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Ranibizumab for retinopathy of prematurity – first line

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LAY SUMMARY

Retinopathy of prematurity (ROP) is when the blood vessels of the eye do not develop normally in babies born prematurely (before their due date). This can cause serious loss of vision or blindness if it is not diagnosed or treated early. Babies born before 32 weeks old or weighing less that 1501g are screened for ROP in the UK. Most babies who have ROP will have a mild form of the condition which will not require any treatment and will get better on its own. However for babies with more advanced ROP the only available treatments involve surgery or laser treatments.

Ranibizumab is a medicinal product already available for treating a range of visual impairments in adult patients. It is injected directly into the eye and it works by preventing abnormal blood vessels from developing and growing in the eye (one of the causes of ROP) by blocking a protein called VEGF. If ranibizumab is licenced for treatment of ROP, it will be the first anti-VEGF medication to be approved for the treatment of ROP. This will potentially provide an alternative treatment to laser and surgical treatments for ROP.

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TARGET GROUP

Premature infants with retinopathy of prematurity (ROP) – first line

TECHNOLOGY

DESCRIPTION

Ranibizumab (Lucentis; Rabinismab; RG-3645; rhuFab V2; VEGF antibody fragment)[1] is a humanised recombinant monoclonal antibody fragment targeted against human vascular endothelial growth factor A (VEGF-A). It binds with high affinity to the VEGF-A isoforms (e.g. $VEGF_{110}$, $VEGF_{121}$ and $VEGF_{165}$), thereby preventing binding of VEGF-A to its receptors VEGFR-1 and VEGFR-2. Binding of VEGF-A to its receptors leads to endothelial cell proliferation and neovascularisation, as well as vascular leakage, all of which are thought to contribute to the development and progression of the retinopathy of prematurity. By blocking this factor, ranibizumab reduces the growth of the blood vessels and controls the leakage and swelling. [2]

In the phase III clinical trial (RAINBOW; NCT02375971) to determine if intravitreal ranibizumab is superior to laser ablation therapy in the treatment of retinopathy of prematurity (ROP), ranibizumab is administered by intravitreal injection at 0.2mg or 0.1 mg in both eyes on day 1 with up to two re-treatments in each eye with a 28 day minimum interval between injections.[3]

Ranibizumab is currently licenced for the treatment of: [2]

- Neovascular (wet) age-related macular degeneration (AMD)
- Visual impairment due to choroidal neovascularisation (CNV)
- Visual impairment due to diabetic macular oedema (DME)
- Visual impairment due to macular oedema secondary to retinal vein occlusion (branch RVO or central RVO)

The most common side effects of ranibizumab (affecting more than one in ten people) include nasopharyngitis, headache, vitritis, vitreous detachment, retinal haemorrhage, visual disturbance, eye pain, vitreous floaters, conjunctival haemorrhage, eye irritation, foreign body sensation in eyes, lacrimation increases, blepharitis, dry eye, ocular hyperaemia, eye pruritus, arthralgia and intraocular pressure increase.[2]

INNOVATION and/or ADVANTAGES

Although the pathogenesis of retinopathy of prematurity (ROP) is not completely understood, vascular endothelial growth factor (VEGF) plays an important role in the development of ROP. It was generally thought that dysregulation of VEGF leads to abnormal vasculogenesis and neovascularization. Conventional laser photocoagulation can reduce the overproduction of VEGF in the retina and induce the regression of new vessels by ablating peripheral retina ischemic areas. Studies have shown that the BEAT-ROP study showed improved outcomes with intravitreal injection of bevacizumab (IVB) compared with conventional laser photocoagulation for zone I ROP. However, more recently studies have shown that bevacizumab escapes from the vitreous into the general circulation and could reduce systemic VEGF levels after intravitreal injection in premature infants. However, other studies have proved that ranibizumab does not alter systemic VEGF levels in adults. Moreover, studies reported that IVB had a risk of late recurrence and development of retinal detachment. It has been proposed that ranibizumab might have a better safety profile for preterm infants compared to bevacizumab.[4]

DEVELOPER

Novartis Pharmaceuticals UK Ltd

PATIENT GROUP

BACKGROUND

Retinopathy of prematurity (ROP) is when the retinal blood vessels do not develop normally in babies born prematurely. This can cause serious loss of vision (blindness) if it is not diagnosed or treated early.[5] ROP is thought to occur because the eyes normally develop rapidly in the last 12 weeks of pregnancy and when babies are born prematurely normal blood vessel development in the eye may stop. This can result in abnormal blood vessel development instead which grow and spread throughout the retina (tissue which lines the back of the eye). These abnormal vessels are fragile and can leak, which can scar the retina and pull it out of position (retinal detachment).[6]

