# RETINOPATHY OF PREMATURITY: PRACTICAL APPROACHES TO PREVENT BLINDNESS

LONDON SCHOOL OF
HYGIENE & TROPICAL MEDICINE

## WEEK 3 SCREENING AND TREATMENT FOR ROP

## Q&A: ROP TREATMENT CHALLENGES

This document is a condensed transcript of our live Q&A session on "ROP treatment challenges" where an international panel of experts came together to tackle some of the complex questions surrounding ROP treatment, sharing their perspectives on the pros and cons of anti-VEGF treatment and its use in combination with lasers or as a rescue treatment when laser has failed.

Experts who took part:

- (Chair) Professor Clare Gilbert, Professor of International Eye Health
- Dr Pramod S Bhende, Director, Shri Bhagawan Mahavir Vitreo-Retinal Services, Medical Research Foundation, (Sankara Nethralaya)
- Graham Quinn, Children's Hospital of Philadelphia and the University of Pennsylvania.
- Umar K. Mian. M.D., Director Retina Service, Department of Ophthalmology and Visual Sciences, Montefiore Medical Center
- Professor Brian Darlow, Clinical Neonatologist
- Dr Linda Visser, Academic Head – Department of Ophthalmology, UKZN
- Dr Andrea Zin, Ophthalmologist and ROP expert, Brazil

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Clare Gilbert: [Hello] everybody and welcome to the ROP MOOC webinar on ROP challenges. You can see in the room, I have got several ROP experts and also a neonatologist because treatment with anti-VEGF agents is obviously of great significance to them and how they care for their preterm babies.

The treatment of the severe sight threatening for the stages in type one ROP used to be fairly straightforward. It was laser treatment which took over from cryotherapy. But more recently, anti-VEGF agents has become available. And there is unfortunately not yet very robust evidence from large scale well conducted

randomised clinical trials, to really guide the development of guidelines and protocols. What treatment should be used under what circumstances? And there are a range of different products on the market. And they can be used in different doses and the timing of treatment and all these things need to be taken into account when deciding how to manage the baby in front of you.

So, before we start on this discussion I'd like the panellists to please introduce themselves to say their name, the institution where they work and which is their role in in ROP and the setting in which they work.

Linda Visser: Good afternoon everyone from South Africa, I'm Linda Visser; I work at the University of KwaZulu-Natal, Durban, South Africa. I'm mainly involved in treatment of ROP, some screening but mainly treatment. Thank you.

Clare Gilbert: Just to add South Africa is the only country in Africa with a national program, isn't it.

Linda Visser: I think Kenya and Nigeria have recently published their screening guidelines as well.

Andrea Zin: Hi, good morning everybody from Rio Brazil. I'm Andrea Zin, a paediatric ophthalmologist involved in screening and treatment of ROP and I was responsible for helping many cities in the country to implement ROP screening and ROP treatment programs.

Graham Quinn: I'm Graham Quinn, I'm at Children's Hospital of Philadelphia, University of Pennsylvania. I've been in and working in ROP, it feels like since the dawn of time, international classifications and worked on both CRYOROP trial, ETROP and EROP and several other ROP trials and I'm delighted to be able to join this group.

Dr Pramod S Bhende: Yeah, Doctor Pramod Bhende from Sankara Nethralaya in the southern part of India, and direct the vitreoretinal services, there. I have a team of 23 Retinologist working with us and we do ROP screening, surgery as well, including anti VEGF. I'm involved in ROP management since last 25 years.

Brian Darlow: So I'm a neonatologist I've been interested in ROP and its epidemiology since the early 1980s. And more recently, I've had the pleasure of working with Claire and Andrea and Graham on workshops trying to prevent ROP, which is I think the main focus of what of what I'm trying to prevent the problem in

the first place. And sorry I I'm based in University of Otago in Christchurch, New Zealand.

Umar K. Mian: Hi, I'm Umar Mian. I'm in based in New York at Montefiore Medical Center. Albert Einstein College of Medicine. I head the retina division and also run the ROP service we have. We are an inner city in New York in the Bronx and I do screening and treatment and with the help of Clare, Graham and a lot of other people I've been pushing to start screening and treatment in Pakistan where we have done guidelines for ROP screening and treatment with them.

Clare Gilbert: Thank you very much. So first, Andrea and then Umar so when they are confronted with a baby who's got type 1 ROP and needs urgent treatment, can you just explain what factors you take into consideration when you decide on what treatment, how to manage that baby?

Andrea Zin: For us, our current guidelines we still use laser for type I ROP. Anti-VEGF is really an exception and we follow the ET-ROP guidelines - treating type I ROP which means stage two or three in zone II with plus disease or zone one with any stage plus. We just go, or think, on anti-VEGF in very special cases where the babies can't be anaesthetised because we do [it] under general anaesthesia or sedation/analgesia if the baby is too sick. We discuss with the neonatologist and the parents the pros and cons of performing the anti-VEGF, and what evidence is a available. And also if the media is opaque if we can't see it much, we're just considering very, very special occasions and obviously we have to discuss in advance with the parents what will be the follow up scheme for that baby in the future because it requires a lot of compromise with the parents and adherence to the follow up programme.

