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# Statement of the German Society of Ophthalmology, the German Retina Society, and the Professional Association of German Ophthalmologists on anti-VEGF therapy of retinopathy of prematurity

Released: 18 May 2020

## Long text

## 1. Introduction and definitions

The purpose of this statement is to assess the clinical evidence on the use of intravitreal injection of the VEGF inhibitors bevacizumab (Avastin®, Roche, Basel, Switzerland), ranibizumab (Lucentis®, Novartis, Basel, Switzerland), and aflibercept (Eylea®, Bayer, Leverkusen, Germany) for the treatment of ROP. Since there are virtually no clinical data on the use of other VEGF-inhibiting drugs than the ones listed above, no conclusions can be drawn in the current statement in this regard.

Of the three drugs discussed here, only ranibizumab at a dose of 0.2 mg is approved for the treatment of ROP. Bevacizumab and aflibercept represent off-label use in ROP, with aflibercept being in a phase III trial that could result in a widening of its indication in the future. A considerable amount of clinical data are now available on functional outcome, long-term course, and possible local and systemic adverse effects of bevacizumab and ranibizumab, whereas there are fewer data on aflibercept.

A major difference between the three drugs is that bevacizumab and aflibercept have a longer systemic half-life following intravitreal administration compared to ranibizumab. There is evidence that bevacizumab and aflibercept suppress systemic VEGF activity, measured in peripheral blood, over several months after a single intravitreal injection for ROP [9, 11]. This appears not to be the case for ranibizumab due to its significantly shorter systemic half-life [3, 22, 23]. This is important for the assessment of the treatment's systemic safety profile since systemic VEGF suppression, theoretically at least, can affect VEGF-dependent processes of tissue and organ maturation, such as neurogenesis and lung maturation (see Sect. 4.3). However, there are no data as yet that unequivocally demonstrate a negative effect of this kind under systemic VEGF suppression.

Irrespective of the choice of drug, the general weighing-up between anti-VEGF therapy and laser therapy is an important fundamental decision in the treatment of ROP. This treatment decision should only be made following a thorough consideration of the arguments in relation to the individual patient, in close liaison with the treating neonatologist, and after providing the parents with detailed information and obtaining their informed consent. The willingness and ability of the parents to participate in long-term follow-up after possible anti-VEGF therapy also needs to be taken into considera-

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The European Foundation for the Care of Newborn Infants (EFCNI, Munich; Silke Mader, Dr. rer. nat. Johanna Pfeil) was invited to comment as patient representative, and their comments were taken into consideration when writing the guideline.

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## Key messages

1. Treatment criteria
The need-to-treat criteria for retinopathy of prematurity (ROP) are independent of the planned treatment modality. Examinations should be carried out in line with the current specialist societies' guideline [27]. Anti-VEGF therapy for ROP should only be carried out at centers that also have the option to perform ROP treatment using laser coagulation.
2. Stage-dependent therapy
ROP up to stage 3 with plus disease requiring treatment [27] should undergo either laser therapy or anti-VEGF therapy. For ROP in zone I and aggressive posterior ROP (AP-ROP), there is evidence that anti-VEGF therapy is superior to laser therapy. Anti-VEGF therapy should not be performed for stage 4 and 5 ROP, since this can induce increased vitreoretinal traction in some cases.
3. Combination and sequential therapy
Simultaneously combined anti-VEGF therapy and laser therapy should not be performed as the first-line treatment for ROP. However, a sequential approach may be beneficial, e.g., laser therapy in the case of reactivation following an initial response to anti-VEGF therapy or laser treatment of residual avascular retinal areas following anti-VEGF therapy.
4. Insufficient response and reactivation
In the case of insufficient response to anti-VEGF therapy, no further anti-VEGF drug should be administered within the first 4 weeks in order to prevent an accumulation of VEGF inhibitors and the resultant risk of increased systemic exposure. In such cases, laser therapy can be considered if treatment criteria are still met. In the case of ROP reactivation following an initially good response, retreatment should be performed if the treatment criteria [27] are met once again, with both repeat anti-VEGF therapy and repeat laser therapy being possible.
5. Drugs and dosage
Only ranibizumab 0.2 mg (40% of the adult dose) is approved for the treatment of ROP. The smallest doses tested to date in prospective studies on ROP and described as effective are 0.004 mg (0.3% of the adult dose) for bevacizumab [24] and 0.1 mg (20% of the adult dose) for ranibizumab [23]. There is only limited evidence to date for the efficacy of aflibercept in ROP. It is important to bear in mind when selecting the drug that the effect of ranibizumab on systemic VEGF activity is significantly lower compared to bevacizumab and aflibercept, which possibly reduces the risk of potential adverse systemic effects in preterm infants [22, 23]. Doses higher than 50% of the adult dose of a VEGF inhibitor have not been sufficiently investigated in studies and should not be used.
6. Patient information and treatment procedure
Anti-VEGF therapy for ROP is an invasive treatment with potential adverse ocular and systemic effects. Therefore, thorough patient information, including written informed consent from the parents, as well as close liaison with the treating neonatologists are essential. To the extent that the infant's health permits, intravitreal injection should be performed by taking into account the relevant statement of the specialist societies [10], in particular the recommendations on a sterile environment. Due to the possible risk of iodine-induced hypothyroidism, this substance should be avoided for the disinfection of the eyelids and periocular skin (alternative: octenidine 0.1% without phenoxyethanol). The conjunctiva should also be disinfected with either an iodine-free product (e.g., polihexanide) or with povidone-iodine. The intravitreal injection can be performed under eye drop anesthesia, sedation, or endotracheal anesthesia. A 30- or 31-gauge hypodermic needle not longer than 13 mm should be used. Depending on the size of the infant, the intravitreal injection should be performed at a distance of 1.0–2.0 mm from the limbus (usual case: 1.5 mm). Due to the larger lens relative to the eyeball in infants compared to adults, it is important to ensure an injection angle aiming at the posterior pole.
7. Follow-up
Follow-up with dilated fundoscopic retinal examination should be performed at least once in the first 4 days following intravitreal injection, in particular to exclude treatment complications such as endophthalmitis, lens damage, and retinal detachment. Thereafter, further regular and long-term follow-up examinations should be performed to monitor the treatment effect and screen for possible ROP reactivation [27]. In order to ensure uninterrupted follow-up after therapy, all relevant treatment and follow-up data should be transferred in writing. The ROP passport shown in **Fig. 1** can be used for this purpose (**Fig. 1**).