There are five different stages of ROP, ranging from mild (stage I) to severe (stage V). Most babies with ROP will have stage I or II ROP which will require no treatment and where eventually normal vision develops. However in a small number of babies, ROP may worsen (sometimes rapidly) into stage III (severely abnormal blood vessel growth requiring treatment to prevent worsening), stage IV (partially detached retina) or stage V (completely detached retina) where there is increased risk of severe visual impairment or blindness. Infants who develop ROP are also at higher risk of developing other eye conditions later in life, such as retinal detachment, myopia, strabismus, amblyopia and glaucoma.[6]

Risk factors for ROP include premature birth (particularly before 32 weeks gestation), low birth weight (below 1500 grams) and oxygen treatment. All babies born in the UK which weigh less than 1501g or born before 32 weeks gestation will have an eye screening examination every 1-2 weeks until about 36 weeks gestation when the risk of developing ROP requiring treatment has passed. ROP can cause temporary or permanent vision problems and even blindness if left untreated. Although the incidence of ROP is increasing due to the increased numbers of premature babies surviving, the improvements in screening, diagnosis and treatment of ROP has led to better visual outcomes for children with ROP.[5]

CLINICAL NEED and BURDEN OF DISEASE

In the UK, over 60% of babies with a birth weight of less than 1251 grams will have ROP, 94% or which will be mild ROP which will not require treatment. Only 6% premature babies will have ROP requiring treatment.[5]

The incidence of ROP in England has increased ten-fold from 12.8 per 1000 in low birth weight babies in 1990 to 125.5 per 1000 low birth weight babies in 2011. This rise in incidence is thought to be due to increased neonate survival and improved awareness and dissemination of guidance on the treatment of ROP.[7]

A systematic review and meta-analysis study of global ROP outcomes estimated that 184,700 babies worldwide developed ROP in 2010. Of these, 20,000 (approximately 11%) babies became blind or severely visually impaired and 12,300 (approximately 7%) developed mild/moderate visual impairment. An estimated 55% of those with visual impairment also had other associated neurodevelopmental impairment.

In high income countries, ROP and associated adverse outcomes were most common in preterm babies born at <26 week gestation. Effective screen procedures and treatments have reduced the burden of blindness and visual impairment due to ROP in high-income countries, however blindness from ROP still persists at a low rate, especially in the extremely pre-term (born at <28 week gestation).[8]

PATIENT PATHWAY

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE guideline. Development follow-up of children and young people born preterm (NG72). August 2017.

NHS ENGLAND and POLICY GUIDANCE

- NHS England. 2013/14 NHS Standard Contract for neonatal critical care. E08/S/a.
- NHS England. 2013/14 NHS Standard Contract for Specialised Ophthalmology (Paediatrics). D12/S/b.

OTHER GUIDANCE

Royal College of Ophthalmologists. Retinopathy of Prematurity Guideline. 2008.[9]

CURRENT TREATMENT OPTIONS

UK recommendations state that all babies born <32 weeks gestational age or <1501g birth weight should be screened for ROP and all babies born <31 weeks gestation age or <1251g birth weight must be screened for ROP. The first ROP screening will normally take place 4-5 weeks postnatally (or before discharge from hospital) for preterm babies and will be repeated weekly or fortnightly. Screening can be stopped when the baby is considered to no longer be at risk of sight-threatening ROP, e.g. once the retinal vessels have entered zone III or for babies with a diagnosis of ROP, when there is clear evidence that the active progression of ROP has halted and regression has commenced.[9]

Timely treatment of ROP is essential to prevent severe visual impairment.[9] Most babies have mild ROP and will not require any treatment as the condition will self-resolve. However, in more severe cases, there are several treatments available from the treatment of ROP:[5]

- LASER treatment: a procedure, conducted under general anaesthetic, where small burns are made on the retina to stop the development of new blood vessels. More than one of these procedures may be required.
- Vitrectomy – performed in babies with stage four or five ROP. A procedure where the vitreous gel in the eye is removed and replaced with a clear solution. This solution holds the detached retina against the back of the eye from the inside.

