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What was known before:
Retinopathy of prematurity is a sight-threatening condition with increasing indicence. New treatment in the form of anti-VEGF-antibodies has entered clinical practice, with variable outcomes, possibly a higher need for long-term follow-up and re-treatments for recurrence of disease activity. Standard treatment remains diode laser photocoagulation of the non-vascularised retina, with increased risk of early emmetropisation and myopia in childhood.

What this study adds:
Visual outcomes after treatment for ROP are good in the majority of children, though a significant minority have poor outcomes and are eligible for sight impairment certification. Retreatment rates appear higher after initial anti-VEGF antibody than after initial diode laser treatment. Refractive outcomes show a trend towards early emmetropia and myopia following diode laser, particularly in more severe ROP.

Retinopathy of prematurity in the United Kingdom: retreatment rates, visual and structural one-year outcomes

Gillian GW Adams[1], Consultant Ophthalmologist

Catey Bunce[1,2], Principal Statistician

Wen Xing[1], Statistician

Lucilla Butler[3], Consultant Ophthalmologist

Vernon Long[4], Consultant Ophthalmologist

Aravind Reddy[5], Consultant Ophthalmologist

UK Retinopathy of Prematurity Special Interest Group[6]

Annegret H Dahlmann-Noor PhD[1], Consultant Ophthalmologist

[1] NIHR Biomedical Research Centre at Moorfields Eye Hospital and UCL Institute of Ophthalmology 162 City Road, London EC1V 2PD, UK

[2] Department of Primary Care & Public Health Sciences, Kings College London, London, UK SE1 1UL

[3] Birmingham & Midland Eye Centre, Dudley Road, Birmingham B18 7QH, UK

Lucilla.butler@nhs.net

[4] St James' University Hospital, Leeds Teaching Hospitals, Beckett Street, Leeds, West Yorkshire, LS9 7TF, UK

vernon.long@leedsth.nhs.uk

[5] Royal Aberdeen Children's Hospital, Westburn Road, Foresterhill, Aberdeen, AB25 2ZG, UK

aravind.reddy@nhs.net

[6] Members of the UK Retinopathy of Prematurity Special Interest Group are listed before the references

Corresponding author: Annegret Dahlmann-Noor; NIHR Biomedical Research Centre at Moorfields Eye Hospital and UCL Institute of Ophthalmology, 162 City Road, London EC1V 2PD, UK, annegret.dahlmann-noor@moorfields.nhs.uk ; +44 20 7566 2013

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The study was approved by the Research Ethics Committee North of Scotland, Aberdeen (13/NS/0059). **This work was registered at clinicaltrials.gov as NCT02484989.**

Abstract

Aims: To evaluate retreatment rates, visual and anatomical outcomes at one year postnatal age in infants treated for retinopathy of prematurity (ROP)

Methods: Longitudinal national surveillance study of infants treated for ROP in the UK between December 2013 and December 2014, supported by the British Ophthalmic Surveillance Unit. Here we report retreatment rates, anatomical, visual and refractive outcomes at one year follow-up.

Results: One-year follow-up forms were completed for 168 children of the original cohort of 327 (51.4%). Twenty-two had at least one retreatment: 17/153 right eyes (RE, 11.1%) after initial diode laser, and 5/14 RE (35.7%) after initial injection of anti- vascular endothelial growth factor (VEGF) antibody. Median (interquartile range) RE best-corrected visual acuity was 0.6 (0.4 to 1.0) (n=46 RE), and median acuity both eyes open 0.4 (0.3 to 0.7) logMAR (n=89). Median spherical equivalent (RE) was 0.44 (-1.3 to 1.3) dioptre (n=116). Median astigmatism (RE) was 0.5 (0 to 1.0) dioptre (n=111), and median anisometropia 0.125 (0 to 0.75) dioptre (n=116). 24 children (20.5%) had been prescribed glasses. Sight impairment certification eligibility information was available for 131 children: eleven (8.4%) were eligible to be certified as sight impaired, and five (3.8%) as severely sight impaired.

