REVIEW ARTICLE

Screening and Treatment in Retinopathy of Prematurity

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SUMMARY

Background: More than 11 000 children are examined for possible retinopathy of prematurity in Germany each year, and 2–5% of them are treated for it. Even though screening and treatment programs are in place, the affected children can still suffer visual impairment.

Methods: In this article, we summarize the pathogenesis, screening, and treatment of retinopathy of prematurity on the basis of a selective review of pertinent literature, retrieved by a PubMed search. The article centers on publications from 2011 to 2015 on the new option of treatment with VEGF inhibitors and discusses it in comparison to laser therapy.

Results: All premature neonates with a low gestational age at birth, low birth weight, or prolonged exposure to supplemental oxygen must undergo screening by an ophthalmologist. Laser therapy is effective for stages 1–3 and for aggressive posterior retinopathy of prematurity. Its disadvantages are the induction of scarring and the development of severe myopia in 17–40% of the children so treated. Anti-VEGF treatment (VEGF = vascular endothelial growth factor) does not induce any visible scarring and seems to cause less myopia, but long-term data on safety, dosing, and the choice of anti-VEGF drug are still lacking.

Conclusion: The available evidence for anti-VEGF treatment is on a much lower level than the evidence for laser therapy. Anti-VEGF may be a way to avoid the disadvantages of laser therapy (scarring and severe myopia). Unlike laser therapy, however, the intravitreal injection of VEGF inhibitors may suppress systemic VEGF levels and potentially harm the developing brain, lungs, or other organs. The currently open questions about anti-VEGF treatment concern its dosing, choice of drug, and long-term safety.

► **Cite this as:**

Stahl A, Göpel W: Screening and treatment in retinopathy of prematurity. *Dtsch Arztebl Int* 2015; 112: 730–5. DOI: 10.3238/arztebl.2015.0730

Ophthalmologic screening for retinopathy of prematurity was performed 11 758 times in Germany in 2014 (1). 242 children (2% of those screened) were found to need treatment. Comparable data from the Retina.net ROP (Retinopathy of Prematurity) registry of the German Retinological Society (*Deutsche Retinologische Gesellschaft*) from the years 2011–2013 revealed a roughly 5% incidence of retinopathy of prematurity needing treatment. Even if the absolute numbers seem low, it must be emphasized that, for every affected child, the quality of vision for the rest of his or her life hangs in the balance. The permanent impairment of quality of life that can be prevented by the timely recognition and treatment of this condition is greater than that of all but a few other eye diseases (2). If untreated, retinopathy of prematurity can render both eyes totally blind; even in less severe cases, central visual acuity often remains markedly impaired.

The definitively identified epidemiologic risk factors for retinopathy of prematurity are gestational age at birth, birth weight, and the duration and intensity of post-natal supplemental oxygen therapy (3, 4). Other postnatal factors, including treatment with nitric oxide (NO), slow weight gain, and low systemic levels of insulin-like growth factor-1 (IGF-1) have also been found to be predictors of retinopathy of prematurity (5–7). The WINROP algorithm, based on the last two risk factors alone, can predict retinopathy of prematurity needing treatment several weeks before it develops, with a sensitivity of 65% (8) to 100% (9–11) and a specificity of 54% (9) to 59% (10).

The success of the WINROP algorithm illustrates the important role of IGF-1 in retinal vascular development (12). Low postnatal IGF-1 levels slow this development, which is slow in any case in the first few weeks after premature birth, when part of the retina is not yet vascularized. The possibility of IGF-1 supplementation for premature neonates in the first few weeks of life is now being studied in clinical trials (13).

Babies born at term, unlike premature neonates, have a fully vascularized retina and are no longer at risk of developing retinopathy (in the absence of other types of developmental disorder) (*Figure 1*).