Earlier treatment of ROP is usually recommended as this stops the development of abnormal blood vessels and prevents retinal detachment from occurring. However some babies may still experience visual impairment after treatment.[5]

EFFICACY and SAFETY	
Trial	**RAINBOW, NCT02375971, EudraCT-2014-003041-10, IRAS-188713; preterm infants with ROP; Ranibizumab vs laser therapy; phase III extension**
Sponsor	Novartis Pharmaceuticals
Status	Complete
Source of Information	Trial registry[3], technical summary[10]
Location	16 EU countries (incl UK), USA, 6 countries in Asia, Egypt, Mexico, Russian Federation
Design	Randomised, active-controlled, open label trial
Participants	n=224; preterm infants with a birth weight of less than 1500g; bilateral retinopathy of prematurity; no previous surgical or non-surgical treatment for retinopathy of prematurity
Schedule	Participants were randomised to one of three treatment arms: 1. Ranibizumab 0.2 mg administered by intravitreal injection in both eyes on day 1, with up to 2 re-treatments in each eye 28 days minimum interval between 2 injections 2. Ranibizumab 0.1 mg administered by intravitreal injection in both eyes on day 1, with up to 2 re-treatments in each eye 28 days minimum interval between 2 injections 3. Active comparator arm: laser therapy treatment om both eyes on day 1 with supplementary laser treatments allowed until 11 days after the first treatment
Follow-up	Follow-up up to 24 weeks
Primary Outcomes	Absence of active retinopathy of prematurity (ROP) and unfavourable structural outcome [Time Frame: 24 weeks after starting investigational treatment]: to achieve this outcome, patients must fulfil all the following criteria, 1) survival, 2) no intervention with a second modality for ROP, 3) absence of active ROP and 4) absence of unfavourable structural outcome
Secondary Outcomes	1. Requirement for intervention with a second modality for ROP [Time Frame: 24 weeks after starting investigational treatment] 2. Time to intervention with a second modality for ROP or development of unfavourable structural outcome or death [Time Frame: 24 weeks after starting investigational treatment] 3. Recurrence of ROP [Time Frame: 24 weeks after starting investigational treatment] 4. Number of patients having any ocular Adverse Event [Time Frame: 24 weeks after starting investigational treatment] 5. Systemic ranibizumab levels [Time Frame: Within 24 hours, 14 days and 28 days after ranibizumab treatment] 6. Systemic Vascular Endothelial Growth Factor (VEGF) levels [Time Frame: Before investigational treatment, 14 days and 28 days after investigational treatment]

	7. Number of ranibizumab administrations [Time Frame: 24 weeks after starting investigational treatment] 8. Number of patients having any systemic adverse event [Time Frame: 24 weeks after starting investigational treatment]
Key Results	Treatment success was highest with ranibizumab 0.2 mg (80%); treatment success with ranibizumab 0.1 mg and laser was 75% and 66.2%, respectively. The odds ratio of 2.19 indicates a clinically relevant ~2-fold higher likelihood of treatment success with 0.2 mg ranibizumab over laser therapy. This treatment difference is considered clinically relevant, even though the primary endpoint did not demonstrate statistical significance as the one-sided p-value (p=0.0254) was marginally above the significance level of 0.025.[10]
Adverse effects (AEs)	The observed safety profile is as expected in a preterm population and ocular AEs and SAEs are generally consistent with the established profile for ranibizumab in adults.[10]
Expected reporting date	Study end date previously reported as Dec 2017

ESTIMATED COST and IMPACT

COST

Ranibizumab is currently marketed in the UK for numerous indications; one prefilled disposable injection of 1.65mg/0.165ml ranibizumab solution costs £551 and one injection vial of 2.3mg/0.23ml ranibizumab solution costs £551.[11] There is a confidential simple discount Patient Access Scheme (PAS) available for ranibizumab in England and Wales since 23 May 2012.[a]

IMPACT – SPECULATIVE

IMPACT ON PATIENTS AND CARERS

☐ Reduced mortality/increased length of survival

☒ Reduced symptoms or disability

☐ Other

☐ No impact identified

IMPACT ON HEALTH and SOCIAL CARE SERVICES

☐ Increased use of existing services

☐ Decreased use of existing services

☐ Re-organisation of existing services

☐ Need for new services

[a] Company confidential information

☒ Other: *new staff training requirements for intravitreal injection*

☐ None identified

IMPACT ON COSTS and OTHER RESOURCE USE

☐ Increased drug treatment costs

☐ Reduced drug treatment costs

☒ Other increase in costs: *additional staff training required, additional costs for intravitreal administration in clinic*

☐ Other reduction in costs

☐ Other

☐ None identified

OTHER ISSUES

☐ Clinical uncertainty or other research question identified

☒ None identified

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