Clare Gilbert: Thank you. Umar, is that similar to New York?

Umar K. Mian: Yeah, we are very similar in New York, a little behind the curve with anti-VEGF. Our basic treatment protocol guidelines which I called ROP protocols is for type I we treat. Zone II is usually laser, zone I we tend to go towards more anti-VEGF.  Like Andrea mentioned one [issue] is the disease in the eye of the baby, whether you can have a clear media where the baby can tolerate laser we tend to do it more under sedation then general anaesthesia, depending on how the neonatologist tells us the patient will be able to tolerate the procedure. Then very importantly, as we are in an inner city in the Bronx, you have to talk to the parents to make sure that they can really come nearly every week for X amount of months. A lot of parents are single mothers and they might come to their mothers for the

delivery and then they kind of move back to wherever they are. So that is a very key thing we look at for deciding whether it's going to be laser or anti-VEGF. We only use Avastin, we haven't gone to any of the other medications yet. It is an exciting time because a lot of data is coming through, but it's still early to really decide which maybe we should go.

Clare Gilbert: Thank you. So, both of you are saying that it's the social factors and the context which are almost as important when you think about using the anti-VEGF agents as laser because adherence to follow up is so incredibly important. And I'll just open the floor now to say if you have treated a baby with an anti-VEGF agent, what's the timing of the first follow-up and how frequently might you follow them up and for how long, and what you're looking for?

Andrea Zin: Well, I can start if I'm not, I would like to say, I'm not sure that I will be able to see the baby as frequent as needed. I strongly consider and discuss with the parents and neonatologist to perform a laser before discharge from hospital. It's something we are doing here for in Brazil. We don't use anti-VEGF as a primary choice in general. All people in Brazil, working with ROP consider lasering first. But if we are able to do it (anti-VEGF) , we have to follow-up two to three days later, and then weekly until 50 weeks and then every two weeks, 60 weeks and then up to 70 [weeks] every three weeks. I don't have angiograms so I'm not able to see a vascular retina. So I'm very afraid and I keep following up to four or five years or even more.

Clare Gilbert: Right, thank you. [Who does] something similar?

Umar K. Mian: Yes, something similar. I just like to add, what I do is if I have a patient that I've given an anti-VEGF [to] and then I think the follow up might not be as good or there's avascular retina that's just not vascularising either - unfortunately Andrea we don't have a angiofluorescein either - what we do is, before discharge, we'll do laser in zone II then I can sleep well and not have to worry. And it does disappear and I'm not worried. The problem becomes that as the kids becomes older, it's very hard to see peripherally. So then while you're exposing them to anaesthesia and I just feel that sitting and watching might be more detrimental than doing a bit of laser to stabilise the retina.

Clare Gilbert: Thank you. Okay, I shall now move on to describe a little case scenario which I'd like to Linda and Pramod to address.

So I just like you to imagine a situation where you examine the creature and baby who was born 200 kilometres away and was initially admitted to a local unit, about which you have no information at all. And then three days later they were transferred to your unit because they can provide more specialist care. The baby had a twin who died at home and there are three other younger siblings and the father is a shopkeeper.

The infant had a birthweight of 950 grams but information on the gestational age is really uncertain. And baby had sepsis and you're now doing the first examination at four weeks, just before discharge. In both eyes you see stage 3 ROP in posterior zone I with plus disease. The pupils dilate recently well.

Linda Visser: That's a common presentation mode to us. We have a lot of patients coming from very far and that we don't know the gestational ages. So in my unit we have for the last 10 years been using anti-VEGF for posterior zone I and posterior zone II disease. So as a default, in a case with posterior disease stage three in zone I, we would probably opt for anti-VEGF. However, the specific case, obviously, one has to take into consideration the fact that the child may not be able to follow regularly because they from 200 kilometres away and have a small kids at home etc. So, in this specific case I'll obviously discuss it with the parents and make sure that they can follow up if they can, if they promise me that they will be able to follow up long term, I would still go ahead with anti-VEGF. In this case, if there's a definite problem with possible follow up. A case like this, I would then do laser. However, I would know that the outcome would be probably not as good - with doing laser so far posteriorly this child will likely have high myopia etc. So I'll discuss this with the parents.

If there's someone in the area who can follow the child, even after I've injected them I could also go ahead with the anti-VEGF and just ask that ophthalmologist in that region to send the baby back should there be problems. What we found however in our set-up because our babies are often slightly more mature than the ones you see in UK and America is we've very seldom have patients that have peripheral avascular retina that does not vascularise completely. So in our cases that we've looked at, we've had full vascularisation in most of our babies, but my protocol would be that at 60 weeks or 70 weeks, it is still avascular retina to also laser that retina, rather than continue follow for five years.

