortality. For the neonatologist, managing oxygen is a very fine line between reducing untreatable outcomes and causing ROP,” said Prof. Marlow.

It is therefore very important that strong protocols are in place to monitor and minimize the use of oxygen, as well as those for identifying babies requiring screening. United Kingdom guidelines recommend screening for babies of birthweight ≤ 1,500 g or ≤ 32 weeks of gestation at birth, with screening at 2-week intervals from 30 to 31 weeks postmenstrual age or 4 to 5 weeks of age, to be increased in frequency based on the presence of signs of ROP.20 “All of this demands close liaison between the neonatologist and the ophthalmic team. Although the baby remains in the neonatal unit, the responsibility for screening and carrying out that screening sits with the ophthalmologist,” said Prof. Marlow.

**Highlights**

- Prematurity is a pervasive problem affecting many organ systems, and long-term impairments are common.
- Close liaison between the neonatologist and the ophthalmologist is required for the care of preterm babies.
- Strong protocols must be in place to monitor and optimize the use of oxygen.
- Developing a screening protocol for retinopathy of prematurity (ROP) is crucial to ensure timely diagnosis and treatment.
ROP: Epidemiology and Clinical Perspective

Maria Ana Martinez-Castellanos

The incidence of ROP has increased in recent years as a result of advances in neonatal care and the subsequent increase in premature births. In 2010, ROP was the cause of severe visual impairment or blindness in 1.1% of children in high-income countries (defined by the World Bank as those with a gross national income per capita of US$12,376 or more in 2018) and 2.5 to 2.8% of children in other regions (including middle- and low-income countries in Eastern Europe, Central Asia, Latin America, and Africa).

In middle-income countries, due to differences in standards of care in neonatal intensive care units (NICUs) compared with high-income countries, use of the same screening standards implemented in high-income countries may not be appropriate. In a study carried out in our hospital, we discovered that 100 of 352 newborns with ROP evaluated between January 2011 and March 2017—nearly one-third—fell outside the current screening guidelines of the American Academy of Ophthalmology, having a birth weight greater than 1,500 g or a gestational age of more than 30 weeks, said Prof. Maria Ana Martinez-Castellanos.

The pathophysiology of ROP is characterized by abnormal neovascularization. The disruption of angiogenesis in preterm infants with ROP typically occurs in two postnatal phases. In phase 1 (from birth up to 30 weeks’ postmenstrual age), hyperoxia inhibits vascular growth in the retina. As the retina becomes more metabolically active (from around 30 weeks’ postmenstrual age), its incomplete vascularization causes it to become hypoxic, resulting in the secretion of various angiogenic factors including VEGF and subsequently to VEGF-driven neovascularization and intraocular fibrosis. Ultimately this can result in retinal detachment and visual disability.

A key early advance in the management of ROP was the formal classification of ROP terminology in the international classification of ROP in the 1980s. With this classification now used worldwide, we’re all talking the same language, which means that we can act appropriately at each stage of the disease,” said Prof. Maria Ana Martinez-Castellanos. According to international classification of ROP terminology, ROP is categorized according to the zones of the retina in which disease is visible via dilated fundus examination and the severity (or stage) of the disease.

Zone 1 includes the macula and optic nerve; it forms a circle, the radius of which is twice the distance from the optic nerve to the macula (Figure 4). ROP in Zone 1 is the most likely to progress and become severe. Zone 2 surrounds Zone 1 and extends to the ora serrata on the nasal side. ROP found here may progress quickly, although warning signs such as increasing vascular dilation and tortuosity usually predate the threshold by a week or 2. Zone 3 is a crescent area of temporal retina, which rarely shows aggressive disease.

When categorizing ROP by disease stage, in Stage 1 a demarcation line can be clearly seen between normally vascularized retina and the peripheral retina with no blood vessels (Figure 5). In Stage 2, the demarcation line is elevated into a ridge, but with no pathological new vessels; in Stage 3 these new vessels are present. Stage 4 and 5 represent partial and total retinal detachment, respectively. Stage 5 is very sad. This means that we are too late to save this eye, and the best outcome following surgery would be only light perception or movement,” said Prof. Martinez-Castellanos. Aggressive posterior ROP (AP-ROP) may also be present. This usually occurs in Zone 1 and can progress very quickly to retinal detachment.