tion (see Sect. 4.1). To enable free choice of the best possible treatment option for the individual patient, and since adjunctive laser therapy is sometimes necessary following anti-VEGF therapy, only specialized centers that additionally have the facilities and sufficient experience to perform laser treatment for ROP should perform anti-VEGF therapies.

### 1.1 Classification of ROP

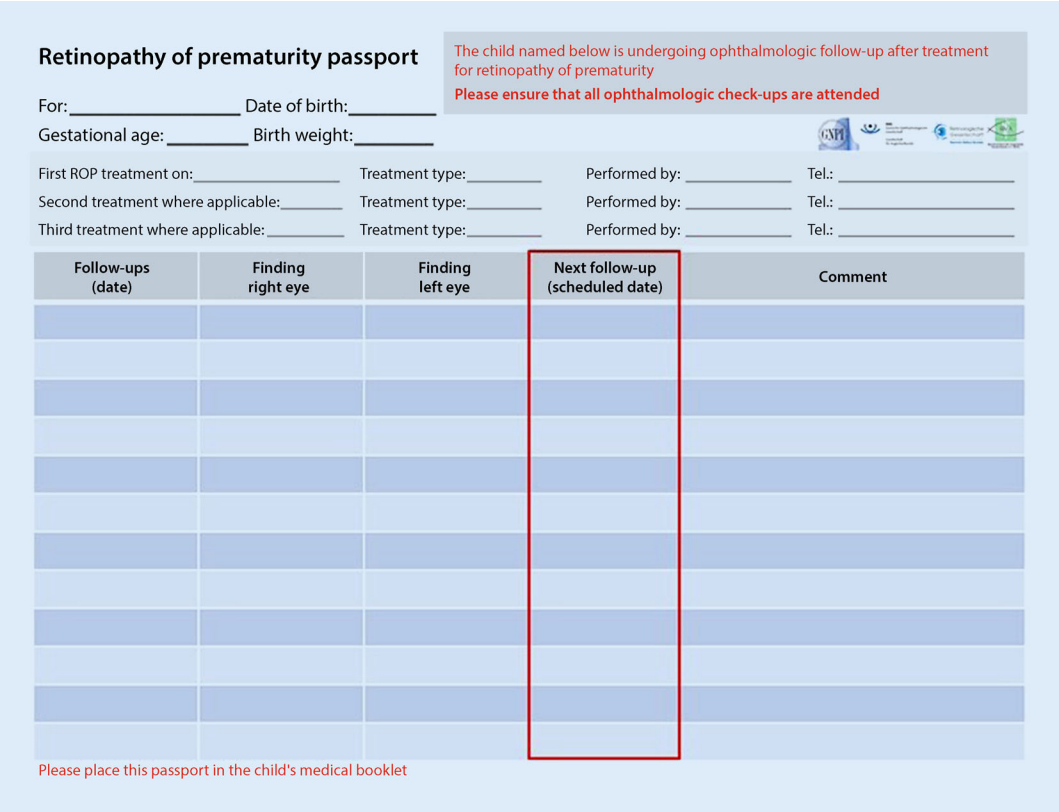
The classification of ROP (zones and stages), as well as the definition of plus disease and AP-ROP, is based on the most recent version of the International Classification of Retinopathy of Prematurity (ICROP), currently the revised 2005 version [19]. A newly revised version is currently in preparation.

