Research Article

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Preferences and Trends in Practices Caring Premature Infants for Retinopathy of Prematurity (ROP): A Web-based Survey

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Abstract

Objectives: To study preferences in treatment, follow-up and conclusion of examination in infants treated with and without bevacizumab (IVB) and/or laser photocoagulation for retinopathy of prematurity (ROP).

Methods: A 22 question web survey was administered to physicians to understand practice patterns for treatment of type 1 ROP, determine timeframe of conclusion of examinations with and without IVB/laser, and to approximate incidence of ROP recurrence post-treatment.

Results: The survey revealed that 73% pediatric ophthalmologists reported not personally performing injections and 54.1% reported not performing laser. In infants with persistent avascular retina without pre-threshold disease, 54.2% continued examination > 50 weeks PMA, 23.3% discontinued at 50 weeks PMA, 3.2% preferred prophylactic laser and 5.1% fluorescein angiography and laser prior to concluding exams. 46.3% of physicians preferred IVB as primary monotherapy, 37.3% laser, and 16.4% both IVB and laser in type 1 ROP. Of those who preferred IVB, 20.4% concluded examination at ≤ 55 weeks PMA, whereas 79.6% continued evaluation >55 weeks PMA (60 to ≥ 80 weeks). Of those who preferred both IVB and laser, 50.6% concluded examination at ≤ 50 weeks PMA, whereas 49.4% continued > 50 weeks (60 to ≥ 80 weeks). 21.1 % of respondents reported recurrence with IVB and 8.8% with dual therapy

Conclusions: Treatment preferences and conclusion of examination in ROP varies considerably without and with treatment. Though a longer follow-up is recommended with IVB, this survey reveals extended examinations beyond 50 weeks PMA in infants with persistent avascular retina requiring no treatment and in the laser treated subgroup. The survey highlights low rates of performing treatments personally by pediatric ophthalmologists, and distinctly variable practice patterns in ROP care

Keywords: Retinopathy of prematurity, Bevacizumab, Laser photocoagulation, practice patterns

Abbreviations: ROP: Retinopathy of Prematurity; PMA: Post Menstrual Age; VEGF: Vascular Endothelial Growth Factor; IVB: Intravitreal Bevacizumab; IGF-1: Insulin Like Growth Factor 1; CRYO-ROP: Cryotherapy for Retinopathy of Prematurity; ETROP: Early Treatment for Retinopathy of Prematurity; BEAT-ROP: Bevacizumab Eliminates the Angiogenic Threat of Retinopathy of Prematurity; AAP: American Academy of Pediatrics; US: United States; AAPOS: American Association of Pediatric Ophthalmology and Strabismus; ASRS: American Society of Retina Specialists; WSPOS: World Society of Pediatric Ophthalmology and Strabismus; EFP: Extraretinal Fibrovascular Proliferation; TRD: Tractional Retinal Detachment; FA: Fluorescein Angiography

Key Messages Box

Retinopathy of prematurity has been a challenge for physicians in terms of screening, diagnosis and providing treatment. The use of intravitreal bevacizumab (Anti-VEGF) injection has gained popularity amongst the physicians. The recently revised 2013 American Academy of Pediatrics (AAP) guidelines has incorporated the use of intravitreal bevacizumab (anti-VEGF) with instructions to follow the infants weekly until the retinal vessels vascularizes completely. This web survey was administered to study the practice patterns of physicians involved in ROP care regarding the use of Anti-VEGF injection and laser photocoagulation. The survey contains some very pertinent and difficult scenario-based questions, where physicians' are unable to make a clear decision and/or may not necessarily follow the AAP guidelines. Contrary to the published guidelines, a distinct variability in physicians' practices were noted in the survey. The study results highlights the distinct variability amongst the physicians in treatment preferences and conclusion of examination in ROP care, as well as low rates of personally performing treatments, whether it be laser photocoagulation or intravitreal injections. The survey results calls for a longitudinal observational clinical trial with uniform use of guidelines to can help avoid unnecessary examinations and improve affordable care.

Introduction

Retinopathy Of Prematurity (ROP) is the second leading cause of blindness in infants in the United States and is an important source of childhood visual impairment worldwide [1-3]. Incidence and severity is associated with younger gestational age and lower birth weights [4,5]. This condition is particularly relevant in developed nations in which advances in neonatal care have increased survival of immature infants.