Dr Pramod S Bhende: I agree with Linda with a few a modifications. First important thing is the baby has had septicaemia, so how the infection is, how stable the

babies I do not know. So that itself can be a risk factor when doing any intraocular injection I will have a question mark if it's a good idea or not.

If pupil dilates  and If I can manage both laser and anti-VEGF is a given option I can do. So  you can dilate, media is clear, zone I stage three ROP somewhere just beyond the macular area. What I do is a combination of both. I treat peripheral retina with a laser probably Ora to just posterior to the equator and also give anti-VEGF.

So what I know is with an immediate crisis probably anti-VEGF will help us to take effect because laser takes around two to three weeks to have an effect and anti-VEGF will take care of existing VEGF and though anti-VEGF will start wearing down by second week laser takes over. I'm not going to do laser right up to the entire avascular retina but somewhere in there in between they  will joined together and vessels start growing up. This is easier to follow-up subsequently and as rightly mentioned because 200 kilometres [travel for family] is an issue.

We try to have a local follow-up but laser will give us the breathing time somewhere in between. That's a general pattern that we follow here. Also, we all know with our experience more than 80% patients we are giving anti-VEGF even eventually end up in a laser, probably, we do not want to wait too long for like a year or two or three all over [as] Dr Umar rightly mentioned. So I prefer my threshold is a little bit low even though situation after a month or two or three events few months, a little first sign of congestion of the vessel I would go ahead and use laser on retina so this particular situation probably I would use combination.

Clare Gilbert: Okay, and which to do first, you do the laser and then immediately follow it with an anti-VEGF injection?

Pramod S Bhende: Probably I will start with anti-VEGF and then within a couple of days try to go ahead with laser.

Clare Gilbert: Okay, you persuade the neonatologist to keep the baby in the neonatal unit.

Pramod S Bhende: Yes, that's right, also injection I would prefer not to do on the same day. We did not do my choice is we all agree with Avastin . But generally, we don't give a same day and during this current scenario with the Covid situation we are holding on because Avastin generally was practice was here as a pool Avastin

because we do not have where somebody can allocates for us. That doesn't happen here so we have to use that Avastin fractionate and pool the patients together. So this scenario, we want to avoid that with Avastin. So we are using Rancuzimab most commonly.

Clare Gilbert: Thank you use one vial of the medication to treat several babies using sterile techniques?

Dr Pramod S Bhende: I am hesitant to do that and we use sperate for two eyes not because of dose but because of infection.

Clare Gilbert: Thank you for clarifying. Thank you so much. I think I was some was very interesting, some similarities and differences. So now I would like to ask Brian to give an neonatologists perspective of antivascular endothelial growth factor agents.

Brian Darlow: Thank you very much. So I think, I think the first thing just to mention is that the evidence base for the advantages or disadvantages of anti-VEGF or laser is pretty poor at the moment. There are at least eight randomised control trials, including the BEAT-ROP study which is the largest, the first be published, [with] 150 infants in it. And there are at least five meta analyses of these trials and they all conclude that the quality of evidence is currently not high. But that anti-VEGF is as it seems to be as effective as laser achieving the initial regression of ROP. There may well be advantages as we've heard for zone I disease and progressive posterior ROP. But importantly, There is really no data on long term systemic and neuro-developmental outcomes associated with anti-VEGF or with either procedure.

VEGF is produced in many cells around the body and has multiple actions around the body. Obviously, it's the key orchestrator of angiogenesis, but it has many other things as well. In the lungs, for instance, it's very important for regeneration, in the central nervous system it's neurotrophic and neuro-protective. It maintains the blood brain barrier and in fact autopsy data on foetuses and newborn infants who have died show very high levels of VEGF, and the main receptives for VEGF in two areas of the brain suggested [that it] has the central role in neuro cell development, migration, synaptic genesis  and myelination. So around 34 to 36 weeks when these high levels of [VEGF are] found this is the time of great brain growth, but it's also the time the babies are likely to be treated with these antiviral agents.

It's important to realize that if you inject drugs into the eye, the drug also escapes from the eye. So particularly Bevacizumab intravitreal injection leads to peak levels

in the serum about a week later, and the levels are still raised eight weeks later. It has a  very long half-life of 20 days. Now the dose used in the BEAT ROP study of 0.65 milligrams is half that used in an adult, but infants have a body size 1/5$^{th}$ of an adult and a blood volume is 1/20$^{th}$ of an adult and it's been estimated that the dose of intravitreal concentrations is 10,000 times what is needed to neutralise the amount of VEGF. So it's a very high dose!