Conclusions: Retreatment rates are in line with previous reports, and appear higher after initial anti-VEGF antibody than after initial diode laser. Refractive outcomes are in line with previous studies, with a trend towards early emmetropia and myopia following diode laser, particularly in more severe ROP.

Background

Timely treatment for sight-threatening retinopathy of prematurity (ROP) aims to enable the child to develop normal vision. Ideally, one treatment application should induce permanent regression of ROP. Current standard treatment is diode laser ablation of the avascular retina, with indications for treatment developed by the Early Treatment of Retinopathy (ETROP) study group. [1] Despite timely treatment unfavourable outcomes can still occur. Unfavourable structural outcomes include macular fold, retinal detachment involving the macula, or a retrolental mass obscuring the view of the posterior pole, and may occur in 9.1%; unfavourable visual outcomes (less than 1.85 cycles on Teller acuity cards) may occur in 14.5% of infants. [1] In addition, the incidence of refractive errors, particularly myopia and astigmatism, is higher in infants who received laser photocoagulation for ROP than in children who did not require ROP treatment. [2 3 4 5]

Intravitreal injection of anti-vascular endothelial growth factor (VEGF) antibodies is an alternative to laser treatment in severe cases of ROP, such as aggressive posterior ROP (APROP), and ROP in zone 1 or posterior zone 2. [6] Different from laser treatment, anti-VEGF antibody injection may allow maturation of the peripheral retina and anterior segment, and reports indicate better structural and visual outcomes (median VA of 0.3 logMAR at around 2 years after treatment for type 1 ROP [7]) and a reduced incidence of myopia compared with laser, [6, 8-16] though not all studies support these findings. [17 18] Anti-VEGF antibody therapy may require more than one treatment application, with reported retreatment rates ranging from 4 to 14%, [6 9 11 12] though higher rates of 27% have also been reported. [7] Retreatment after laser is generally expected in around 13.9% [1], though recently higher retreatment rates of 26 to 32% have been reported. [6 19]

The aim of the present study was to report retreatment rates, visual and refractive outcomes in the national cohort of children treated for ROP over a 12-month period in the United Kingdom (UK) for whom we previously reported initial treatment data. [20]

Methods

Our case ascertainment and data collection method have previously been described in detail. [20] In brief, between 01/12/2013 and 30/11/2014, ROP practitioners throughout the UK prospectively reported new cases of infants requiring treatment for ROP to the British Ophthalmic Surveillance Unit (BOSU) using an established reporting system. In addition, we set up an electronic UK-ROP-Special Interest Group. We sent practitioners who had reported ROP-treated infants two case report forms: one after initial notification, and another 12 months later. Here we report data from the 12-month-follow-up.

Statistical analysis

Data from the case report forms were entered onto an electronic Microsoft Office Access database. A random sample of forms was inspected to ensure data quality. Data were transferred into Stata version 14.0 for analysis. Characteristics of infants requiring ROP treatment were summarized using means and standard deviations for approximately Gaussian variables and medians and interquartile ranges for non-Gaussian continuous variables. Categorical variables are reported as numbers and proportions**.** This study was not powered to test for statistical significance of any prior hypotheses.

Results

Children's characteristics

We received one-year follow-up forms for 168 children of the original cohort of 327 (51.4%). Gestational age, age, birth weight, gender, ROP severity, primary treatment modality and number of treatments were similar in infants for whom follow-up data were available and those for whom follow-up data were not available.

At last follow-up, median age (interquartile range IQR) was 14 (12 to 17.8) months. 76 children (45.2%) were girls. At the time of the follow-up report, 130 children (77.4%) were under follow-up at the same unit where they had received ROP treatment. 15 children (8.9%) were under the care of a

different eye unit, 7 (4.2%) were reported to have been discharged, 3 (1.8%) lost to follow-up, and 13 (7.74%) had died. Causes of death were reported in six children, and included Beckwith-Wiedemann syndrome (n=1), renal failure after laparotomy for necrotizing enterocolitis (1), severe bronchopulmonary dysplasia in extreme prematurity (1), severe hydrocephalus and respiratory failure (1), unknown (2).