Retinal vessels grow more slowly after birth than in utero, even with normal IGF-1 levels, because of the switch from placental blood oxygenation to breathing through the lungs. The retina is exposed to much higher partial pressures of oxygen after birth than in utero

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Figure 1: Retinal vascular growth in the right eye. The temporal portion of the retina is shown at left in each picture, the nasal portion at right. The small circle marks the optic nerve, and the black cross marks the fovea. During intrauterine development, the retinal vessels grow slowly outward from the optic nerve to the periphery. Only around the time of the expected due date is the retina fully vascularized (graphic on the right). Premature birth interrupts retinal vascularization; the earlier this occurs, the larger the area of the retina that blood vessels have not yet reached. The different shadings in the figure indicate the zones into which the retina is divided for the classification of retinopathy of prematurity. Zone I is a circle around the optic nerve whose radius is twice the distance from the optic nerve to the fovea; zone II is a circle around the optic nerve whose nasal portion reaches the ora serrata; zone III is the residual half-moon-shaped portion of the retina on the temporal side.

(14). The physiological tissue hypoxia that drives the growth of retinal blood vessels is reduced. VEGF, an important mediator of this process, is induced by hypoxia and expressed locally in appropriate amounts to stimulate vascular growth (15).

No treatment is yet available for early (phase I) retinopathy of prematurity—nor is it necessary in many cases, as the great majority of neonates can resume the initially delayed vascular growth, so that blood vessels reach the retinal periphery in the first few weeks of life.

Phase II retinopathy of prematurity is characterized by acceleration of physiological vascular growth a few weeks after birth. This is thought to be due to maturation of the retinal periphery leading to a greater metabolic demand (16). The ensuing tissue hypoxia in turn induces the greater expression of growth factors, including VEGF (17), that mediate a transition from slowed to newly accelerated vascular growth. This is a critical period for the development of the eye: what happens now determines whether the avascular areas in the retinal periphery will acquire functional vessels or, alternatively, the excessive expression of VEGF will induce uncontrolled growth of vessels from the retina into the vitreous body (18, 19). This largely VEGF-induced overgrowth of vessels from the retina into the vitreous body is the pathological correlate of retinopathy of prematurity that needs treatment. Increased oxygen supplementation in this critical period, with the aim of keeping VEGF expression within safe bounds, was found to be unsuccessful in a clinical trial (20).

Ophthalmologic screening and the decision to treat

The goal of ophthalmologic screening for retinopathy of prematurity is to detect the transition from phase I to phase II, i.e., the reactivation of retinal vascular growth. Screening should generally be performed from the 6th postnatal week onward, or from a post-menstrual

age of 31 weeks onward (21). Screening studies are repeated at variable intervals depending on the findings (from twice weekly to once every two weeks) until it is clear that the retinal periphery is adequately vascularized without excess vascular growth (21). In a screening study, a lid retractor is inserted under topical anesthesia, and the entire retina, including the periphery, is searched for changes that might need treatment, in all directions of gaze and with gentle pressure on the eyeball. Alternatively, wide-angle photographs of the retina can be assessed via telemedicine (22). If the telemedicine findings are suspect or uncertain, however, an ophthalmologist must perform a fundusoscopic examination.

Retinopathy of prematurity is classified into stages and zones according to internationally accepted criteria. The zones are shown in color in *Figure 1*. The stages and corresponding treatment recommendations according to the guidelines for ophthalmologic screening of premature infants in Germany (21) are listed in *Table 1*.

The “plus disease” criterion is important for the decision whether to treat or not. This consists of markedly dilated and tortuous vessels at the posterior pole of the eye that can be seen by the ophthalmologist via funduscopy. The presence of plus disease indicates high levels of angiogenic growth factors and thus a high risk of disease progression.

Even faster progression can be expected if the findings indicate aggressive posterior retinopathy of prematurity (AP-ROP). This variant of the disease, which is rare in Germany, is characterized by extremely intense vascular activation that can progress within a few days, carrying a high risk of serious complications such as retinal detachment. Stage 3+ retinopathy of prematurity is much more common than AP-ROP and is the usual indication for treatment in Germany (*Figure 2*).