High-unregulated elevated oxygen levels were considered a strong driver in the development of ROP [6-8]. The pathogenesis of ROP has been demonstrated to be more complex and involves not only high oxygen concentrations at birth, but also fluctuations in supplemental oxygen, as well as episodes of bradycardia and apnea during the infant's course in NICU [9-12]. Vascular Endothelial Growth Factor (VEGF) is an important growth factor involved in normal retinal vascular development and development of ROP. Current models suggest a biphasic process in which an initial interruption of normal retinal development at the time

of preterm birth accompanied by a sudden reduction in insulin-like growth factor-1 (IGF-1) and VEGF induces vaso-obliteration followed by second phase of ROP at 32-34 weeks Post-menstrual Age (PMA) characterized by increased hypoxia of the avascular retina [13,14]. The vascular obliteration secondary to hypoxic stimulation triggers increased levels of VEGF and erythropoietin, causing neovascularization [15]. IGF-1 regulates the neovascularization within this stage by acting as an amplifying factor for VEGF [13].

Both the Cryotherapy for Retinopathy of Prematurity (CRYO-ROP) and the Early Treatment for Retinopathy Of Prematurity (ETROP) trials established peripheral retinal ablation of avascular retina as an effective traditional treatment in infants with threshold ROP [16,17]. Laser ablation was favored as it reduced unfavorable visual acuity outcomes from 19.8% to 14.3% and unfavorable structural outcomes from 15.6% to 9%. The ETROP recommended peripheral retinal laser ablation to be considered in any eye with type 1 ROP (defined as zone I with any stage ROP with plus disease, zone I, stage 3 with/without plus and /or zone II, stage 2 or 3 with plus disease). However, laser ablation may be technically challenging in infants with an unstable clinical course who may be at higher risk of complications from anesthesia, and may have increased vascular congestion of the anterior segment precluding adequate visualization. Furthermore, infants with type 1 and aggressive posterior ROP may require treatment of significant portions of avascular retina.

More recently, intravitreal anti-VEGF agent bevacizumab has gained popularity as a potential treatment for ROP. In a recent multi-center trial, Bevacizumab Eliminates the Angiogenic Threat of Retinopathy of Prematurity (BEAT-ROP), intravitreal bevacizumab (IVB) use was associated with a significant benefit in infants with zone I stage 3+ ROP as compared to infants treated with laser [18]. However, the BEAT-ROP study raised some concerns as to the incidence and frequency of late recurrence of ROP with IVB treatment when compared to laser.

The American Academy of Pediatrics (AAP) policy statement for screening, treatment, follow-up and conclusion of retinal examination in premature infants for ROP was revised in 1996 and 2013 [19]. To our knowledge, there have been no prior studies published in the literature examining how ophthalmologists conform to existing guidelines for the care of infants with ROP. Our study evaluated United States (U.S) and

international ophthalmologists' preferences regarding treatment, screening frequency and conclusion of retinal examinations in premature infants with ROP.

Methods

This study was approved by the Institutional Review Board of University of Pittsburgh and was compliant with the Health Insurance Portability and Accountability Act. The web-based survey comprised of 22 questions (Appendice 1) that were primarily multiple-choice questions with an option to write free text for further clarification. In January 2014, a web-based survey questionnaire was distributed to the active members of American Association of Pediatric Ophthalmology and Strabismus (AAPOS), American Society of Retina Specialists (ASRS) and World Society of Pediatric Ophthalmology and Strabismus (WSPOS). The survey was completed using a web-link (called Survey Monkey) that automatically collated submitted information. These multiple choice questions with the option to free-text responses addressed several specific domains, including (a) demographic information of the respondent physician, (b) patient volume seen and treated by the physician, (c) self-treated or referred practice in providing laser and anti-VEGF treatment, (d) practice preference in treatment for type 1 ROP, (e) frequency of follow-up examination, (f) postmenstrual age (PMA) at conclusion of retinal examination with and without anti-VEGF/laser treatment and (g) incidence of late recurrence or tractional retinal detachment both with and without anti-VEGF/laser treatment.

Data analysis was performed with the Statistical Analysis System for Windows, version 8 (SAS Institute Inc., SAS Campus Drive, Cary, NC). Descriptive statistics and frequency distributions were calculated for specific variables. Comparisons were made between US and international practitioners, as well as pediatric

ophthalmologists and retina specialists, by using the chi-square test. Missing data were taken into account when analyzing the data. Free-text responses were reviewed and re-categorized into an existing question response if relevant.

In particular, with regards to Question # 6 ("level of training"), participants were grouped by highest level of training. If they chose that they had training in a fellowship as well as in general ophthalmology, they were sorted into the fellowship they had trained in. Also, for Question # 17 ("treatment of infants with 'type 1 ROP'"), the participants' responses were considered for type 1 ROP including infants with aggressive posterior ROP.