Retreatment rates

We calculated retreatment rates with a denominator of n=168, the number of children for whom follow-up data were available (Table 1). Twenty-two of 168 (13.1%) infants had at least one retreatment. Treatment was similar between the right and left eye; we report here the treatment details for the right eye (RE). Five of 14 RE which had anti-VEGF antibody injection as primary treatment (11 bevacizumab, 3 ranibizumab) required retreatment (35.7%). Anti-VEGF antibody had been administered exclusively for APROP and type 1 ROP only; retreatment rates were 50 and 36.4%, respectively. Retreatment rates after diode laser for APROP and type 1 ROP were 37.5 and 9.4%, respectively (Table 1).

The retreatment given was laser in 8 RE, and anti-VEGF antibody in 8 eyes, anti-VEGF plus laser for 2 eyes, surgery for 1 eye and laser plus surgery for 1 eye; retreatment information was not available for 2 eyes. Table 2 summarises retreatment details.

The median interval from primary to secondary treatment was 17 (IQR 7-33, range 2 to 106) days, and the median interval from secondary to tertiary treatment was 36 (IQR 27-48, range 13-119) days.

For some infants, information about retreatment was available from the original incidence case report forms. We carried out a secondary analysis of retreatment rates, using all available retreatment information, with n=327, the original cohort population size, as denominator. Forty-two children (12.8%) of the original cohort required at least one retreatment, so the results of this analysis were similar to our initial retreatment analysis (supplementary material, Table 5-6).

Visual and refractive outcomes one year after ROP treatment

Best corrected visual acuity in logMAR in the right eye was available in 46 children, and with both eyes open, 89 children. Median (IQR) right eye acuity was 0.6 (0.4 to 1.0) logMAR, and median acuity with both eyes open was 0.4 (0.3 to 0.7) logMAR (Table 3). The median (IQR) spherical equivalent, calculated as spherical correction plus half of astigmatic correction, of right eyes was 0.44 (-1.3 to 1.3) dioptre (n=116). Median (IQR) astigmatism of right eyes was 0.5 (0 to 1.0) dioptre (n=111). Median (IQR) difference in refractive error between the two eyes was 0.125 (0 to 0.75) dioptre (n=116). 24 children (20.5%) had been prescribed glasses.

The proportion of eyes with myopia of 5 DS or more was highest in those with type 1 ROP: 5.3% (7 of 133 eyes) after laser, and 31% (5 of 16 eyes) after anti-VEGF antibody. Overall, the proportion of eyes with myopia of 5 DS or more was greater in the anti-VEGF antibody group than the laser group (26.3 versus 6.7%, 5/19 versus 14/209 eyes) (Table 4).

Eligibility for sight impairment certification was reported for 131 children. Eleven (8.4%) were eligible to be certified as sight impaired, and five (3.82%) as severely sight impaired (3.8%).

Anatomical outcomes one year after ROP treatment

Unfavourable anatomical outcomes were reported in a total of 6 eyes (3 each right and left eyes). Macular status at last follow-up was reported in 142 children. The macula of two right eyes (1.4%) was “dragged”, and one right eye (0.7%) had a retinal fold involving the macula. Figures for left eyes were identical. The retina was attached in both eyes at the last follow-up visit in all children.

Strabismus and nystagmus

21 of 168 (12.5%) children developed esotropia, 3 exotropia (1.8%); none had a vertical deviation. Thirteen children (7.7%) developed nystagmus.

Other unfavourable ocular and neurological outcomes

One child developed cataract (0.6%), one glaucoma and one unilateral phthisis. Other structural ocular conditions were reported in 3 cases: residual vitreous haemorrhage (eye not given), optic atrophy and a previous exudative retinal detachment in one left eye. Amblyopia was reported in one child. Seven children (4.2%) were diagnosed with cerebral visual impairment. Twenty children had neurological impairments: cerebral palsy in 7 (4.2%), quadriplegia in one, and developmental issues or motor delay in 8 children (4.8%). 3 children had hydrocephalus and 1 had periventricular haemorrhage. In addition, eight had a hearing impairment (4.8%).