And the systemic concentrations with Bevacizumab you get from that individual injection is still 1000 times the serum VEGF concentrations. What you see as a fall in this serum concentrations levels and they remain low for several weeks. Now, does this matter? Well, we don't know for certain, but there's a lot of suggestive evidence that it does matter. And some of that evidence comes from animal models. And I'll just mention one example, if in newborn rats you gave a systemic dose of a VEGF receptor inhibitor it produces lung changes that look exactly like bronchial dysplasia. And what's more, they persist into the rats' adulthood. So, it may be very difficult to tell the side effects from the consequences of extreme prematurity

So There are two human trials, there are no randomised control trials. So, we have observational and usually retrospective observational data. There are two I think good studies which come from large North American neonatal networks.

The first is from the Canadian National Network. They had something like 3200 infants in the database and 174 of these were treated for ROP. They had follow up data on 124 of them. 27 were treated with Bevacizumab and 98 by laser. In the Bevacizumab group they had significantly poorer motor outcomes at 24 weeks with neurodevelopmental impairments and severe development impairments. In that latter group the severe neurodevelopment impairment remained after correction for a number of other factors, such as how sick the baby was!

The other one comes from the NICHD Research Network and kind of very large North American network in the best units 405 babies treated for ROP, 181 with Bevacizumab and 224 by laser. The follow up at 18 to 28 months and IVB (intravitreal Bevacizumab) had significantly increased, corrected, odds of death by 2.54. Of cognitive score less than 85 of 1.78 and of motor problems 1.7. So you know that doesn't prove that Bevacizumab causes these problems, but it's worrying and it's suggestive. And to me, it suggests that you should avoid using these drugs.

We've heard already from others, circumstances that seem very reasonable to use these treatments, but for bigger babies with zone II disease for me, there's absolutely no reason to use it, and particularly in many other middle-income

countries for instance, as these sort of bigger babies who are getting ROP are less likely to have other complications of prematurity. So, why give a drug that may be causing these complications when laser we know works perfectly well in that situation.

I have some other questions about, about the drugs, but maybe I should leave it there and we'll come back to these other questions.

Clare Gilbert: Thank you very much. Brian, I mean, what you have told us it really food for thought both for clinicians but also for researchers and people designing future studies because they really do need to be large with a longer follow up to be able to assess infants who have had laser or anti-VEGF, and at an age when they can perform the range of different tests that are needed.

Brian Darlow: Can I come back to what you said [about] future studies. I think this is really, really important because in fact, overall, you need at least one hundred babies to answer the questions. I think it's absolutely vital that there's a coming together of, you know, the ophthalmologists, neonatologists, parents and others to decide what the question should be, what the right study should be that will have the right numbers and that has the long term follow up. Lots of little studies doing different things is somewhat useful, but many are not very useful.

Clare Gilbert: Completely agree, and I think neonatologists are just a fantastic collaborators in research. It was a big oxygen trials that were done in eight centres, was it?

Brian Darlow: Will, but there are five studies?

Clare Gilbert: but the design was very similar across all studies presentation the outcomes.

I think it's up to ophthalmologists and we need to collaborate better in research neonatologist miles ahead of us actually so thank you very much, Brian. I'm sure if we have time, you can come back to discuss some of these issues if we can. So Graham can you just give us a little summary of the dosing trials being done in the US.

Graham Quinn: It follows on what Brian was just saying there's a need to know what safe levels are? What might be useful if you're using an IVB (intravitreal Bevacizumab)?