The zone and stage of ROP can be combined to give the ROP ‘type’ (Figure 6), which differentiates eyes with significant changes of ROP that require treatment (Type 1) from eyes with significant changes that do not require treatment but must be carefully monitored (Type 2). Severe ROP leads to long-term visual loss, with blindness in the most severe cases, so timely treatment is vital.

ROP is also associated with a range of other eye problems later in life, such as retinal detachment, glaucoma, and refractive errors, so lifelong monitoring is required. Traditional treatment options for ROP include cryotherapy and surgery, though these are associated with complications. Laser therapy is the current standard of care for treating ROP, but it is an invasive, resource-intensive...
Retinopathy of Prematurity: Transforming Treatment Paradigms

Clinical Research—Studies on Anti-VEGFs

Andreas Stahl

In 2011, BEAT-ROP became the first randomized, multicenter trial of anti-VEGF therapy in ROP, reporting significant treatment effects for bevacizumab over laser therapy for Zone 1 (but not Zone 2) disease in infants with Stage 3+ ROP. However, BEAT-ROP left some unresolved questions regarding the appropriate dose for anti-VEGF therapy in infants with ROP. BEAT-ROP used half the dose of bevacizumab usually used (off-label) in adults with retinal disorders, but without conducting dose-finding studies. The majority of infants with ROP require bilateral treatment for ROP, so according to the BEAT-ROP protocol, they ultimately received a total dose of bevacizumab therapy equivalent to that which an adult receives (off-label) for unilateral treatment. "There's certainly room for discussion here as to whether this is the right dose," said Prof. Andreas Stahl. "Another open question is that of systemic safety. We know from studies in infants with ROP that an ocular injection of bevacizumab reaches the circulation and suppresses VEGF, not only in the eye, but also systemically."

In order to collect further evidence on the use of anti-VEGF therapy in infants with ROP, the German Retina.net ROP registry was set up in 2012 with the aim of capturing treatment patterns and outcomes. It now includes data from over 330 treated patients, which corresponds to around 10 to 15% of all treated ROP infants in Germany. Analysis of the registry data reveals that treatment patterns have changed over time in Germany, with anti-VEGF treatment given to 10% of treated eyes in 2011 but to 56% and 30% in 2014 and 2015, respectively (Figure 7). Almost all eyes with AP-ROP or Zone 1 disease received anti-VEGF treatment, while Zone 2 disease was predominantly treated with laser. "We're currently looking at the data from 2016 and onwards to see how these trends developed further in the following years," said Prof. Stahl.

More recently, the CARE-ROP study was an interventional investigator-initiated study performed to investigate the use of ranibizumab in 19 infants with ROP, given at two different doses: 0.12 mg and 0.20 mg, corresponding to 24% and 40% of the adult dose. CARE-ROP was a blinded, randomized, multicenter study performed in Germany, with the primary endpoint (the proportion of infants who did not require rescue therapy) at 24 weeks and follow-up ongoing to 5 years. In the group who completed the study, 88.9% of infants (94.4% of eyes) in the 0.12-mg group and 85.7% of infants (92.9% of eyes) in the 0.20-mg group did not require rescue therapy at 24 weeks, suggesting that both doses were equally successful in controlling ROP. VEGF plasma levels were not altered in either group, indicating a limited systemic drug exposure.