Discussion

The key findings of this study are that retreatment rates appear higher after initial anti-VEGF antibody than after laser, and that visual outcomes are generally good, with a median acuity with both eyes open of 0.4 logMAR at age 14 months, which is within the normal range for this age when measured with acuity cards. [21 22 23] However, over 12% of children were eligible to be certified as sight impaired or severely sight impaired, comparable to the rate of unfavourable visual outcomes reported in the ETROP trial. [1] In addition, a high proportion of children (20.5%) had started to wear glasses. Twenty children (12%) had been diagnosed with conditions affecting the central nervous system.

The robust case ascertainment methodology which allowed collection of data at national level is a strength of this study. A limitation is the high loss to follow-up since treatment, due to anonymised data collection and discharge from treating centres to referring units. Clinical assessment of visual acuity at the young age of a median of 14 months is often difficult, but the median we observed is within the normal range for this age. Reporting visual outcome might be more reliable at later ages, but further loss to follow-up may weaken data. Similarly, we report early refractive outcomes, 12 months after treatment, but myopia may develop or progress later. However, we observe a clear trend towards emmetropia and towards a greater prevalence of myopia even at this young age.

Our study contributes to the ongoing discussion about advantages and disadvantages of anti-VEGF antibody treatment compared with diode laser. The retreatment rates we observe are in line with previous reports. [1 6 7] Whether retreatment rates after anti-VEGF antibody are truly higher than after diode laser will require further studies, ideally randomised controlled trials; one such trial is currently enrolling participants (NCT02375971). Due to the high loss to follow-up and the possible selection bias towards inclusion of more severe cases our figures may overestimate the actual retreatment rates.

As the majority of children in our study received laser treatment we expected refractive outcomes similar to those reported by the ETROP trial: myopia of -0.25D or greater in two-thirds of children, and of 5 diopters or more in a quarter of children. [24] However, we found myopia of -0.25 diopters or more in only 36.4% (83/228 eyes), and high myopia of 5 diopter or more in 8.33% (19/228 eyes), possibly due to the inclusion of children treated for milder forms of ROP in our study (type 2 plus, disease milder than type 1 with plus or pre-plus, for example zone 3 disease with plus or zone 2 stage 1 with plus). [20] Median spherical equivalent (SE) was 0.44 DS, which is a favourable outcome for children who required ROP treatment, although it is lower than in healthy children and in children born prematurely, but without ROP. [25] Our observed rate of astigmatism of 1D or more (37.8%, 84/222 eyes) is in line with the 32-42% reported by the ETROP trial and rates reported by other studies. [2 3] Our prevalence of anisometropia of 1D or more (21.7%, 25/115 children) is higher than the 6.5% reported by others. [3]

Twelve percent of children treated for ROP had been diagnosed with neurological or developmental problems by the age of 12-14 months, which is comparable with figures reported by the EPICURE studies. [26] As developmental concerns may become more apparent with increasing age, this figure may be an underestimate of long-term neurological impairments.

In conclusion, visual outcomes after treatment for retinopathy of prematurity are good, with most children developing acuity normal for their age. Retreatment rates after initial anti-VEGF antibody appear higher than those after diode laser. Over 12% of infants have poor outcomes and are

certified as sight impaired or severely sight impaired. Neurological impairments are common and affect 12% of children treated for ROP.

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Members of the UK ROP Special Interest Group:

Abbott, Joseph; Aclimandos, Wagih; Adams, Gill; Al-Khaier, Ayman; Allen, Louise; Arashvan, Kayvan; Ashworth, Jane; Barampouti, Faye; Barnes, Jonathan; Barrett, Victoria; Barry, John Sebastian; Bates, Adam; Berk, Tulin; Biswas, Susmito; Blaikie, Andrew; Brennan, Rosie; Bunting, Howard; Butcher, Jeremy; Butler, Lucilla; Chan-Ling, Tailoi; Chan, Jonathan; Child, Christopher; Choi, Jessy; Clark, David; Clifford, Luke; Dabbagh, Ahmad; Dahlmann-Noor, Annegret; Dawidek, Gervase; Dhir, Luna; Drake, Karen; Edwards, Richard; Esakowitz, Leonard; Escardo-Paton, Julia; Evans, Anthony; Fleck, Brian; Geh, Vernon; George, Nick; Gnanaray, Lawrence; Goyal, Raina; Haigh, Paul; Hancox, Joanne; Haynes, Richard; Heath, Dominic; Henderson, Robert; Hillier, Roxane; Hingorani, Melanie; Jain, Saurabh; Jain, Sunila; Jones, David; Kafil-Hussain, Namir; Kelly, Simon; Kenawy, Nihal; Kipioti, Tina; Kulkarni, Archana; Lavy, Tim; Laws, David; Lawson, Joanna; Leitch, Jane; Ling, Roland; Long, Vernon; Macrae, Mary; Mahmood, Usman; Markham, Richard; Marr, Jane; May, Kristina; McLoone, Eibhlin;

Moosa, Murad; Morton, Claire; Mount, Ali; Muen, Wisam; Mulvihill, Alan; Munshi, Vineeta; Muqit, Mahi; Murray, Robert; Nair, Ranjit; Newman, William; O'Colmain, Una; Patel, Chetan; Patel, Himanshu; Pedraza, Luis Amaya; Pilling, Rachel; Puvanachandra, Narman;Quinn, Anthony; Rathod, Dinesh; Reddy, Aravind; Reddy, Ashwin; Rowlands, Alison; Scotcher, Stephen; Scott, Christopher; Sekhri, Rajnish; Shafiq, Ayad; Sleep, Tamsin; Tambe, Katya; Tandon, Anamika; Tappin, Alison; Taylor, Robert; Theodoro, Maria; Thomas, Shery; Thompson, Graham; Tiffin, Peter; Ullah, Muhammed Aman; Watts, Patrick; West, Stephanie; Whyte, Iain; Wickham, Louisa; Williams, Cathy; Wong, Chien; Wren, Siobhan; Zakir, Rahila

Legends for figures and tables

Table 1. Retreatment rates by ROP severity at presentation (reporting unit: right eyes).

*No information on primary treatment was available for one infant.

Table 2. Details of secondary, tertiary and any further treatment following initial laser or anti-VEGF antibody treatment, based on 168 children for whom one-year follow-up data were available (reporting unit: right eye).

Table 3. Clinical details of children and binocular outcomes (reporting unit: child).

Table 4. Visual and structural outcomes after laser and anti-VEGF antibody treatment (reporting unit: eyes). Data were available for 307 of 366 eyes; 26 eyes from 13 babies who died during the study were excluded due to incomplete data, 2 did not have primary treatment details, 1 eye did not have sufficient data to determine ROP severity.

Supplementary material: Tables 5-6, Retreatment rates (table 5), retreatment with secondary, tertiary and any further treatment (table 6) following initial laser or anti-VEGF antibody treatment, based on 327 children of original cohort, and retreatment information from follow-up (reporting unit: right eye).

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	total n	at least one re-treatment	%	Primary treatment laser	at least one re-treatment	%	Primary treatment anti-VEGF antibody	at least one re-treatment	%
APROP	10	4	40	8	3	37.5	2	1	50
Type 1	107	13	12.1	96	9	9.4	11	4	36.4
Type 2 plus	40	2	5	39	2	5.1	1	0	
Type 2	6	1	16.7	6	1	16.7	0	0	
Mild*	3*	0	0.0	2	0	0.0	0	0	
partial RD	2	2	100	2	2	100	0	0	
	168*	**22**	**13.1**	**153**	**17**	**11.1**	**14**	**5**	**35.7**

Table 1. Re-treatment rates by ROP severity at presentation (reporting unit: right eyes).
*No information on primary treatment was available for one infant.