Results
Participant demographics

A total of 285 physicians participated; however, 18 participants were excluded from analysis because they responded that they did not treat or care for ROP patients or answered fewer than 2 questions. Therefore, 267 physician responses were eligible for analysis. Table 1 summarizes participant demographics. Of the 267 physicians who completed the survey, 183 (68.5%) were practicing physicians from the United States and 84 (31.5%) practiced internationally. Pediatric ophthalmologists comprised 82.4% (n = 220), retinal specialists 8.2% (n = 26), and the remaining 7.6% (n = 21) of respondent physicians identified themselves as general ophthalmologists, dual trained pediatric/retinal specialists and neuro-ophthalmologists. 40.4% (n = 108) physicians were in practice for more than 16 years and the remaining ranged from < 2 years to 15 years. Similarly, 40.1% (n = 107) respondents are affiliated with a university academic practice, 35.6% (n = 95) private group practice, 19.5% (n = 52) in multispecialty hospital and 12.7% (n = 34) as solo practitioners. A majority of the physicians screened 0-5 infants (36.9%) and 6-10 infants

Table 1: Summary of survey participant demographics.

Practice Location	183 (68.5%) U.S.	84 (31.5%) International		
Sub-specialty	220 (82.4%) Pediatric	26 (8.2%) Retina	21 (7.6%) Other	
Duration of Practice	159 (59.6%) 15 years or less	108 (40.4%) 16 years or more		
Type of Practice	107 (40.1%) University Academic	95 (35.6%) Private Group	52 (19.5%) Multispecialty	34 (12.7%) Solo practice
ROP Practice Volume	99 (36.9%) 0-5 infants/week	83 (31.2%) 6-10 infants/week	76 (28.4%) 11-30infants/week	9 (3.4%) 30+ infants/week

(31.2%) weekly in their practice. Few screened more than 10 infants to 30 infants weekly (28.4%) and very few screened more than 30 infants weekly (3.4%).

Treatment for Type 1 ROP

Two hundred forty-four physicians reported their primary preference in treatment of infants with type 1 ROP. 46.3% (n = 113) of physicians preferred IVB as primary therapy, 37.3% (n = 91) preferred laser photocoagulation, and 16.4% (n = 40) preferred dual IVB and laser photocoagulation as primary treatment (Figure 1).

Figure 1: This graph shows the preferred practice patterns for treating type 1 ROP disease in premature infants by all respondents to the survey.

Additional stratified analyses did not reveal any statistically significant differences in responses between U.S. and international physicians. 46.2% of U.S. physicians preferred IVB as primary therapy, 39.3% preferred laser photocoagulation, and 14.5% preferred dual IVB and laser as primary therapy. Similarly, 46.5% of international physicians preferred IVB as primary therapy, 32.4% preferred laser photocoagulation, and 21.1% preferred dual IVB and laser as primary therapy.

Conclusion of retinal examination in infants with persistent peripheral avascular retina at 50 weeks PMA (stage 1 or 2 and zone II/ zone III ROP without plus disease) when no treatment is necessitated

Of 253 physicians who responded, 23.3% (n = 59) of physicians reported that they would conclude retinal examination in clinic at 50 weeks PMA following the AAP guidelines, 54.2% (n = 137) reported that they would continue retinal examinations until outpatient evaluation was difficult, 3.2% (n = 8) reported that they would perform laser photocoagulation to avascular retina prior to concluding further examinations and 5.1% (n = 13) said they would perform both fluorescein angiography and laser prior to concluding retinal examinations. The

remaining 14.2% (n = 36) had differing opinions with regards to conclusion of retinal examinations (Figure 2A).

Figure 2A: This graph shows the preferred practice pattern of concluding retinal examinations in infants with persistently avascular retina (stage 1 or 2, Zone II/ III ROP without plus disease) once the infant has reached 50 weeks PMA (when no treatment is necessitated/given).

Some individuals reported that they would refer patients out to other ophthalmologist colleagues. One physician reported discomfort with all of the options provided. In the free text option for this question, the clinician wrote that laser treatment is "malpractice; there is no data to support such a practice at all....[use of] (FA) is bordering on malpractice, as FA is completely unnecessary in routine/uncomplicated ROP...(A) there are no treatment or diagnostic guidelines or real data on FA and ROP, let alone what to do at such a late age; (B) I don't understand - how would you discharge someone from care because they are too difficult to examine? if you are concerned about something you do an EUA - but stage 1/2 that persists you are not concerned about really".