Building on the evidence of CARE-ROP, the RAINBOW study was the first global, phase 3 randomized controlled trial on ranibizumab in ROP. A total of 225 patients from 87 centers were enrolled and randomized 1:1:1 to ranibizumab 0.2 mg, ranibizumab 0.1 mg, or laser. The primary outcome measure was survival with no active retinopathy, no unfavorable structural outcomes, and no need for a different treatment modality at or before 24 weeks. Treatment success occurred in 80% of infants receiving ranibizumab 0.2 mg compared with 75% of infants receiving ranibizumab 0.1 mg, laser, or no treatment. The primary outcome measure was survival with no active retinopathy, no unfavorable structural outcomes, and no need for a different treatment modality at or before 24 weeks.
ranibizumab 0.1 mg and 66% of infants after laser therapy (Figure 8). Statistical significance in the comparison of ranibizumab 0.2 mg versus laser therapy was narrowly missed (odds ratio 2.19 [95% CI 0.99-4.82]; \( P = .0507 \)). “One might ask why this success rate was lower compared to CARE-ROP? First, the definition of treatment success in RAINBOW was quite strict, including the fact that to qualify, infants had to survive until the primary endpoint. In addition, they obviously could not have any active ROP at the primary endpoint and no treatment except study treatment, but they could also not have any unfavorable structural outcomes,” said Prof. Stahl. Unfavorable structural outcomes (defined as any one of retrolental membrane obscuring the view of the posterior pole; substantial temporal retinal vessel dragging causing abnormal structural features or macular ectopia; posterior retinal fold involving the macula; and retinal detachment involving the macula) were found more frequently in the laser arm than in the ranibizumab 0.2-mg arm. In terms of safety, death, serious and non-serious systemic adverse events and ocular adverse events were evenly distributed between groups. Plasma VEGF levels were measured at baseline and at around days 14 and 28 in each treatment group, and these showed no evidence of systemic suppression (Figure 9). The 5-year extension study of RAINBOW is currently ongoing, with results expected in 2022.

Based on the results of RAINBOW, ranibizumab was approved in the European Union in September 2019 for the treatment of ROP in preterm infants with Zone 1 (Stage 1+, 2+, 3 or 3+), Zone 2 (Stage 3+), or aggressive posterior-ROP disease.

**Highlights**

- Retinopathy of prematurity (ROP) registries provide important information on the real-world use of anti-VEGF therapy in ROP.
- In the RAINBOW study, a treatment success rate of 80% was achieved with ranibizumab 0.2 mg versus 66% with laser.
- Infants treated with ranibizumab 0.2 mg were twice as likely to achieve treatment success versus laser which was considered clinically relevant.
- Ranibizumab 0.2 mg was well tolerated in patients with ROP and the safety profile was as expected in a preterm population.
- In September 2019, ranibizumab was approved in the European Union for the treatment of ROP in preterm infants with Zone 1 (Stage 1+, 2+, 3 or 3+), Zone 2 (Stage 3+), or aggressive posterior-ROP disease.

**Discussion: Current Clinical Considerations on ROP**

Neil Marlow, Maria Ana Martinez-Castellanos, and Andreas Stahl

Andreas Stahl moderates a discussion session in which the panel responds to questions relating to the clinical management of patients with ROP.

**How should the neonatologist and ophthalmologist ideally interact when it comes to therapy, screening, and treatment?**

Prof. Marlow: This is a key question because ROP involves a small number of patients for whom treatment is time critical. It can be very difficult to examine the eyes of a baby in a neonatal unit who’s undergoing critical care, who’s on a ventilator, and who may have other headgear on for other forms of ventilation. Of course, these babies are the ones who we really don’t want to miss. The level of skill required on the part of the ophthalmologist to identify those that need to be considered for treatment is very high. For this reason, in the United Kingdom, standards of care for ROP were developed by a group of clinicians that included both neonatologists and ophthalmologists. Our National Audit program records not whether ROP was screened for successfully or what the retinal stage was, but rather did the retinal screening occur on time, because that’s the most critical thing.

Prof. Martinez-Castellanos: In Mexico, the situation is complicated. As in any middle-income country, we have both very good and very bad NICUs. We can see the results of this, both good and bad, in the babies that are treated there. In the worst NICUs, oxygen is given at 100% concentration without oximetry, resulting in very severe cases of ROP. What standard of NICU a premature infant
is treated at depends on the economic background of the family. There are fewer cases of ROP in families that are able to pay for a better standard of care, but in poorer families many babies go blind because of poor oxygen management in the NICU.

Do you as a neonatologist ask ophthalmologists their opinion when it comes to setting the right oxygen level?