	Secondary treatment			
	Argon laser	Anti-VEGF antibody	Missing data	Total
Initial treatment				
Argon laser	5	7	2	14
VEGF-inhibitor	0	2	1	3
Total	**5**	**9**	**3**	**17**
	Tertiary treatment			
	Argon laser	Anti-VEGF antibody /plus laser	Surgery	Total
Initial treatment				
Argon laser	3	0	2	5
VEGF-inhibitor	0	1	0	1
Total	**3**	**1**	**2**	**6**
	Any further treatment at 1 year			
	Argon laser	Anti-VEGF antibody /plus laser	Surgery	Total
Initial treatment				
Argon laser	3	1	1	5
VEGF-inhibitor	0	2	0	2
Total	**3**	**3**	**1**	**7**

Details of secondary, tertiary and any further treatment following initial laser or anti-VEGF antibody treatment, based on 168 children for whom one-year follow-up data were available (reporting unit: right eye).

reporting unit: children	Laser							Anti-VEGF antibody			
	APROP N=8	type 1 N=96	type 2 plus N=39	type 2 N=6	mild N=2	partial retinal detachment N=2	TOTAL N=153	APROP N=2	type 1 N=11	type 2 plus N=1	TOTAL N=14
Gestational age at birth, median (IQR)	25.1(24.3-25.9)	25.1(24.4-26)	25.3(24.4-26.4)	25.2(24.7-26.6)	26.1(25.9-26.3)	24.4(24-24.7)	**25.1(24.4-26)**	24.9(24.4-25.4)	24.9(23.7-25.9)	27.6	**25.1(24.3-25.9)**
Birth weight (g), median (IQR)	680(630-840)	715(641-824)	740(660-830)	721(670-850)	781(752-810)	622(610-634)	**716(642-830)**	723(655-790)	590(565-710)	780	**625(585-757)**
Proportion of female children, n(%)	4(50)	45(46.9)	15(38.5)	3(50)	1(50)	1(50)	**69(45.1)**	1(50)	6(54.6)	0	**7(50)**
Age at first treatment (days), median (IQR)	70(63-73)	83(73-97)	78(68-92) n=38	85(83-93)	137(111-163)	82(80-83)	**81(71-96) n=152**	74(71-76)	73(66-80)	64	**72(66-80)**
Age at follow-up visit (years), median (IQR)	1.5(1.2-1.6) n=5	1.1(1.0-1.4) n=84	1.2(1.0-1.5) n=36	1.3(1.1-1.9) n=5	1.4(1.4-1.5)	1.2 n=1	**1.2(1.0-1.5) n=133**	1.0 n=1	1.2(0.9-1.5) n=9	1.2	**1.2(0.9-1.5) n=11**
Children with anisometropia of 1D or more, n(%)	1(25) n=4	12(17.7) n=68	6(22.2) n=27	0 n=3	1(50)	0 n=1	**20(19) n=105**	0 n=1	5(62.5) n=8	0	**5(50) n=10**
Anisometropia, median (IQR), n(%)	0.5(0.31-0.75) n=4	0.25(0-0.69) n=68	0(0-0.5) n=27	0(0-0.63) n=3	1(0-2)	0 n=1	**0.13(0-0.63) n=105**	0 n=1	1(0.13-1.75) n=8	0	**0.63(0-1.25) n=10**
Glasses prescribed, n(%)	2(50) n=4	15(21.1) n=71	3(12) n=25	0 n=5	0 n=1	1(100) n=1	**21(19.6) n=107**	0 n=1	3(42.9) n=7	0	**3(33.3) n=9**
Manifest strabismus, n(%)	2(40) n=5	15(18.1) n=83	6(16.2) n=37	1(20) n=5	0 n=2	1(100) n=1	**25(18.8) n=133**	0 n=1	2(22.2) n=9	0	**2(18.2) n=11**
Nystagmus	2	8	1			1	**12**		1		**1**

Table 3. Clinical details of children and binocular outcomes (reporting unit: children).