TABLE 1

Staging and treatment indications in retinopathy of prematurity

Stage	Key features	Frequency [Ref. (1)]	Treatment [Ref. (18)]
1	Flat strip delimiting vascularized from avascular retina	9%	Only in zone I, in the presence of plus disease (ROP 1+ in zone I)
2	Prominent bar between vascularized and avascular retina	5.3%	Only in zone I, in the presence of plus disease (ROP 2+ in zone I)
3	Prominent bar with extraretinal vascular growth	3.8%	In zone I, with or without plus disease (ROP 3 +/- in zone I) or in zone II, in the presence of plus disease (ROP 3+ in zone II*)
4	Partial retinal detachment	0.1%	Surgery
5	Total retinal detachment	0.05%	Surgery
Aggressive posterior ROP (AP-ROP)	A special form with severe vascular changes at the posterior pole	No data	Immediate treatment is indicated (for details, see text)
Plus disease	Increased posterior vascular tortuosity and dilatation	No data	An important criterion for the decision whether to treat (see above and in the text)

For stages 1 to 3 and AP-ROP, laser therapy is well established. According to the ophthalmological societies, anti-VEGF treatment can also be considered if treatment is indicated because of disease in any of these stages affecting central zones of the retina (36). Surgery is the only possible treatment for stages 4 and 5 and usually yields a very limited functional outcome

* In Zone II, stage 3 disease must be present in at least 5 contiguous, or 8 non-contiguous, "hours" (as on a clock-face)

A finding such as that shown in *Figure 2* would be considered to necessitate treatment by the criteria of all current guidelines. The recommendations regarding the treatment of milder stages may vary from one country to another. In many English-speaking countries, for example, stage 2+ disease in zone II is recommended to be treated, according to the criteria of the ETROP study (23). The German guideline committee decided not to recommend treatment in such cases (21), as about 30% of children have a good spontaneous course even if untreated, and treatment may promote myopia (24).

Treatment modalities

The prophylactic treatment of retinopathy of prematurity consists of lessening risk factors such as long-term artificial ventilation and uncontrolled oxygen supplementation. The opportunity to do these things for extremely premature neonates is limited (25), as shown in *Table 2*.

If retinopathy of prematurity progresses further despite optimal prophylactic measures, laser coagulation is available as an established and safe treatment for most stages of the condition that require treatment, with an over 90% rate of success (i.e., of lessening disease activity) (26). Laser treatment works by destroying peripheral areas of the retina that produce growth factors and converting them into non-functional scar tissue. Thus, the more centrally the retinopathy has reached a stage that needs to be treated, the more retinal tissue must be destroyed by laser to prevent excessive VEGF expression and disease progression. The adverse effects of laser treatment include central retinal traction due to scar tissue, which can be seen in up to 15% of

treated children (26), and severe myopia in 17–40% (24, 27, 28).

Anti-VEGF treatment is a pharmacological alternative to laser therapy that has been developed in the last few years. Figures collected by the German nationwide quality-assurance program in neonatology (*Bundesweite Qualitätssicherung Neonatologie*) reveal that this method has rapidly come into widespread use. In 2013, 145 children (76%) underwent laser therapy, and 46 (24%) underwent anti-VEGF treatment; in 2014, only 108 children (45%) underwent laser therapy, while 134 (55%) underwent anti-VEGF treatment (1). These data point to the therapeutic potential of the method, but they also arouse concern, because the long-term effects of anti-VEGF treatment in premature neonates have not yet been well studied.

Unlike laser therapy, VEGF inhibition does not rely on the destruction of peripheral retinal areas to lessen the production of angiogenic growth factors; rather, VEGF (the main such factor) is directly bound and pharmacologically neutralized. VEGF inhibitors have been used successfully since 2005 to treat age-related macular degeneration (AMD) in the elderly (29–31); the initial case reports of intravitreal anti-VEGF treatment for retinopathy of prematurity appeared in 2007 (32). Anti-VEGF treatment for AMD is supported by high-level evidence from multiple randomized, controlled phase III trials; in contrast, the evidence for anti-VEGF treatment for retinopathy of prematurity is much less consistent and must be interpreted with caution.

Aside from the absence of long-term data, there have not yet been any dose-finding trials of anti-VEGF treatment in premature neonates. Based on the initial case

reports mentioned above, the administration of bevacizumab in half the adult dose has become established in the literature. Bevacizumab is an anti-VEGF antibody that was originally developed for intravenous tumor treatment and has been found very effective in the eye when given off-label to adult patients (33, 34).

