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Research Article

Pegaptanib sodium influences capillary nonperfusion secondary to diabetic retinopathy

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Abstract

Purpose: To determine the effect of pegaptanib sodium on retinal capillary nonperfusion in eyes with diabetic retinopathy.

Study Design: Prospective case series.

Methods: Eight eyes of eight subjects with diabetic retinopathy found to have retinal capillary nonperfusion by widefield fluorescein angiography were included in this study. Study eyes received a series of three injections of pegaptanib sodium at six-week intervals, then as needed for the remainder of the study. Total area of capillary nonperfusion as assessed by widefield fluorescein angiography (Optos P200A, Edinburgh, Scotland) was the primary endpoint.

Results: Average age of subjects was 58.3 ± 15.2 years with an average follow-up length of 58.3 ± 10.9 weeks. The mean number of injections was 4.0 ± 0.5. When injections were scheduled, five eyes (62.5%) demonstrated reperfusion and three eyes (37.5%) showed no change in ischemia. When injections were given as needed, five eyes (62.5%) had an increase in ischemia, two eyes (25%) had a decrease, and one eye (12.5%) had no change. The regions of ischemia in the two eyes showing reversal of capillary ischemia were a particular focus of this case series. During a six-month period without injections in this study, seven eyes (87.5%) showed a net increase in their total area of ischemia, one eye (12.5%) had no change, and no eyes showed a decrease in ischemia.

Conclusion: Intravitreal injection of pegaptanib sodium halted and sometimes reversed capillary nonperfusion in eyes with diabetic retinopathy.

Keywords: Diabetic retinopathy, Capillary dropout, Pegaptanib sodium

Introduction

Retinal capillary nonperfusion is a hallmark of numerous retinal disease processes including diabetic retinopathy, retinal vascular occlusions, sickle cell retinopathy, as well as infectious and inflammatory diseases of the retina. Capillary nonperfusion in the macula, or ischemic maculopathy, typically leads to photoreceptor death and irreversible visual impairment [1,2]. Capillary nonperfusion outside of the macula can also have devastating consequences by promoting production of vascular endothelial growth factor (VEGF). VEGF overproduction increases vascular permeability [3], contributing to macular edema, as well as promoting neovascularization and its associated complications [4].

The relationship between capillary nonperfusion and VEGF is cyclic. Worsening of retinal capillary nonperfusion leads to increased levels of VEGF, and increased levels of VEGF can trigger retinal capillary nonperfusion. Mechanisms by which VEGF may promote proliferation of retinal vascular endothelial cells have been outlined in several animal and tissue studies. In a study examining the effect of intravitreal VEGF-165 in primate eyes, Tolentino et al. [5] reproduced ischemic changes typical of diabetic retinopathy, noting upregulation of proliferating cell nuclear antigen in the vascular endothelium on immunostaining. VEGF may also produce capillary nonperfusion via an interaction with intracellular adhesion molecule-1 (ICAM-1). The link between VEGF and ICAM-1 was established by Lu et al. [6] who demonstrated that VEGF upregulates ICAM-1 levels in capillary endothelium in the human brain.

Using a rat model, Miyamoto et al. [7] and Joussen et al. [8] showed that capillary nonperfusion was specifically related to upregulated ICAM-1 mediating leukostasis. VEGF has also been found to cause capillary luminal narrowing in monkeys further contributing to capillary nonperfusion [9]. Furthermore, Kim et al. [10] compared diabetic and nondiabetic monkeys and found an increase in the number of leukocytes adjacent to areas of capillary nonperfusion. Given the role of VEGF, not only as a downstream product, but as a key regulator of nonperfusion, VEGF inhibition may influence retinal ischemia.

Retrospective analysis of large clinical trials focusing on intravitreal anti-VEGF support the notion that VEGF suppression can halt or even reverse capillary nonperfusion. These for the most part described changes in summated regions of nonperfusion, but did not focus on individual regions where changes in perfusion occurred. For example, retrospective analysis of the Study of the Efficacy and Safety of Ranibizumab Injection in Patients with Macular Edema Secondary to Branch Retinal Vein Occlusion (BRAVO) and the Study of the Efficacy and Safety of Ranibizumab Injection in Patients with Macular Edema Secondary to Central Retinal Vein Occlusion (CRUISE) found that treatment with ranibizumab in eyes with retinal vein occlusion did not worsen retinal nonperfusion and in some cases actually induced reperfusion [11]. Similar results were noted in retrospective analyses of a Study of Ranibizumab Injection in Subjects with Clinically Significant Macular Edema with Center Involvement Secondary to Diabetes Mellitus (RISE and RIDE) demonstrating that ranibizumab treatment in eyes with diabetic macular edema could slow progression of capillary closure [12]. These studies were limited in their retrospective design and, more importantly, in their use of standard 7-field fluorescein angiography (FA) that cannot image the far retina periphery. Widefield FA can provide detail of capillary perfusion in the far periphery and also has the advantage of visualizing capillaries at the same time point in the angiogram, rather than introducing timing differences when separate fields are merged together after fluorescein transit [13].