Conclusion of retinal examination in infants on nasal oxygen and or with tracheostomy with persistent peripheral avascular retina at 50 weeks PMA (stage 1 or 2 and zone II/ zone III ROP without plus disease) when no treatment is necessitated

Two hundred forty-four physicians answered the above question (Figure 2B).

Even when infants are on chronic oxygen, 19.7% (n

= 48) physicians reported that they discontinue retinal examinations per AAP guidelines at 50 weeks of PMA, while greater than half of physicians (54.5%, n = 133) reported that they would continue retinal examinations until outpatient evaluation was difficult. Approximately 2.5% (n = 6) reported that they would perform laser photocoagulation to avascular retina prior to concluding further examinations and 6.1% (n = 15) said they would perform both fluorescein angiography and laser prior to concluding retinal examinations. A very small minority of 0.8% (n = 2) would perform only fluorescein angiography before concluding examinations at 50 weeks PMA. The other 16.4% (n = 40) of physicians chose the free text option, and responses could not be categorized in any of the above categories.

Figure 2B: This pie chart shows the preferred practice pattern of concluding retinal examinations in infants on nasal oxygen and/or with tracheostomy with persistent peripheral avascular retina at 50 weeks PMA (stage 1 or 2 and zone II/ zone III ROP without plus disease) when no treatment is necessitated (n=244).

Frequency of follow-up examinations beyond 50 weeks PMA in infants with persistent avascular retina when no treatment is necessitated with and without chronic oxygen therapy

The frequency at which physicians screened infants with persistent peripheral avascular retina was variable among physicians, and varied from weekly to monthly. Of the physicians who screened beyond 50 weeks PMA both with and without chronic oxygen support, overall the most common follow up interval was monthly examinations (mean 27.6%), followed by performing examinations every two weeks (mean 23%) (Figure 3A).

Figure 3A: This graph shows follow-up examination pattern practiced by physicians when infants with persistent avascular retina are followed beyond 50 weeks PMA in situations both on and/or without chronic oxygen support.

Conclusion of retinal examination and follow-up interval in infants treated with intravitreal injections as monotherapy if disease has regressed with treatment

Of the 238 physicians that responded to this question, 40.3% (n = 96) reported that they do not use IVB in their practice. Of the remaining 142 physicians who used intravitreal injections, there was significant variability with which retinal examination is concluded in this subset. In this subset of physicians, 65.4% (n = 93) reported conclusion of retinal examinations varying anywhere from 45 weeks of PMA to greater than 80 weeks of PMA. Many physicians (23.65%, n = 22 of 93) commonly pursue examinations beyond 80 weeks PMA. While 34.5% (n = 49) physicians answered "other" and generated free text responses that did not fall within the existing answer choices. Of physicians who clearly specified the weeks of PMA they preferred concluding retinal examination when treating infants with IVB monotherapy (n = 93), 20.4% (n = 19) preferred concluding examination at 55 weeks PMA or less, whereas 79.6% (n = 74) continued evaluations beyond 55 weeks PMA even with the regression of the disease (Figure 3B).

There was no significant difference noted on conclusion of retinal examination following IVB monotherapy between U.S and international physicians. For the physicians who chose "other", free text responses included the following: conclusion of examinations at 20 weeks post-injection, until complete vascularization, or referral to colleagues. Furthermore, there was variability

in the frequency at which these infants were evaluated. This ranged from weekly exams to monthly exams, with a larger group choosing to evaluate infants every two weeks (22.3%).

Figure 3B: This graph shows the preferred pattern of concluding retinal examination in infants treated with intravitreal bevacizumab injections as monotherapy if disease has regressed with treatment (n = 238).

Conclusion of retinal examination and follow-up interval in infants treated with dual treatment

Of 227 physician respondents, 116 reported that this question was not applicable as they were using either laser photocoagulation or intravitreal injection exclusively as primary therapy. Of the remaining physicians (n = 111) who reported using dual treatment (defined as intravitreal bevacizumab and laser photocoagulation) to treat infants with ROP, 37.8% (n = 42) of physicians concluded examination at 50 weeks or less, 36.9% (n = 41) reported considerable variability (60 weeks to 80+ weeks PMA) in concluding examination and 25.2 % (n = 28) chose the “other” category. On excluding 28 respondents who reported “other” and other free text answers such as “dependent on retina colleague” or “until complete retinal vascularization”, 50.6% (42 of 83) of physicians preferred conclusion of retinal examination at 50 weeks or less, whereas 49.4% (41 of 83) continued evaluation beyond 50 weeks PMA (Figure 4A).