The BEAT-ROP trial

Despite the absence of dose-finding trials, the first randomized controlled trial of bevacizumab for the treatment of retinopathy of prematurity (the BEAT-ROP trial) was published in 2011. Bevacizumab was given in half the adult dose. In this multicenter trial, conducted in the USA, the effect of bevacizumab was compared to that of conventional laser therapy in 150 children with retinopathy of prematurity (35). The primary endpoint was the number of recurrences that needed to be treated up to a post-menstrual age of 54 weeks, corresponding to a mean follow-up time after treatment of about 20 weeks. In this period, the patients in the bevacizumab group had a 4.3% recurrence rate, compared to 22% in the laser group. 23 of the 32 recurrences in the laser group arose in premature neonates with zone I disease; for this zone, the superiority of bevacizumab over laser therapy was statistically significant. On the other hand, there was no statistically significant difference between the two treatments in zone II. It has to be noted, however, that the recurrence rate in the laser group was substantially higher than the recurrence rates reported in other trials. Another limitation is that recurrences after VEGF treatment may occur later than the end of follow-up in this trial; in contrast, no late recurrences are expected after laser treatment, because of peripheral retinal scar formation (36, 37).

Despite these limitations, the BEAT-ROP trial yielded a number of important conclusions:

- Intravitreal anti-VEGF treatment can stop the progression of retinopathy of prematurity in over 90% of cases without inducing visible retinal scarring.
- Anti-VEGF treatment leads both to the regression of pathological vascular proliferation and to the resumption of desirable, centrifugal vascular growth into the retinal periphery.
- The main potential advantage of anti-VEGF treatment over laser therapy lies in the treatment of centrally located abnormalities.

The later course of the patients in the BEAT-ROP trial has now been documented in further publications, in which it is reported that the patients treated with VEGF inhibitors became less strongly myopic than those given laser therapy (27). High-grade myopia arose in only 2.7% of the patients in the anti-VEGF group, compared to 42% in the laser group (27). It must be pointed out, however, that no long-term data on the neurological outcome of the patients in the BEAT-ROP trial have yet been published. This is regrettable, because the intravitreal administration of VEGF inhibitors suppresses systemic VEGF levels and may thus

Figure 2: A typical finding requiring treatment in stage 3+ retinopathy of prematurity affecting the central zone II. The optic nerve is seen at right. The vessels proceeding outward from the optic nerve display the typical dilatation and tortuosity of "plus disease." Extraretinal proliferations on a prominent ridge separating vascularized and non-vascularized portions of the retina are seen at left

TABLE 2

The likelihood of retinopathy of prematurity (ROP) needing treatment as a function of gestational age

Gestational age at birth	Likelihood of ROP needing treatment (Sweden)	Likelihood of ROP needing treatment (Germany)
22 weeks	72%	33%
23 weeks	51%	23%
24 weeks	15%	17%
25 weeks	17%	7%
26 weeks	6%	4%

Epidemiologic data reveal that extremely premature neonates have a high rate of retinopathy requiring treatment. Swedish data from (22); German data from the German Neonatal Network, 2009–2014

potentially harm the developing brain, lungs, or other organs (38).

Thus, the current state of anti-VEGF treatment for retinopathy of prematurity can be summarized as follows: On the one hand, the trials published to date document its high efficacy, with the potentially greatest advantage in the treatment of abnormalities in central retinal areas, where laser therapy can cause broad scarring and, over the long term, myopia. On the other hand, laser therapy is a well-established, effective, locally restricted treatment, while the intravitreal administration of VEGF inhibitors may have systemic effects and long-term data are not yet available concerning its potential local and systemic adverse effects. Moreover, the optimal dosing and choice of drug for anti-VEGF treatment are still unknown.