### 1.2 Need for treatment of ROP

The need-to-treat criteria for ROP are defined in the most recent version (2020) of the guideline on the ophthalmological screening examination of premature infants (*Leitlinie zur augenärztlichen Screening-Untersuchung von Frühgeborenen*) of the DOG, the RG, and the BVA under the auspices of the German Society for Neonatology and Pediatric Intensive Care Medicine (*Gesellschaft für Neonatologie und Pädiatrischer Intensivmedizin*, GNPI) [27].

### 1.3 BEAT-ROP study

Based on a series of case reports and uncontrolled case series, the study "Bevacizumab eliminates the angiogenic threat of retinopathy of prematurity" (BEAT-ROP) investigated, for the first time, the effect of bevacizumab compared to conventional laser therapy in 150 infants in a prospective and randomized design. Here, recurrence rates following a single treatment were investigated up to a postmenstrual age of 54 weeks [16]. The study showed a statistically significant advantage for bevacizumab therapy compared to laser therapy (recurrence rate 6% vs. 42%) in ROP in zone I, whereas no statistically significant difference was seen in ROP in posterior zone II. Functional


Retinopathy of prematurity passport

The child named below is undergoing ophthalmologic follow-up after treatment for retinopathy of prematurity

Please ensure that all ophthalmologic check-ups are attended

For:_____ Date of birth:_____

Gestational age:_____ Birth weight:_____

First ROP treatment on:_____ Treatment type:_____ Performed by:_____ Tel.:_____

Second treatment where applicable:_____ Treatment type:_____ Performed by:_____ Tel.:_____

Third treatment where applicable:_____ Treatment type:_____ Performed by:_____ Tel.:_____

| Follow-ups (date) | Finding right eye | Finding left eye | Next follow-up (scheduled date) | Comment |
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Please place this passport in the child's medical booklet

**Fig. 1** ◀ Retinopathy of prematurity (*ROP*) passport to be placed in the personal child health record or in the follow-up care passport for preterm infants

data from the follow-up of infants treated in the BEAT-ROP cohort reveal a reduction in the development of ROP-related myopia following treatment with bevacizumab compared to laser therapy ([6], see Sect. 4.4).

## 1.4 CARE-ROP study

The study "Comparing Alternative Ranibizumab Dosages for Safety and Efficacy in Retinopathy of Prematurity" (CARE-ROP) investigated the treatment of ROP with ranibizumab at two different doses, 0.2 mg and 0.12 mg, in a prospective, blinded and randomized design [22]. The rationale for choosing ranibizumab as the anti-VEGF drug was its significantly shorter systemic half-life and, as a result, the potentially reduced risk of negative systemic effects compared to bevacizumab [3, 12]. In addition, with 0.2 mg (40% of the adult dose) and 0.12 mg ranibizumab (24% of the adult dose), lower doses than in the BEAT-ROP study (0.625 mg bevacizumab, 50% of the adult dose) were investigated.

The primary endpoint of the CARE-ROP study was treatment success at 24 weeks after treatment. Both study arms had high success rates (93% and 94%, respectively) for all patients treated according to protocol. However, disease reactivation was also seen following treatment, which was treated by re-injection of the study drug as permitted by the study protocol. The extent of residual peripheral avascular retinal areas was assessed in only a portion of eyes due to poor accessibility to examination. Neither of the two study arms (0.12 mg and 0.2 mg) showed suppression of systemic VEGF levels as a result of treatment. Data on follow-up at 1, 2, and 5 years are pending.

## 1.5 RAINBOW study

The study "Ranibizumab Compared with Laser Therapy for the Treatment of Infants Born Prematurely with Retinopathy of Prematurity" (RAINBOW) was a prospective controlled study conducted by Novartis to compare ranibizumab at two different doses (0.1 mg and 0.2 mg) with laser therapy for the treatment of ROP [23]. The study recruited 225 children with ROP requiring treatment worldwide. The inclusion criteria were very broad and included ROP 1+, 2+, and 3± in zone I, ROP 3+ in zone II, and AP-ROP, and are in line with the German criteria for the indication to treat ROP. The percentage of eyes with ROP in zone I was 38% and 62% in zone II. Although photo documentation of retinal findings was not mandatory, it was carried out for the majority of eyes.