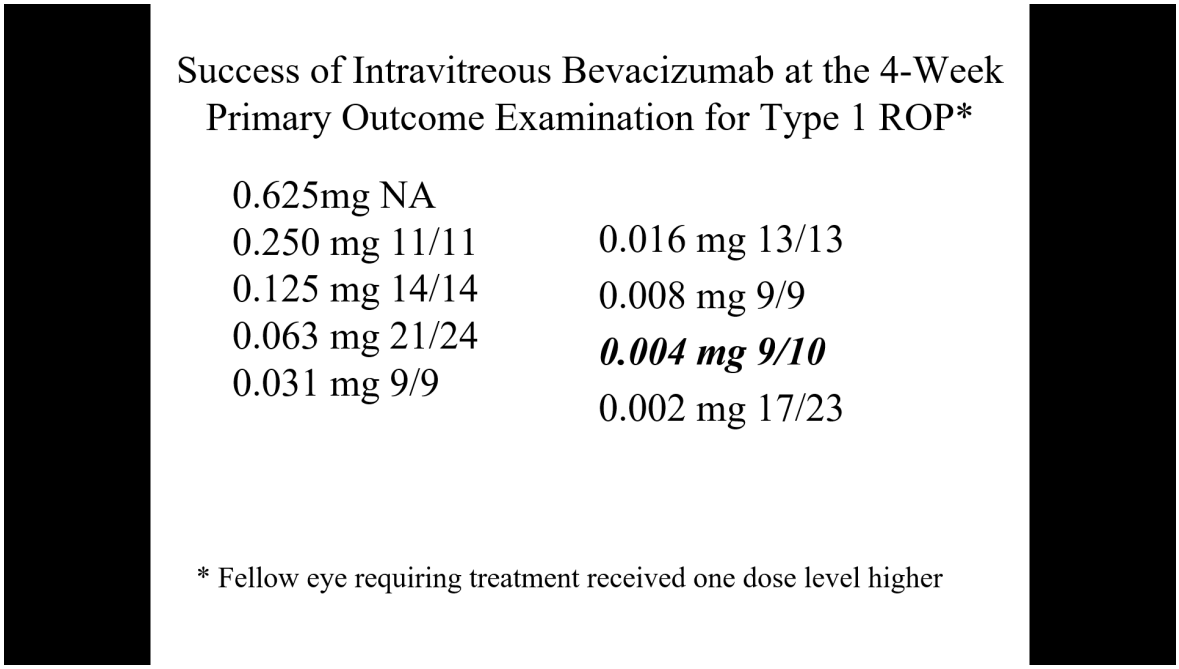
And David Wallace and through the Jade centre and the national institute are doing a dosage trial doses looking for the lowest effective dose for severe ROP. It is not yet a trial of effectiveness, that's really important to remember. So far, they've been 114 children with type 1 ROP who were involved in this de-escalation study, meaning that they started the treatments in one eye had about 50% of what the Hytner study did and in cohorts of about 10 to 14 kids.

Clare Gilbert: That is less then half of 0.625?

Graham Quinn: Actually, it's less than half. They started at 0.25. In groups of 10 to 14 children, which obviously can't prove whether there's a benefit or not from the thing. But just to see whether there is an effect.

They started in 10 to 14 children in one eye. success was defined is improvement within five days and no recurrence at four weeks, requiring additional treatment. And if you could put the slide up there.

That would be useful right now. And this slide shows




Anyway, as you can see that they've used a decreasing doses by about a half at each of these nine levels and it went down to 0.02 milligrams, which is an incredible decrement from the original 0.625 milligrams. And you can see that it's largely effective in until you get to the point 0.004 in 9 out of 10.

When you go below 0.004 mg that only about 75% are effective and that's really quite important to think about. So, what, what conclusions can we draw from, from a table like this, and that is that the lowest effective level seems to be the 0.004 milligrams. Which is about point 6% of the dose used in the BEAT ROP study, lower than that is less effective. So, what conclusions could we draw?

There seems to be a lower limit if I do be effectiveness and cutting the dose seven times in this study, and it still seems to be effective. So in this preliminary study that's just looking to find the lowest dose that's effective, that's a setup for a larger study where you could compare effectiveness of IVB (intravitreal Bevacizumab) versus laser and that is in process of getting funding from NIH [National Institutes of Health, USA], it is not funded yet, to my knowledge.

So, what we talked about what are the advantages of Avastin, it's easier and faster. And it's certainly easier for the ophthalmologists but, as Brian so nicely pointed out, there are concerns about the systemic and ocular effects with possible interference in normal development. And we also have to remember that we really have a treatment that works - laser - and if it can be done not under general anaesthesia, but under local. Then perhaps that's the way that most of the children should go.

But again, this is a dosing study, not a trial of effectiveness, and I think that's the whole key to this and it's a logical first step, a step which I wish we had taken 10 or 15 years ago, rather than doing the catch up now. Thank you.

Clare Gilbert: Thank you. And I would just like to comment on this study, because I think what is incredibly important. First, or should remember this the type 1 ROP With a  constellation of different signs of sight zone stage and what it is plus disease and the risk of progression to more severe disease.

And so how Type 1 disease is now described there is a 15% risk of progression. That's what that means in effect is that for every six babies you treat five of them, the disease, which is regressed without treatment. And only one of those which have progressed, and I think we need to bear that in mind when we're treating anyway.

And the risk of progression more posterior the disease is. So the risk of progression of that disease in zone one is much higher than the risk of progression in zone two.

So the 15% risk is an average which hides the very high risk of an aggressive posterior ROP and in posterior one ROP with plus disease.

And once you start getting out more into Zone II and almost into Zone III there the risk of progression will be much, much lower.

And I think from hearing what you're saying - you very much bear this in mind when you're deciding what treatment to give - it some risk of this this particular baby losing sight. It comes into that equation. And I think with this trial this dosing study, it slightly worries me because the numbers are so small. So I think I added it up to 90 babies were included in that table you showed, and can remember it was in the next slide six of them know 15 progress. So, is exactly one in six. Exactly what would have happened if you've done nothing.