Prof. Marlow: No, because clinical trials have been performed, which provide us with this information. However, although the relationship of ROP with oxygen was recognized in the 1940s, it has only been over the last 10 years that these studies have been performed to refine the relationship further, and there is still more to learn in terms of understanding how we use oxygen. To improve mortality and reduce the risk of necrotizing enterocolitis, which is a systemic and quite catastrophic disease, we currently have to tolerate levels of retinopathy that we would have hoped to reduce.

What are the factors that influence your decision on the treatment modality to use?

Prof. Martinez-Castellanos: In Mexico, the decision depends on what is available in that area. Laser is available in some, but not all, NICUs. This means that anti-VEGF therapy is the only treatment option available for ROP in some units.

Prof. Stahl: Where possible, however, the availability of treatment shouldn’t affect the treatment decision. Whenever the options of laser therapy versus anti-VEGF injections are presented, we should be able to offer both at an equal quality. This is why treatment for ROP should always take place at centers with expertise in this area and with both treatment options available at the same quality, because otherwise there is always a tendency to favor one treatment over another depending on what is available or what we can do best. These factors should not, however, be guiding our treatment decisions.

Prof. Marlow: I agree; it is clear that ROP cases should be managed in specialized centers by doctors with a high level of expertise. Another factor to consider is the circumstances of the patient’s family. It can be quite challenging for families to go to the expense of traveling to a center frequently over a number of months, but if they are not able or willing to bring the child back to the clinic for follow-up then it might actually be dangerous to use an anti-VEGF agent. If anti-VEGF therapy is to be used, it is the responsibility of the ophthalmologist to educate the family on the importance of follow-up.

What are the next steps in ROP that you would like to see following these developments in anti-VEGF therapy?

Prof. Martinez-Castellanos: Having access to screening is a key point, as not every country has a real screening program for ROP yet. Next, good communication between ophthalmologists and neonatologists is important, so that they can liaise efficiently to ensure that all babies at risk of developing ROP receive screening. Finally, in cases where babies do develop ROP, good communication with the parents regarding treatment and follow-up is required. Parents need to understand that ROP is a lifetime disease. Even though we can cure it, it can have long-term consequences, following either laser or anti-VEGF therapy.

Prof. Stahl: Yes, we need a screening program that detects ROP before the disease reaches its worst extent. We then need a second lifelong ‘screening phase’ to ensure that we limit the number of amblyopia from strabismus or from refractive errors and that we pick up retinal changes that may lead to late retinal detachment.

Prof. Marlow: Neonatologists should attempt to reduce the amount of respiratory disease in our client population. Currently in the United Kingdom, the majority of women who deliver prior to 32 weeks receive antenatal steroids. We are also now beginning to use much less oxygen in the delivery room, as it may cause hyperoxia, which we know is potentially very dangerous, even over a relatively short period of time. In addition, we are learning that cutting the umbilical cord immediately after birth promotes respiratory disease, if it is done too quickly, so we are trying to delay this procedure until the circulation becomes stable. With these developments, plus others relating to treating infection and preventing lung disease, which drives the need for oxygen, we should be able to reduce the risk of ROP considerably.

Summary and Closing Comments

Andreas Stahl

In conclusion, retinopathy of prematurity (ROP) is one of the most common causes of avoidable blindness in children, causing irreversible visual impairment in over 32,000 infants worldwide each year. “Prevention is at the core of neonatal intensive care,” said Prof. Stahl. “Careful management of supplemental oxygen therapy, screening, and timely referrals are key clinical considerations.”

In the RAINBOW study, a treatment success rate of 80% was achieved with ranibizumab 0.2 mg compared with 66% with laser, and ranibizumab 0.2 mg was well tolerated in patients with ROP. RAINBOW is the first study to report pharmacokinetics and systemic VEGF data in ROP. The results of its 5-year extension study are expected by 2022. Based on the results of RAINBOW, ranibizumab is now the first anti-VEGF therapy to be approved for the treatment of ROP.
Retinopathy of Prematurity: Transforming Treatment Paradigms

View the full webcast, including live Q&A session, at this address bit.ly/ROPwebinar1

or by scanning the QR code below