The results of the RAINBOW study at 24 weeks post therapy revealed treatment success in 80% of infants treated with 0.2 mg ranibizumab, 75% of those treated with 0.1 mg ranibizumab, and 66% of those treated with laser. For ROP in zone I, the success rates in the three treatment arms were 68%, 70%, and 61%, while for zone II they were 88%, 78%, and 69%. The overall lower success rates compared to the CARE-ROP study may be due to the different standards in neonatal intensive care in a global study on the one hand, and the definition of success criteria on the other. Treatment was only deemed successful if the treated patients: (i) survived until the primary endpoint

**Table 1** Comparison of the advantages and disadvantages of laser and anti-VEGF therapy. (Table modified from the CME article *Therapie der Frühgeborenen-Retinopathie* ("Treatment of retinopathy of prematurity") by Dr. M. Grundel [28])

| | | |
|---|---|---|
| Laser therapy | Advantages | No intraocular surgery and, thus, no risk of endophthalmitis<br>Definitive treatment usually achieved with one treatment session |
| | Disadvantages | Time-consuming intervention that generally needs to be performed under anesthesia<br>High level of expertise required of the treating physician<br>Longer time until onset of treatment effect<br>Irreversible destruction of the lasered retinal area and possibly impaired visual fields |
| Anti-VEGF therapy | Advantages | Short treatment duration<br>Can also be performed without general anesthesia<br>Normal retinal vascularization can continue to grow, thereby potentially avoiding visual field impairment<br>Lower risk of ROP-associated high myopia |
| | Disadvantages | Risk of endophthalmitis<br>Effect diminishes with time, repeat injections or secondary laser therapy needed in the case of ROP reactivation<br>Late recurrences are possible, making long-term regular follow-up exams necessary |

(24 weeks post treatment), (ii) had no active ROP present at the primary endpoint, (iii) had received no treatment apart from the study treatment, and (iv) had no negative structural outcomes to the retina. These negative structural outcomes included, e.g., macular distortion (macular dragging, macular fold), as well as other changes that can affect eyesight, such as retinal detachment (ROP stages 4 and 5) and retrolental membranes. The likelihood of treatment success according to these criteria was statistically 2.19-fold higher for treatment with 0.2 mg ranibizumab compared to laser therapy (odds ratio). The 95% confidence interval for this value was 0.99–4.82 and the *p*-value was 0.051. Thus, the study narrowly missed the predefined *p*-value of 0.05 for statistical significance to demonstrate the superiority of ranibizumab compared to laser therapy.

The results of the RAINBOW study led to the approval in September 2019 of ranibizumab at a dosage of 0.2 mg for the treatment of ROP stages 1+, 2+, 3± in zone I, ROP 3+ in zone II, and AP-ROP, i.e., all stages deemed to require treatment by the German ROP guideline. Since the RAINBOW study also permitted reinjection for disease reactivation requiring treatment, such reinjection is likewise covered by the approval after a treatment-free interval of at least 28 days.

As previously found in the CARE-ROP study, the RAINBOW study found no measurable suppression of systemic VEGF levels following treatment with ranibizumab. Neither study measured VEGF levels in all patients. In some cases, low VEGF levels below the limit of detection were found even before injection. Data on ophthalmological and pediatric follow-up at 1, 2, and 5 years are pending.

### 1.6 FIREFLEYE study

The Aflibercept for Retinopathy of Prematurity—Intravitreal Injection versus Laser Therapy (Firefleye) study, which is currently in the recruitment phase, is a phase III trial being conducted by Bayer on the treatment of ROP with aflibercept compared to laser therapy. A total of 113 children will be included worldwide. The indication to treat includes all those stages that were included in the RAINBOW study, as well as stage 2+ in zone II, which, according to data from the ETROP study, can also be an indication for treatment [4]. Results of the Firefleye study are not yet available.

## 2. Treatment recommendations

With regard to the type of therapeutic intervention, no universally valid recommendation can be made on the choice between laser and anti-VEGF therapy. In each individual case, the advantages and disadvantages of the two treatment options need to be weighed up taking into account the situation of the individual infant (◘ **Table 1**).

### 2.1 ROP in zone II (stage 3+)

Stage 3+ ROP in zone II is by far the most prevalent treatment indication in Germany [13, 25]. Zone II is divided into the posterior (central) and anterior (peripheral) zone II, with the border between anterior and posterior zone II defined as a line around the optic disc with a radius equal to three times the distance between optic disc and fovea. In the BEAT-ROP and CARE-ROP studies, children with zone II disease were only included if ROP was localized in posterior zone II [16, 22]. Although in the BEAT-ROP study there was a trend in favor of bevacizumab therapy in terms of the recurrence rate in posterior zone II, there was no statistical difference between bevacizumab and laser therapy, meaning that both treatment modalities can be considered as equally effective with regard to the frequency of recurrence.