Similarly, there was distinct variability in the frequency at which these infants were evaluated. This ranged from weekly exams to monthly exams, with many choosing to evaluate infants weekly (20.7%, n = 47).

Figure 4A: This graph shows the preferred pattern of concluding retinal examination in infants treated with intravitreal bevacizumab (IVB) and laser photocoagulation when disease has regressed with treatment (n = 111).

Incidence of recurrence or late stage retinal detachment in infants on chronic oxygen with persistent avascular retina when received no treatment and followed beyond 50 weeks of PMA

Only 18 (7.4%) of 244 physicians reported recurrence or late stage retinal detachment in infants on chronic oxygen treatment with persistent avascular retina when followed beyond 50 weeks of PMA. Within this cohort of physicians, twenty infants were reported to progress to stage 3 or have a late tractional retinal detachment.

Incidence of recurrence or late stage retinal detachment in infants treated with intravitreal bevacizumab monotherapy after 50 weeks PMA

Physicians were also asked to report their experience with recurrence of ROP or late stage retinal detachments post 50 weeks PMA in infants treated with bevacizumab. Of 233 physicians who answered this question, 54.9% (n = 128) reported that they had treated an infant with IVB therapy. Of 128 physicians, 71.8% (n = 92) reported that they had not encountered a patient with recurrence or retinal detachment, 21.1% (n = 27) reported a recurrence, 4.7% (n = 6) reported late stage retinal detachment, and 2.3% (n = 3) reported both. Fifteen physicians (6.4%) reported recurrence in 33-39 infants, and five infants subsequently experienced a late RD with IVB monotherapy.

Of U.S physicians (n = 85) who treated infants with IVB, 70.6% (n = 60) reported that they had not encountered

a patient with recurrence or retinal detachment, 22.4% (n = 19) reported a recurrence, 4.7% (n = 4) reported late stage retinal detachment, and 2.3% (n = 2) reported both.

Of international physicians (n = 43) who treated infants with IVB, 74.4% (n = 32) reported that they had not encountered a patient with recurrence or retinal detachment, 18.6% (n = 8) reported a recurrence, 4.7% (n = 2) reported late stage retinal detachment, and 2.3% (n = 1) reported both.

Incidence of recurrence or late stage retinal detachment with dual treatment after 50 weeks PMA

We also asked respondents to note the number of infants they noted with late stage complications after dual therapy. Of 204 physicians who answered this question, 18 reported that they had treated an infant with dual therapy. Those physicians reported having five infants with recurrence and 3-4 infants with a late retinal detachment.

Personal Experience with Treatment Modalities

Overall, 98.1% (n = 262) of physicians reported their practice patterns regarding laser photocoagulation for ROP. Of 220 physicians with fellowship training in pediatric ophthalmology, less than half or 45.9% (n = 101) of pediatric ophthalmologists reported performing their own laser treatment in premature infants with ROP whereas 54.1% (n = 119) referred the infant for laser photocoagulation treatment to their colleagues. Of physicians with fellowship training in retina (n = 26), 80.8% (n = 21) reported they performed laser on their own (Figure 4B).

Figure 4B: This graph shows the percentage of physicians who personally perform intravitreal injections and laser photocoagulation for the treatment of ROP.

When stratified by location of practice, international pediatric ophthalmologists were more likely to perform laser photocoagulation (self or referral to another pediatric ophthalmologist) than their US counterparts ($p = 0.03$).

Seventy-nine percent (n = 207) of physicians reported on their practice patterns regarding intravitreal injections in infants for ROP. Approximately one-fourth (26.9%, n = 59) of fellowship-trained pediatric ophthalmologists reported that they perform their own intravitreal injections as compared to 73.1% (n = 19 of 26) retina specialists. A majority of pediatric ophthalmologists (73.1%) referred infants to their colleagues for intravitreal injections (Figure 4B). When stratified by location of practice, international pediatricians were more likely to perform intravitreal injections than their U.S counterparts but this was not statistically significant ($p = 0.06$).

Discussion

This web-based survey exposes the preferred practice patterns among the physicians caring for premature infants with retinopathy of prematurity. The pertinent findings from the survey are as follows:

More than half (54.1%) of pediatric ophthalmologists reported that they do not personally perform laser photocoagulation and three-fourths (73.2%) reported that they do not personally performing intravitreal injections in infants with ROP.