So, I'm very concerned about going from a dosing study straight to a trial. Because it may be that that 0.004 milligrams is actually not doing anything. I would like to see an intermediary step, where they treat a large enough number of babies to see whether it's effective or not, or they limit who they recruit to the study with babies that have got disease at a much higher risk of progression or did they do that. It was all type I, any type I.

Graham Quinn: Right, and it was pretty evenly distributed across the types of type I. But I think a really important point to consider is that to me, this should be a three-arm study, it should be a laser versus a higher dose IVB (intravitreal Bevacizumab) and a low dose IVB, and then perhaps not the same numbers randomized within that, but some kind of trial like that, rather than just a low dose verses laser.

Clare Gilbert: I agree. I think that's completely okay. And as you can see there is still a lot to debate.  Within anti-VEGF and laser and we don't want to get too technical.

Brian Darlow: I would like to say something. Just a practical problem with this study that I see is with current formulations in drawing up and administering these tiny doses and you know David Wallace has an expert pharmacy to back him up. But you know, that's a major problem that needs to be sorted, doesn't it, for this to go anywhere.

Clare Gilbert: And I think what we're saying to all who are listening. There is no good evidence that very dilute anti-VEGF agents work so please don't over dilute. How much do you use Umar?

Umar K. Mian: We are using ½ to 40%, so instead of 0.25ml (I'm sorry I don't have the conversion to the milligrams), we use 0.1ml.

Clare Gilbert: Which agent?

Umar K. Mian: Avastin basically

Clare Gilbert: Andrea, what do you use?

Andrea Zin: The first time I'm seeing Umar here, but we are doing the same thing.

Clare Gilbert: Okay, and Linda

Linda Visser: We are still using the the Hytner dose that's the 0.625 milligrams in 0.25ml or half volume half dose basically

Clare Gilbert: Thank you so much. Pramod?

Dr Pramod S Bhende: Yeah, it's a probably is a 0.02ml because again it's nice to say half dose those, but to get that 0.05 it's a practical issue. That's what we inject but what I agree with Dr. Brian, that's a practical difficulty [as we] have a needle which indicates 0.06. So really to go too low, you do not know how much you are injecting or not at all.

Clare Gilbert: Yeah, sounds that we need to get onto the pharmaceutical Industry and ask them to make a more dilute version. I guess when evidence comes available then they will make it more standardized. Andrea?

Andrea Zin: I would like just to go back to laser because if you look at the result from all different studies, I always think that the results are quite bad and talking to many colleagues that perform laser, I don't re-treat that much and I don't know what's going on. If it's different people doing laser expertise but it's not that bad.

Obviously, we know that we have long term myopia and but you know I don't re-treat that much. It's, I would say, looking back, I would say it's 5% of those treated in the last 25 years so.

Clare Gilbert: You are saying that good laser done well – works!

Andrea Zin: Yeah yeah

Graham Quinn: And I think that's a key point. Yeah, I think expertise in laser ROP has really gone down as people have just quickly adapted to the injection, because it's easier for the them all.

Clare Gilbert: Umar?

Umar K. Mian: I think the problem we're having is that the neonatologist, I shouldn't blame them for it but still, they're saving much smaller kids. You have now have 23-24 week old babies surviving and those kids I've noticed they don't respond similarly to anti-VEGFs or laser. So recently we had a kid who was 24 weeks old and we gave Avastin and was not the 0.1 dose was like but gave a higher 0.15, so slightly higher than we give. And in four days it stabilised. You know you didn't have that, "Wow. Oh my god, it's all gone." It just kind of still the plus disease was there. Later we did laser. There was a little haemorrhage but that kid now has peripheral traction, thank god. The macula is stable.

But I've noticed that the smaller kids 25 weeks or less, they just behave differently. So, I think we do compare one against the other. But I think there should be an arm in which we do combined. You give the Avastin - anti-VEGFs - to buy you time and so you don't want to do laser immediately because we'll go more into the body. And then after four weeks, which I feel is a reasonable time - if you break the blood ocular barrier it's not going to go into the body - then you do the laser and we should be done! So I think any studies should have a hybrid arm to tell us that maybe that is a good option. And especially, I mean in Pakistan and everywhere else, they don't have really the luxury of one or the other, and I know a lot of people in Pakistan who are re-injecting anti-VEGF once and then four weeks later, as they would for adults.

Clare Gilbert: Linda you want to say something?

Linda Visser: Well, I just wanted to emphasise that we do use anti-VEGFS a lot for zone I disease, but we still do laser for them to disease that's the protocol. And, so far, I've never injected more than once. I've never given a second dose of anti-VEGF. So that's the other thing I just wanted to say that. I don't think it's a good thing to do, to give the doses second time. If there's still active new vascularisation then laser should be done. The second time.