The RAINBOW study made no distinction between posterior and anterior zone II. The results of the RAINBOW study show a higher rate of successful treatment for 0.2 mg ranibizumab (88% treatment success) versus laser therapy (70% treatment success) for stage 3+ ROP in zone II. The reasons for the low success rate with laser therapy compared to other studies is due, at least in part, to the strict definition of treatment success, which additionally deemed the presence of unfavorable structural changes, among other things, as failure (even in the presence of an otherwise controlled disease activity).

### 2.2 ROP in zone I (stage 1+, 2+, and 3±)

Zone I ROP differs from zone II ROP in that it responds less well to laser therapy, with a significantly higher rate of insufficient treatment response or reactivation after therapy, and is possibly even based on different underlying disease processes.

In contrast to posterior zone II, the BEAT-ROP study revealed a significantly lower recurrence rate for zone I after bevacizumab therapy compared to laser coagulation (6% vs. 42%).

The RAINBOW study found a trend towards higher rates of successful treatment with ranibizumab compared to laser (68% vs. 61%), but this did not reach statistical significance ($p = 0.051$). A direct comparison of success rates between bevacizumab and ranibizumab is not possible since the inclusion criteria as well as the endpoints were very differently defined. For example, the BEAT-ROP study included only stage 3 disease, whereas the RAINBOW study additionally included all stages in zone I with plus disease, as well as stage 3 in zone I without plus disease and AP-ROP.

One must bear in mind that laser therapy in zone I destroys large areas of the retina, areas that are then transformed into non-functioning scar tissue. Anti-VEGF therapy, on the other hand, enables continued vascularization of the peripheral retina and thus, theoretically at least, the formation of functional neuronal tissue. Analyses of the German Retina.net-ROP registry show that anti-VEGF therapy has become the almost exclusively used treatment of choice for zone I ROP and AP-ROP [25].

### 2.3 Stage 4–5 ROP

Anti-VEGF therapy should not be performed in advanced stages of ROP with tractional retinal detachment (stages 4 and 5), since a number of case reports have described the development of severe tractional vitreoretinopathy with increased retinal detachment after anti-VEGF therapy in such situations, much like the known effect of intravitreal VEGF inhibition for proliferative diabetic retinopathy with tractional changes. Instead, particularly in stage 4, surgical treatment by means of scleral buckling surgery or vitrectomy performed at specialized centers can be beneficial.

## 3. Treatment procedure

### 3.1 Parent information

Anti-VEGF treatment of ROP is an intraocular procedure that carries a risk for adverse ocular and systemic effects. Therefore, it should only be performed following a thorough informed consent process. The informed consent conversation should include the following: injection-related risks of the treatment such as endophthalmitis, advantages and disadvantages of anti-VEGF vs. laser therapy, differences between the anti-VEGF drugs, treatment procedure, and the need for regular follow-up. Care should be taken to use layman's terms and ensure parents understand the difficult subject matter.

### 3.2 Drugs

Ranibizumab is currently the only drug approved for the treatment of ROP. Its efficacy has been proven in prospective studies [22, 23]. In most cases, a single intravitreal injection is sufficient. However, in cases of disease reactivation, repeated intravitreal injections are required.

Bevacizumab's efficacy for ROP has also been proven in prospective studies [16]. However, its use in ROP is off label. This aspect needs to be taken into account in the informed consent process. There is also evidence of efficacy for other VEGF inhibitors in ROP, such as aflibercept; however, the results of larger prospective studies are pending. The various drugs differ in terms of their pharmacokinetic properties (see Sect. 4.3).

### 3.3 Dosage

Ranibizumab is approved for the treatment of ROP at a dose of 0.2 mg in 0.02 ml (equivalent to 40% of the adult dose), which proved effective in the RAINBOW and CARE-ROP studies [22, 23]. According to the product information, a specially developed hypodermic syringe (Visisure®, Novartis) should be used to enable precise measurement of the small injection volume.