In infants with persistent peripheral avascular retina at 50 weeks PMA without prethreshold disease or worse ROP and with or without oxygen support (requiring no treatment ever), a majority (54%) of the physicians prefer to continue retinal examination beyond 50 weeks PMA until infants become too difficult for examination in clinic. Less than one-fourth (23%) prefer to conclude examination at 50 weeks PMA, whereas only 5% preferred prophylactic laser and/or fluorescein angiography prior to concluding retinal examination.

In infants with type 1 ROP, 46% of physicians preferred intravitreal bevacizumab (IVB) as primary monotherapy, 37% laser photocoagulation and 16% preferred dual therapy (IVB and laser treatment).

Of those who prefer IVB monotherapy, 80% continue retinal examination beyond 55 weeks PMA (range = 60 to ≥ 80 weeks) even when the disease is regressed, and only 20% prefer to conclude at ≤ 55 weeks PMA.

Of those who preferred dual therapy (IVB and laser treatment), 49% of physicians still prefer to continue examination beyond 50 weeks PMA (range = 55 to $\geq$ 80 weeks).

Recurrence or late-onset retinal detachment reported with dual therapy (IVB and laser) is much lower than when treated with IVB monotherapy.

Frequency of follow-up in all groups (without treatment, treatment with primary IVB, and dual therapy) is extremely variable amongst physicians (weekly to every 4 weeks) beyond 50 weeks of PMA.

The 2013 AAP guidelines describe the criteria for conclusion of acute retinal screening examinations which are: 1) zone III retinal vascularization attained without previous zone I or II ROP, 2) full retinal vascularization in close proximity to the ora serrata for 360 degrees, 3) regression of ROP, and/or 4) PMA of 50 weeks and no prethreshold disease (defined as stage 3 ROP in zone II, any ROP in zone I) or worse ROP is present. The survey suggests that while physicians tended to conclude retinal examinations when the first three criteria are met, they prefer to extend examination beyond 50 weeks PMA in infants who continue to have persistent avascular retina in situations when no treatment is necessitated ever during the entire follow-up course with or without chronic oxygen therapy. A minority of physicians consider prophylactic laser to the avascular retina and prefer concluding retinal examination by 50 weeks PMA. Several themes were identified through the responses of physicians as to why this may be the case. Physicians may be concerned about underlying liability and malpractice given the rare, though severe, complication of retinal detachment. In addition, lack of training and experience in terms of screening and treatment modalities as shown by some of the study responses influences them to continue the extended retinal examinations.

The 2013 AAP guidelines also state that infants treated with IVB should be monitored weekly until retinal vascularization is completed. In the BEAT-ROP study, recurrence of ROP after bevacizumab occurred later (16 ± 4.6 weeks vs 6.2 ± 5.7 weeks) than those treated with peripheral laser ablation and it was recommended that these infants should be followed longer to ensure ROP requiring treatment does not recur. Several studies have reported follow-up on the growth of peripheral retinal vessels post-injection with bevacizumab and noted persistent large areas of avascular retina at the periphery

well beyond nine months after treatment [2,20]. In infants treated primarily with IVB, it is quite difficult to say whether discontinuing retinal examinations at 55 weeks of PMA in this subset of infants is justified or for how long the infants should be followed in clinic. Surprisingly, the survey also revealed that 50% of physicians prefer extended retinal examinations beyond 50 weeks PMA, even following laser photocoagulation, which could suggest a concern for insufficient laser treatment cover to produce prompt disease resolution or inadequate training.

Case reports of late reactivation, progression, and other serious adverse events after intravitreal monotherapy have been published [21-24]. In their retrospective review of 9 patients (17 eyes) following treatment with IVB, Hu and colleagues showed mean age for treatment-requiring recurrence of 49.3 weeks PMA (minimum, 37 weeks; maximum, 69 weeks) [21]. In their series, five eyes progressed to retinal detachment and the age of detachment ranged from 49 to 69 weeks PMA with a mean of 58.4 weeks. Authors noted anterior, posterior or both anterior-posterior Extraretinal Fibrovascular Proliferation (EFP) with absence of fibrous elements but in all their cases found them elevated well into the vitreous and less symmetric in the vascular distribution. In few other reports of recurrences and late retinal detachment following IVB injection, one infant had extraretinal fibrovascular proliferation extending more than 180 degrees prior to the treatment, and another one had partial Tractional Retinal Detachment (TRD) (stage 4A with plus disease following laser) [22,23]. In another study, three of five eyes had fibrous tractional membranes along the major vascular arcades prior to injection [24]. It is not surprising that all cases reported with late tractional detachment had an elevated EFP either prior to treatment with IVB or at recurrence of disease. These studies suggest that the presence of preexisting elevated EFP prior to treatment or at recurrence of disease should caution the use of IVB. Bevacizumab transiently decreases the VEGF levels and regresses the neovascularization, but the presence of fibrous component will eventually undergo cicatricial fibrosis leading to tractional detachment. Furthermore, delaying laser ablation in eyes with elevated EFP can lead to higher incidence of tractional retinal detachment.