reporting unit: eyes	Laser							Anti-VEGF antibody			
	APROP N=14	**type 1 N=176**	**type 2 plus N=76**	**type 2 N=12**	**mild N=5**	**partial retinal detachment N=2**	**TOTAL N=285**	**APROP N=2**	**type 1 N=19**	**type 2 plus N=1**	**TOTAL N=22**
BCVA, median (IQR)	0.65 (0.6 to 1.2) n=6	0.65 (0.4 to1) n=46	0.5 (0.3 to 1) n=31	0.45 (0.35-0.5) n=4	0.4 n=1		**0.6 (0.4 to 0.98) n=88**		0.6 (0.4 to 0.6) n=3		**0.6 (0.4-0.6) n=3**
Sph Equv, median (IQR)	-6.5 (-8 to-5.31) n=8	0.5 (-1.25to1.25) n=133	0.5 (-0.38 to1.25) n=57	1 (1-1) n=5	0 (-1 to1.5) n=4	3 (3-3) n=2	**0.5 (-0.13 to 1.25) n=209**	1 (1-1) n=2	-0.25 (-5.63 to 0.88) n=16	-0.5 n=1	**0 (-5.25-1) n=19**
Range of Sph Equiv	-9.5 to -4.5 n=8	-16 to 10 n=133	-7.8 to 7 n=57	1 to 3.63 n=5	-2 to3 n=4	3 to 3 n=2	**-16 to 10 n=209**	1 (1-1) n=2	-7.5 to 4 n=16	-0.5 n=1	**-7.5 to 4 n=19**
Astigmatism, median (IQR)	0 (0 to 0.5) n=8	0.5 (0 to 1) n=130	0.63 (0 to1.5) n=56	0.5 (0-1.88) n=4	0 (0-0) n=4	0 (0-0) n=2	**0.5 (0 to1.13) n=204**	0 n=2	0.5 (0 to 1) n=15	2 n=1	**0.5 (0-1) n=18**
Proportion of eyes with SE =<-0.25DS, n(%)	8 (100) n=8	50 (37.6) n=133	15 (26.3) n=57	0 n=5	1 (25) n=4	0 n=2	**74 (35.4) n=209**	0 n=2	8 (50) n=16	1 (100) n=1	**9 (47.4) n=19**
Proportion of eyes with SE=<-5DS, n(%)	6 (75) n=8	7 (5.3) n=133	1 (1.8) n=57	0 n=5	0 n=4	0 n=2	**14 (6.7) n=209**	0 n=2	5 (31) n=16	0 n=1	**5 (26.3) n=19**
Proportion of eyes with astigmatism =>1D, n(%)	0 n=8	50 (38.5) n=130	25 (44.6) n=56	2 (50) n=4	0 n=4	0 n=2	**77 (37.7) n=204**	0 n=2	6 (40) n=15	1 (100) n=1	**7 (38.9) n=18**
Proportion of eyes with astigmatism= >2D, n(%)	0 n=8	15 (11.5) n=130	11 (19.6) n=56	1 (25) n=4	0 n=4	0 n=2	**27 (13.2) n=204**	0 n=2	1 (6.7) n=15	1 (100) n=1	**2 (11.1) n=18**
Proportion of eyes with attached macula at last visit, n(%)	10 (100) n=10	154 (98.1) n=157	70 (98.6) n=71	11 (100) n=11	5 (100) n=5	2 (100) n=2	**253 (98.4) n=257**	2 (100) n=2	15 (88.2) n=17	1 (100) n=1	**18 (90) n=20**
Proportion of eyes with dragged macula, n(%)		3 (1.9) n=157	1 (1.4) n=71				**4 (1.6) n=257**				
Proportion of eyes with macular fold, n(%)									2 (11.8) n=17		**2 (10) n=20**
Proportion of eyes with attached retina at last visit, n(%)	10 (100) n=10	153 (100) n=153	68 (100) n=68	9 (100) n=9	4 (100) n=4	2 (100) n=2	**246 (100) n=246**	2 (100) n=2	15 (100) n=15	1 (100) n=1	**18 (100) n=18**
Proportion of eyes with further treatment, n(%)	1 (7.1)	3 (1.7)	4 (5.3)			2 (100)	**10 (3.5)**		5 (26.3)		**5 (22.7)**

Table 4. Visual and structural outcomes after laser and anti-VEGF antibody treatment (reporting unit: eyes). Data were available for 307 of 366 eyes; 26 eyes from 13 babies who died during the study were excluded due to incomplete data, 2 did not have primary treatment details, 1 eye did not have sufficient data to determine ROP severity.