Bevacizumab has been used at a dose of 0.625 mg in 0.025 ml (50% of the adult dose) to treat ROP in the majority of studies to date, e.g., the BEAT-ROP study [16]. In a dose de-escalation study on bevacizumab therapy in ROP, an initial treatment response was seen even at a dose of 0.004 mg (0.3% of the adult dose) in 90% of treated eyes [24]. There are no long-term follow-up data for this dose as yet. These results suggest that the optimal dose of bevacizumab for ROP is possibly significantly lower than 0.625 mg. Doses higher than 0.625 mg bevacizumab (50% of the adult dose) or 0.20 mg ranibizumab (40% of the adult dose) should not be used in order to avoid increasing the potential risk of adverse systemic effects.

### 3.4 Anesthesia

The intravitreal injection can be performed under local anesthesia, sedation, or endotracheal anesthesia, always under the supervision of an anesthesiologist or neonatologist.

### 3.5 Disinfection

In line with the recommendations of the specialist societies on performing intravitreal injections, and if the infant's general condition permits, anti-VEGF therapy should be performed in an operating room or procedure room in order to reduce the risk of endophthalmitis [10]. Povidone-iodine can induce hypothyroidism in preterm neonates due to increased iodine absorption [1, 26]. Possible neurotoxic effects in preterm neonates have been discussed in relation to the phenoxyethanol in Octenisept® (Schülke & Mayr, Norderstedt, Germany) [26]. Therefore, disinfection of the eyelid and periocular skin should be performed using iodine-free disinfectant agents (e.g., octenidine 0.1% without phenoxyethanol) instead of povidone-iodine. Octenidine can be obtained from the manufacturer of Octenisept® and prepared in pharmacies as a 0.1% solution.

The conjunctiva should also be disinfected either with iodine-free substances (e.g., polihexanide) or with povidone-iodine. The comparatively low iodine exposure due to the small mucosal surface, the short duration of exposure when rins-

ing, as well as the proven good efficacy of povidone-iodine support the use of this antiseptic agent in the disinfection of the conjunctiva. Sufficient evidence for a recommendation is not available. The decision on disinfection should be taken in consultation with the treating neonatologist, not least to give them the opportunity to postoperatively monitor thyroid values in the case that povidone-iodine is used.

### 3.6 Distance from the limbus

For injections in the studies published to date, a distance of 1.0–2.0 mm from the limbus was used and is considered a good guidance for safe intravitreal injection in preterm infants. Since the width of the pars plana increases significantly in the final trimester with both age and axial length [7], the postmenstrual age and maturity of the individual infant needs to be taken into consideration in the context of the abovementioned limits when choosing the distance from the limbus. When measuring the donor eye of a preterm infant with a PMA of 36 + 1 week, 1.5–2.0 mm from the limbus was shown to be the ideal area for injection [12]. This value may be lower in younger preterm infants. In most cases, with the possible exception of very young or very old preterm infants, 1.5 mm is a good guidance for injections. Determining the distance by means of transillumination is also possible [18]. For injection, a 30- or 31-gauge injection needle not longer than 13 mm should be used. The fundus should be checked immediately after anti-VEGF therapy.

### 3.7 Simultaneous combination of laser and anti-VEGF therapy

Although individual case studies report positive effects for combination treatment comprising laser and anti-VEGF therapy, no comparative conclusions can be drawn in relation to monotherapy due to the lack of controls. However, since suitable monotherapy with either laser or anti-VEGF therapy usually achieves adequate treatment success in the majority of cases, simultaneous combination therapy to increase the treatment effect is generally not necessary. Moreover, combination therapy would also combine the disadvantages of the two monotherapies, in particular the peripheral retinal damage caused by laser and the potential adverse systemic effects of anti-VEGF therapy. Since laser therapy results in temporary disruption of the outer blood–retinal barrier, there is also speculation that combination therapy could potentially cause increased leakage of VEGF inhibitors into the circulation, accompanied by an increased risk of adverse systemic effects. Therefore, until relevant study results are available, the simultaneous combination of laser and anti-VEGF therapy, especially as a first-line treatment for ROP, does not appear to be advisable, as compared to monotherapy, based on the theoretical considerations discussed above. However, a sequential approach can be beneficial, e.g., laser therapy in the case of reactivation after an initial response to anti-VEGF therapy or laser treatment for residual avascular areas of the retina following anti-VEGF treatment.

## 4. Follow-up and long-term sequelae

### 4.1 Follow-up

In order to exclude treatment-related complications following anti-VEGF therapy, at least one follow-up examination should be performed in the first 4 days following injection. Since anti-VEGF therapy is an intraocular procedure, particular attention needs to be paid during this follow-up examination to signs of endophthalmitis. A handheld slit lamp can be used to evaluate anterior chamber reaction. In addition, intraocular pressure and retinal perfusion should be checked, at least as a guide, and lens damage and retinal detachment ruled out by means of dilated fundoscopy.