Based on our study, there may be some underlying discomfort with regards to personal ability to treat infants with ROP. Notably, more than half (54.1%) of pediatric ophthalmologists in our survey reported

not personally performing laser photocoagulation and three-fourths (73.2%) reported not performing intravitreal injections. These findings raise concerns about the adequacy of ROP screening and laser training during fellowship. Our results are in line with previous studies that have demonstrated this variation [25-27]. Retina fellows showed high accuracy for detecting ROP as compared to pediatric ophthalmology fellows. In part, this is due to variability in fellowship training. A web-based survey performed by Wong et al demonstrated that over the course of fellowship training, U.S. pediatric ophthalmology fellows performed significantly fewer ROP laser photocoagulation procedures than retina fellows [27]. The authors proposed a need to establish a minimum number of ROP examinations and laser procedures required during fellowship training. Bradley and Motley's survey administered to recently graduated pediatric ophthalmologists revealed that one-half believed that their ROP laser training during fellowship was adequate for clinical practice and the mean number of ROP laser procedures performed during fellowship was 6.4 [28]. The authors stated that the amount of laser experience during fellowship strongly influences the confidence in laser skills of recently graduated pediatric ophthalmologists and the desire to perform laser procedures in their clinical practice. Given these findings, it may be of benefit to focus efforts on training pediatric ophthalmologists on how to perform treatment for ROP in order to decrease the burden on families and improve care.

With increasing survival and better NICU care, more infants with persistent avascular retina are seen beyond 50 weeks PMA. Infants with ROP present with numerous systemic comorbidities that require a team of providers to implement care. Wang et al discussed the mistakes and gaps in preterm ophthalmologic care and strategies that hospitals and ophthalmology practices should adopt to share the responsibility of coordinated ROP care [29]. In a focus group of parents, resources required to attend appointments and number of specialty follow-up appointments were cited as reasons for inconsistent ophthalmologic care. Additionally, reports suggest a perceived feeling that there are not enough ophthalmologists to treat ROP [30]. Both provider shortage and inadequate training in ROP majorly affects the care provided by the physicians. Uniform and coordinated care by trained physicians is required for ROP care to avoid the burden of unnecessary extended visits due to fear of litigation.

Additionally, some physicians reported concerns with lack of data concerning indications for Fluorescein Angiography (FA) as well as for performing prophylactic laser photocoagulation. The survey revealed that a minority of physicians utilize FA and laser photocoagulation prior to concluding retinal examinations in the outpatient setting. Use of fluorescein angiography has increased recently with the goal of better visualization of peripheral retinal vascular abnormalities [20,31-35]. However, indirect ophthalmoscopy and retinal fundus imaging have been the standard for ROP examinations and there is currently no evidence demonstrating superiority of angiography to standard of care. FA has shown different patterns of vessels branching at the junction between vascular and avascular retina, hypoperfused retinal areas with or without hyperfluorescent "cotton-wool-like" or "popcorn-like" lesions due to dye leakage posterior to the vascular-avascular junction, focal dilatation of capillaries, capillary tufts formations, rosary-bead-like hyperfluorescent lesions inside the vessels, macular abnormalities including absence of foveal avascular area and variability in both retinal circulation and choroidal filling pattern [32]. Comparable vascular abnormalities by FA are observed in human ROP patients, as well as in a mouse Oxygen-induced Retinopathy (OIR) model [36]. In eyes treated with bevacizumab, the studies have reported that although bevacizumab is effective in bringing resolution of zone I and posterior zone II ROP and allowing growth of peripheral retinal vessels, greater than 50% of eyes were noted on FA to have large areas of avascular retina, abnormal branching, shunt vessels at the periphery and hyperfluorescent lesions and absence of foveal avascular zone posteriorly well beyond nine months after treatment [20,31]. FA may help to accurately determine the vascular-avascular junction and leaking vessels but does not seem to be superior to fundus imaging or gold standard indirect ophthalmoscopy. FA may hold value in eyes treated with bevacizumab to study the growth and pattern of peripheral retinal vasculature, though there is no real data to prove it.