Current developments

Two of the most pressing open questions in anti-VEGF therapy concern the dosing and choice of drug for anti-VEGF treatment. These two questions are currently being addressed in the CARE-ROP trial, a phase II trial currently in progress in Germany. This multicenter, randomized, double-blind trial (clinical trials identifier NCT02134457) is intended to test the safety and efficacy of ranibizumab at two different doses. This drug is a VEGF inhibitor like bevacizumab, but it is considerably more expensive (ca. €1000 versus ca. €50 per injection). The two substances have comparable ocular efficacy and kinetics, but ranibizumab is eliminated much more rapidly from the systemic circulation and is thus theoretically less likely to harm other organs. The primary endpoint of the CARE-ROP trial is the number of children who do not need any rescue treatment in the 24 weeks after treatment with ranibizumab. The follow-up period after treatment is five years. A further goal of the CARE-ROP trial is to determine whether a lower dose than the currently used half-adult dose might suffice for the treatment of retinopathy of prematurity. Two other trials are now in progress to study similar questions: a dose-de-escalation trial of the U. S. National Institutes of Health (clinical trials identifier NCT02390531) and a Mexican trial (clinical trials identifier NCT02090322).

Overview

The position paper issued by the German ophthalmological societies in 2012 and the Revised Joint Policy Statement issued in 2013 by the American Academy of Pediatrics, the American Association of Pediatric Ophthalmology and Strabismus, and the American Academy of Ophthalmology can be used as guides to the procedure to be followed in concrete cases of retinopathy of prematurity (39, 40). It is stated in both of these publications that the main advantage of VEGF inhibition lies in the treatment of central abnormalities. Better ocular outcomes after anti-VEGF treatment have also been reported for AP-ROP, a special variant of retinopathy of prematurity (e1). It must nevertheless be emphasized that laser therapy remains an established

treatment for which long-term follow-up data are available, with a level of evidence as yet unmatched by anti-VEGF treatment. The anti-VEGF trials that are now underway will provide more clarity over the next few years.

It must also be emphasized that much longer ophthalmological follow-up is needed after anti-VEGF treatment than after laser therapy. The mean time from treatment to recurrence in the BEAT-ROP trial was 6.2 ± 5.7 weeks in the laser group and 16 ± 4.6 weeks in the bevacizumab group. The currently available data do not point to any significant difference between anti-VEGF treatment and laser therapy with regard to the intermediate-term prognosis for vision (e2, e3). It does appear, however, that severe myopia may be less common after anti-VEGF treatment (e4–e6).

It would broaden our understanding of retinopathy of prematurity if the currently available findings from interventional trials could be augmented by the documentation, in epidemiologic registries, of the greatest possible number of premature neonates who need treatment. To this end, premature neonates can be included in the German Neonatal Network (GNN) and epidemiologic data on their disease course can be entered into the Retina.net ROP registry (www.rop-register.de).

Conflict of interest statement

Professor Göpel has received reimbursement of travel and accommodation expenses and payment for preparing scientific meetings from the Chiese, Abbvie, and Novartis companies.

Dr. Stahl receives consulting fees, reimbursement of travel and accommodation expenses, payment for preparing scientific meetings, and funds paid into a third-party account for a research project that he initiated, all from Novartis.

Manuscript submitted on 10 February 2015, revised version accepted on 15 July 2015.

Translated from the original German by Ethan Taub, M.D.

KEY MESSAGES

- Comprehensive ophthalmologic screening of premature neonates is essential for the prevention of severe visual impairment and blindness.
- The transition from phase I to phase II of retinopathy of prematurity is a critical period in which VEGF-induced retinal vascular growth is accelerated.
- Laser therapy is an established, safe treatment for most stages of retinopathy of prematurity. Its disadvantages include the induction of retinal scarring, sometimes over a broad area, and the frequent development of severe myopia.
- VEGF inhibition is a newer treatment that causes no visible scarring and is less prone to cause myopia. Dose-finding trials of VEGF inhibitors have not yet been carried out, however, nor are there any data on their local and systemic effects over the long term.
- Trials are currently in progress to study lower doses of bevacizumab and other types of VEGF inhibitors, with the aim of effectively combating retinopathy of prematurity with the lowest possible systemic drug exposure.

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Supplementary material

eReferences:

www.aerzteblatt-international.de/ref4315

Supplementary material to:

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Dtsch Arztebl Int 2015; 112: 730–5. DOI: 10.3238/arztebl.2015.0730

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