Thereafter, further regular and long-term follow-up visits should take place to monitor treatment effect with disease regression and to screen for possible late reactivation of ROP. Reactivation of this kind can occur far later following anti-VEGF therapy than after laser therapy and has been described up to a postmenstrual age of 69 weeks and 35 weeks following anti-VEGF therapy [8, 15]. The duration and frequency of follow-up visits should be guided by the clinical findings and are defined in the updated 2020 version of the specialist societies guideline on ROP screening [27]. In order to ensure uninterrupted follow-up, all relevant treatment and follow-up data, including the recommended time for the next follow-up visit, should be provided to the parents in writing. The ROP passport shown in **Fig. 1** can be used to this end. The parents should be made aware of the importance of continued follow-up visits as scheduled.

### 4.2 Treatment for insufficient regression or reactivation of ROP

When assessing ROP requiring retreatment following previously completed therapy, a distinction needs to be made between insufficient response to the primary therapy with insufficient regression of ROP and reactivation of ROP following an initially good response to primary therapy.

In the case of insufficient regression of ROP following primary therapy, secondary treatment should be performed. Following primary anti-VEGF therapy, one needs to decide whether, depending for instance on the interval since the previous injection, repeat anti-VEGF therapy or a switch to a different form of treatment is preferrable. Reinjection within 28 days should only be performed if there is doubt regarding whether the initially administered drug dose reached the vitreous cavity and remained there in a large enough quantity [2]. In all other cases, no repeat anti-VEGF therapy should be performed within 28 days, but rather laser therapy to prevent an accumulation of the VEGF inhibitors and the resultant risk of increased systemic exposure. Following primary laser therapy, secondary treatment can consist of extending laser therapy to as yet insufficiently coagulated avascular areas or, particularly if the maximum extent of laser coagulation has already been performed, secondary anti-VEGF therapy.

In the case of disease reactivation following an initially good response to primary therapy, secondary treatment

should be performed as soon as the need-to-treat criteria [27] have been met once again. Secondary treatment following primary anti-VEGF therapy can comprise either laser therapy or, if the last intravitreal injection was performed more than 28 days previously, repeat anti-VEGF therapy. According to the ranibizumab product information, up to three intravitreal injections per eye can be performed within 6 months. A reactivation of ROP following laser therapy and temporarily stable retinal findings is unusual. Cases of this kind are more likely to be due to smoldering disease activity, i.e., disease activity that never completely abated. Additional anti-VEGF therapy should be carried out in such cases, especially if maximum laser coagulation has already been performed.

### 4.3 Neurological development

Bevacizumab and aflibercept suppress systemic VEGF levels for several months following intravitreal injection therapy for ROP [9, 11]. The effect of ranibizumab on systemic VEGF activity is significantly less pronounced compared to bevacizumab and aflibercept [3]. Since organ development in the preterm infant may be VEGF dependent, possible risks for developmental disorders due to VEGF suppression following intravitreal anti-VEGF therapy are being discussed, but have so far not been demonstrated. In retrospective studies to compare the neurological development of bevacizumab- and laser-treated preterm infants [14, 17], the baseline parameters in the two treatment groups differ so significantly that a comparison of treatment results is not feasible. Prospective controlled studies on this subject are not available. Therefore, given the current lack of evidence, it is left to the practitioner to decide to what extent he/she takes into account the potential risk to neurological development in his/her selection of an anti-VEGF drug.

### 4.4 Myopia development

ROP is associated with a significantly increased risk for the development of high myopia and a correlation is seen between the severity of ROP and myopia [20]. Myopia associated with ROP is generally not axial myopia, but is instead associated with a steeper corneal radius and greater lens thickness, possibly due to malformation of the anterior segment of the eye [5]. Although ablative treatment of avascular retinal areas can effectively treat ROP, it has no effect (neither positive nor negative) on the development of myopia [21]. Bevacizumab treatment, in contrast, not only had a positive effect on ROP, but also significantly reduced myopia development [6]. Despite the fact that ROP-related myopia is generally not associated with increased axial length, this type of high myopia still has negative sequelae, such as, e.g., dependence on glasses and possible development of amblyopia, meaning that this positive aspect of anti-VEGF therapy on high myopia development should be taken into account when deciding which ROP treatment modality to select.


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Prof. Dr. med. Armin Wolf, Ulm


## Compliance with ethical guidelines

**Conflict of interest.** See **Table 2** in the Appendix.

For this article no studies with human participants or animals were performed by any of the authors. All studies performed were in accordance with the ethical standards indicated in each case.


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## Appendix

### Appendix

Declarations of interests are summarized in **Table 2**, as are the results of the assessment of conflicts of interests and the measures that were decided upon and implemented following discussion of the issues during the consensus conference.