While prophylactic laser photocoagulation is not currently standard of care in infants with persistent avascular retina and may be argued by some (5% of physician respondents) there are potential benefits to laser ablation compared to extended examinations. Prophylactic laser to avascular retina can lower the risk of late recurrence or retinal detachment, alleviate the challenges of examining older infants, and reduce the burden of time involved in travel and examination by both the parents/physicians which improves the complexity

and time in care and scheduling visits. This may benefit reducing medico-legal concerns related to missed visits. Ho et al reported a series of nine premature infants with peripheral avascular retina at 45 weeks post-gestational age where the authors supported laser photocoagulation when prematurely born babies reach 45 weeks PMA with incomplete retinal vascularization, peripheral neovascularization and/or zone III ROP with persistent plus disease [37]. Though, there are no substantial evidence to support prophylactic laser photocoagulation to persistent avascular retina in infants.

The currently accepted treatment for type 1 ROP is laser or cryo-ablation of the peripheral avascular retina, though laser is preferred as it causes less disruption of the blood-retinal barrier and less inflammation. In infants with aggressive posterior disease in zone 1, laser ablation leads to permanent destruction of a large area of peripheral retina, leading to peripheral visual field loss and significant high myopia [38,39]. In recent clinical trials in animal models and humans, anti-VEGF drugs have been tested in subjects with severe ROP. Animal model studies have shown that VEGF is important in causing both pathologic retinal neovascularization and normal physiologic retina vascular development [40-43]. The BEAT-ROP study compared IVB as primary monotherapy to conventional laser therapy and showed significant treatment benefit with IVB for zone I disease. IVB for zone II disease is effective, but has no benefit over laser. American Academy of Pediatrics introduced in the new guidelines that consideration may be given to treatment of infants with zone I, stage 3+ ROP with IVB [19]; however, bevacizumab is not approved by the US Food and Drug Administration for the treatment of ROP. This survey reveals more physicians (46%) are opting for IVB monotherapy in infants with type 1 ROP as compared to laser ablation (37%). Surveys have shown that use of bevacizumab as primary monotherapy has increased over the last few years for type 1 ROP, despite the many unknowns associated with the use of anti-VEGF.

In our study results, it is noted that physicians have distinct variability in practice patterns regarding ROP treatment, follow-up and extended examinations beyond suggested guidelines. Recurrence and late-onset tractional retinal detachments with and without treatment were infrequent but did occur among some. It raises the question of the use of fluorescein angiography and prophylactic laser ablation in infants with persistent avascular retina. However, it is clear that bevacizumab is becoming part of the treatment arsenal for type 1 ROP,

given the percentage of individuals in our study providing care to infants that have received intravitreal therapy (46%). An establishment of an international registry of bevacizumab patients to assess long-term outcomes as proposed by Mintz-Hittner in 2010 may aid in further elucidation of the effects of this medication.

Our study is limited in some ways. The data are self-reported, so their validity depends on the extent to which ophthalmologists can accurately report their practice patterns. Furthermore, electronic surveys allow for rapid distribution and data collection but suffer from a limited response rate. Additionally, there is an element of recall bias when asked about experiences regarding late stage RD or ROP recurrence. Nevertheless, our findings suggest important implications for the delivery of ROP care and for the enhancement of ROP training programs. First, they demonstrate that there is considerable variability in screening duration and treatment for ROP, despite the existence of guidelines in treatment. Second, they highlight the differences in who treats ROP. Ultimately, even the best evidence-based recommendations serve to improve care only if the clinicians charged with their implementation find them both scientifically convincing and clinically practical. In the case of the 2013 AAP guidelines, the experts still face the substantial challenge of convincing practitioners that the recommendations represent the best interpretation of the data and of assisting those practitioners in overcoming barriers to their implementation. Further multi-center observational studies are necessary to determine the appropriate age for conclusion of retinal examination, doses and long-term effects of IVB and the role of fluorescein angiography and prophylactic laser photocoagulation in premature infants.

Competing Interests

The author(s) declare that they have no competing interests.

Authors'contributions

SAS: conceptualized, designed study, acquired, analysed and interpreted the data, drafted the manuscript, revised it critically for intellectual content, gave final approval of the version for submission

AW: acquired, analysed and interpreted the data, drafted the manuscript

SA: revised the manuscript and figures

All authors read and approved the final manuscript.

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American Society of Retina Specialist Annual meeting, San Diego, CA, United States on August 1, 2014

Vision Research Meeting, UPMC, Pittsburgh, PA, United States on June 13, 2014

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