Dr Pramod S Bhende: Right, right. I just thought to add and I totally agree with Dr Umar. Because of this 24 - 28 weeks old with 700 - 800g weight the type of ROP we see is totally different. What we see a, like a case yesterday we had a whole

proliferation fluffy thing coming right over the disc just coming all over the fundus, hardly any vision of the fundus. This type of again babies like somebody has described as a funnel or kidney shaped proliferation along the way so long. As the names are being given, but they probably only laser may not work out in these babies. Yes. But what we also do is a combination of anti-VEGF with laser. One anti-VEGF and laser takes over. My treatment plan for these babies [with] very, very low birth weight but yes zone II it will be only laser as before.

Clare Gilbert: Thank you so much. Sure. I think we need to wrap up this part of the webinar. Now, and then see if there any questions. So I'll just try and summarise the discussion. Which, if we go back to the original question I asked Andrea and Umar was, what do you consider when you're deciding how to treat a baby?

It's not only the disease and how severe it is and risk of progression but you have to think of the general health of the baby and other stability and incredibly important is the context of the family, how far away they live and whether they're going to be able to comply with follow up and, very importantly, all the concerns about the risk of  adverse events. So, at the moment, until there is more really robust evidence of anti-VEGF agents I think most of you are using it cautiously and only when there are very specific indications - medical or social.

And I don't think I've had anyone who's actually repeating it. It's one dose and after that it is laser. But what I'm hearing from everyone of you is that laser remains the mainstay in treatment but it must be of high quality and done by an expert and by someone who really knows what they're doing, so that they can do a complete treatment.

Have I missed anything else, or is that a fair summary? Okay, thank you so much, and I shall not see if we've got any questions for the panel.

Romulo Fabunan: Hi, thank you. Claire and to all of our panelists either and hello to everyone joining the webinar today and thank you for your questions.

The panel have already provided a great deal of knowledge and with respect to the time we have collected a few of your questions from the chat and also from the ROP MOOC [https://www.futurelearn.com/courses/retinopathy-of-prematurity-practical-approaches-to-prevent-blindness] for the panel to answer the next 10 minutes or so before we wrap up, So, the first question comes from one of our MOOC participants. If our ROP treatment as we understand it needs to take place

in 24 to 48 hours, how often are you able to do this when the babies are not near the treatment centre, or after telescreen?

Clare Gilbert: [Let's] start with Linda and how urgent is urgent in your setting?

Linda Visser: Unfortunately, because of the medical, legal reasons, urgent, urgent. So, we tend to do a proper reciprocity within 48 hours but we actually allow three days - 72 hours - for the non-aggressive type. So, we usually get it done within two to three days. Generally, I think we've had one or two cases where we couldn't get it done because the child was ill or whatever. But yes, we always strive to do it within 48 to 72 hours.

Andrea Zin: Yeah, it's pretty much the same. We tend to, if not aggressive posterior disease, we tend to do up to 72 hours. And we are able to arrange transfer. If the baby's not in our centre and calm and go back or depend on the situation. But we have to remember that we can't discharge a baby right after the treatment, so we have to provide care after the laser.

Clare Gilbert: That is regardless of whether they've had sedation or general anesthesia. They need careful monitoring as it can make them quite unstable. Umar?

Umar K. Mian: So we have a couple of outlining NICU (neonatal intensive care units) that send to us for treatment. And what we do with them is, basically, they have to send the patient before the patient reaches type 1. So when they're type 2 like a week to 10 days before they expect the patient to get to the treatment stage . They will transfer the baby and watch them to see whether they reach the [treatment stage] because it's sometimes very hard when the baby's sick and just gets transferred takes them 24 to 48 hours to settle down from the transport.

However, back in Pakistan  the biggest problem is getting anaesthesiologists to give sedation or anaesthesia for babies for laser. So over there, they tend to use a lot more anti-VEGF because there've been cases in the research that we were looking at [where] the baby could not get sedated to get the laser and their [retina] detached while they were waiting. So there it's a completely different ball game, unfortunately.

Clare Gilbert: Is sedation essential for Laser?

Umar K. Mian: Yes, sorry to jump in because the two things that I've noticed one is if the baby keeps moving it's very hard to do a complete treatment. And if you take

longer and the cornea starts getting hazy, then you're really up the creek without, you know what, because you can see you can laser you're increasing intensity it's hurting the baby more in your neck and back and its telling you that enough is enough. Okay.

Andrea Zin: We don't have anaesthesiologist here as well. So [from] when Brian was here we follow his recommendation. So, [the] neonatologists do sedation and analgesia. But I think the laser is quite painful Clare and sometimes we'll have to do more than 1000 spots. And I think is very stressful for the baby and I know in India, they do with topical anaesthesia and the babies are bigger, but I dont know how to do it, but I think it's very difficult. And I agree with you Umar that it's very hard to do it.

Clare Gilbert: Pramod?