**Table 2** Declaration of interests and handling of conflicts of interest

| | Consultancy, expert opinion | Paid employment in a scientific advisory board | Paid lecture or training activities | Paid authorship or coauthorship | Research projects/clinical trial implementation | Ownership interests (patent, copyright, shareholding) | Indirect interests | Topics in the statement affected by COI, classification in terms of relevance, consequence |
|---|---|---|---|---|---|---|---|---|
| Dr. Teresa Barth | No | Novartis | No | No | CARE-ROP study | No | DOG, DKVB | Moderate |
| Prof. Bernd Bertram | Care administration in North Rhine-Westphalia, advisory committee of the North Rhine Medical Association | No | No | No | No | No | North Rhine Medical Association: member of the board, member of the committees Professional Code, Medical Fee Schedule, Cooperation of the Health Professions and Healthcare Sectors, delegate to the German Medical Assembly, North Rhine Association of Statutory Health Insurance Physicians: member of the Assembly of Representatives, deputy member of the Expert Advisory Committee Specialist Physicians in the Federal Association of Statutory Health Insurance Physicians, second chairman of the Professional Association of German Ophthalmologists (BVA), member of the presidium of the German Ophthalmological Society, spokesman of the DOG and BVA Guideline Commission, spokesman of the DOG and BVA Ophthalmological Rehabilitation Commission, spokesman of the DOG and BVA Macula Commission, spokesman of the DOG and BVA Commission for Training and Continuing Education, expert in the Working Group of the Joint Federal Committee: Visual Aids, OCT, Corneal Cross-Linking | None |
| Prof. Nicolas Feltgen | Bayer, Roche | Roche | Bayer, Novartis, Roche, Allergan, Almera, Heidelberg | – | Bayer, Novartis, Apellis Roche, Chengdu Kanghong | Bayer, Roche | Board of the German Retina Society, member of the DOG Presidium, BVA | Low |

**Table 2** (Continued)

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Prof. Ulrich Kellner | Grünenthal, Roche | Bayer Health | – | – | Bayer Health, Novartis, Samsung | – | Memberships: German Ophthalmological Society (DOG), German Retina Society (RG), Professional Association of German Ophthalmologists (BVA) subject/related to the GL: YES; German Association of Ophthalmic Surgeons (Chairman), Association for Research in Vision & Ophthalmology, International Society for Clinical Electrophysiology of Vision, International Society for Genetic Eye Disease and Retinoblastoma, Pro Retina Deutschland e. V. (Scientific & Medical Advisory Board) | Low |
| Prof. Tim U. Krohne | Roche | Alimera, Novartis | Alimera, Allergan, Bayer, Novartis, Roche | – | Bayer, Novartis | – | German Ophthalmological Society (DOG), Association of Research in Vision and Ophthalmology (ARVO), Professional Association of German Ophthalmologists (BVA), European Society of Retina Specialists (EURETINA), German Retina Society (RG), Federal Association of German Ophthalmic Surgeons (BDOC) | Moderate |
| Prof. Wolf Lagréze | Boehringer Ingelheim | Boehringer Ingelheim | Santhera | – | – | – | Membership: DOG, BVA, EUNOS, Bielschowsky Society, ARVO, ISER | None |
| Prof. Birgit Lorenz | – | Novartis | Novartis | – | – | – | Member: BVA, DOG; Pro Retina Scientific Advisory Board, Pro Retina Working Group on Clinical Issues | Low |
| PD Dr. Amelie Pielen | Roche Pharma AG, Novartis Pharma GmbH | Novartis Pharma GmbH, Bayer AG | Bayer AG, MVZ der Klinik Dardenne GmbH, Bayer VITAL GmbH, ADCD Augen Diagnostik & Congresse Detmold GmbH, Novartis Pharma GmbH, Sanofi-Aventis Deutschland GmbH, BVA, Pharm Allergan GmbH | Novartis Pharma GmbH, Bayer AG | Novartis Pharma GmbH, Roche, Chengdu Khanghong, Boehringer Ingelheim, Bayer, Bioeq | – | German Ophthalmological Society (DOG), Professional Association of German Ophthalmologists (BVA), German Retina Society (RG), Association of North German Ophthalmologists | Moderate |
| Prof. Andreas Stahl | – | Novartis, Bayer | Allergan, Bayer, Novartis | – | Novartis, Bayer | – | Member of the DOG, member of the board of the German Retina Society (RG) | Moderate |
| Prof. Armin Wolf | Novartis, Bayer | Novartis, Bayer, Alimera | Novartis, Bayer | Novartis, Bayer | Novartis, Bayer | – | DOG and BVA Member | Moderate |

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