Dr Pramod S Bhende: Yeah, we do under topical anaesthesia. Agree , and we've got used to it being that now I'm just, I'm generally there's no issue at all. We have two sets one baby with comes to our clinic. Generally we manage to do laser on the same day, or by next day if we do laser in the OR [operating room] and we have an anaesthesia  team which helped me do all my ROP surgeries. So they are pretty much comfortable handling this baby, but it is done in the topical but have a continuous monitoring by anesthesiologists and all parameters are being monitored by anaesthetists.

Clare Gilbert: Do you give any analgesia when it's topical. Nothing systemic?

Dr Pramod S Bhende: Only topical anaesthesia. it is the same thing we do when we visit when we get a call from a nearby NICU generally we travel nowadays with the portable laser. And, if necessary, we finished them the same sitting or same day. If they want you to see extra baby and we have just go for follow up without machinery. Then probably by next day one of our colleagues will go and finish later. So, generally we manage between 24 to 48 hours.

What we do quite some time, because as a longer duration of laser, they may go hypoglycaemic. So we use sucrose in the baby's mouth, they keep on sucking, so that act as a pacifier. That is also sort of relief for pain, to some extent, babies are much more comfortable with that and yes when extensive laser is necessary, I personally prefer to finish in [the] same sitting. But when there's a very large area to cover and sometimes have difficulty we do a second sitting

Clare Gilbert: Brian What's your take on pain control during laser.

Brian Darlow: I think it's essential personally that it should be there, but I must say I'm a little bit out of touch with where we are with this topic. At the moment there are concerns about general anaesthetics in preterm babies and long-term problems from general anaesthetic itself. So, I think there's a lot more thought needs to go into it, but I think that needs to be analgesia and sedation. I don't think you can really go without analgesia.

Dr Pramod S Bhende: Yeah, let me add here. Sorry, what you are rightly concerned, we are that because of that concern, even after laser, we do not send baby back home immediately but kept under monitoring and maybe after half an hour to One hour the anaesthetist make a call and all parameters are stable and ensure that baby takes a feed comfortably and then only baby will be sent back home or we will be holding baby.

Umar K. Mian: I just want to add before we start using anti-VEGF we looked at our old data is unpublished right now. We're hoping to get it published by Graham and what we looked at that the neonatologists decided whether the patient should get intubated or not. And we saw that the babies who were not intubated one third of them crashed during the laser treatment and had to be intubated urgently, thank God they were - there was no mortality. So that's the thing you look at that. If you don't intubate one third might crash so you should be really well prepared for that.

And if you intubated the babies before laser. There was no delay in discharge, feeding or anything else. Unfortunately, data wasn't geared to look at effects of general anaesthesia. In any case, but it's mainly support of ventilation intubation. We do not paralyse them.

Clare Gilbert: Thank you very much. I think I see we should not carry on talking [much longer], can I squeeze in one last question?

Romulo Fabunan: Yes. No problem. And so this one also came from a MOOC participant and so the baby has sepsis, but also found to have type 1 ROP stage 3 with plus disease. Do you treat for ROP? What are the challenges that the neonatologist has to look out for after laser treatments in sick babies?

Clare Gilbert: Okay, I think we kind of covered some of the latter part. So who would like to address the first part, she said very sick baby needs treatment.

Brian Darlow: I mean, I think you can do both. To be honest, I think if you know you have to make a decision if the baby is well enough for treatment but, as a neonatologist, I really don't want the ophthalmologist to delay treating that baby. So, in general, I think you can do both, you know, hopefully, if you know the baby's got sepsis, you're treating the sepsis. So I would personally not wanted to delay, not  a very good answer!

Clare Gilbert: Thank you. Rom, can we squeeze in one more quickly.

Romulo Fabunan: As you are aware, there are different cadres of eye health  that are taking our ROP MOOC. So, are there any examples known to the panellists, if non ophthalmologists have been trained to deliver ROP treatment?

Clare Gilbert: I'm absolutely not aware of this and nurses give anti-VEGF injections in adults. But laser treatment is very, very specialised and it means very, very high levels of expertise and for anti-VEGF injections you also need to completely understand the anatomy of a preterm eye  and the relative proportions of different. Me, I would be extremely hesitant about recommending that [non-ophthalmologists] treat.

Umar K. Mian: Especially, I mean, even though we talked about anti-VEGF can be sort of easy to give. But if you accidentally hit the lens and baby develops a cataract that is going to be amblyogenic even if you do cataract surgery or not. So, you really need to be very careful and know what you're doing.

Clare Gilbert: And you can make a hole in the retina, which is a disaster or introduce infection. So, um, I think it's time for us to now start to wrap up unless and if you've got anything really pressing you'd like to say? No? So thank you so much. I think we've had a very interesting discussion and we covered a wide range of different topics and I look forward to seeing you all again in person. Once the COVID pandemic is no longer blighting our lives. So bye all. Thank you.

All panellists: [Bye]