This pilot study sought to determine the effect of intravitreal injection of pegaptanib sodium (Macugen), a VEGF-165 inhibitor, in eyes with non-proliferative diabetic retinopathy (NPDR) and proliferative diabetic retinopathy (PDR) that demonstrated peripheral capillary nonperfusion at baseline utilizing widefield FA.

Methods

IRB approval and ethical compliance

This was a single center case series involving eight eyes of eight patients with capillary nonperfusion who were treated serially with intravitreal pegaptanib sodium by the Retina Service at University of Pittsburgh Medical Center. The study was done early on before pegaptanib sodium was used clinically for the treatment of diabetic retinopathy in the United States. Hence, an investigational new drug (IND) application was needed from the FDA (IND Number 73903). The University of Pittsburgh Institutional Review Board approved this study (IRB# PRO07020108). The study adhered to the tenets of the Declaration of Helsinki for research involving human subjects and complied with the Health Insurance Portability and Accountability Act (HIPAA).

Subjects

Subjects ages 18 and older with diabetic retinopathy were eligible for enrollment if they were found to have more than two-disc diameters of retinal capillary nonperfusion in one eye. Inclusion criteria included baseline Early Treatment Diabetic Retinopathy Study (ETDRS) best corrected visual acuity between 20/40-20/320. Additionally, for women of childbearing age, negative pregnancy test and agreement to utilize contraception for the duration of the study was required prior to enrollment.

Patients were excluded from this study if they had any of the following ocular comorbidities: significant cataract, age-related macular degeneration, glaucoma, uveitis, or tumor. Additional exclusion criteria included concomitant retinal disease, or history of anti-VEGF injections in the previous six months. Patients with history of chronic ischemia defined as greater than six months in duration were excluded as well. Other exclusion criteria were history of intraocular surgery in the three months prior to enrollment, as well as, spontaneous improvement within the preceding six months. Spontaneous improvement was defined as improvement of greater than 15 letters of vision or thinning of ETDRS central foveal on Cirrus Ocular Coherence Tomography (OCT) of greater than 20% from baseline. Finally, patients with allergy to povidone iodine were excluded as this was used in preparing the eye for the intravitreal injections.

Given these strict inclusion and exclusion criteria, nine patients were eligible for this study, eight eyes of eight patients with diabetic retinopathy were enrolled including five males and three females ranging in age from 25.5 to 74.6 years old (one was lost to follow up prior to conclusion of the study).Written informed consent was obtained for all subjects.

Study design

Study eyes were examined at a minimum on day 0, week 6, week 12, and week 36. At these visits each subject had refraction of the study eye, visual acuity and intraocular pressure measurement as well as examination by slit lamp microscopy and indirect ophthalmoscopy. At these visits, Cirrus OCT of the macula as well as Optos P200A widefield FAs were obtained. Intravitreal injection of pegaptanib sodium (0.3 mg) was performed at day 0, week 6, and week 12. Additional injections were allowed after 36 weeks as needed at the discretion of the retina specialist. All subjects were followed for a minimum of 36 weeks (ranging from 253 days to 542 days). The study design was empiric in nature as widespread experience with pegaptanib sodium for the treatment of diabetic retinopathy did not exist at the time of the IND application.

Primary and secondary endpoint data analysis

The primary endpoint in this study was total area of capillary nonperfusion in study eyes. Fluorescein angiograms were interpreted by two masked observers who were retina attendings or fellows. The images were read in an arbitrary sequence for each subject. First, the best arteriovenous phase digital image at each visit was selected for interpretation. Next, the entire extent of retinal vasculature was delineated on each image and the total number of pixels captured by each widefield retinal image was recorded using Adobe Photoshop software using the histogram mode. Then, regions of capillary nonperfusion as observed by the readers were enclosed by a border drawn on the computer screen using a mouse. The number of pixels enclosed was summed to determine the extent of ischemia for a given subject at each time point. The results of the two readers were independently reviewed to adjudicate any large disparities (greater than or equal to 10%) by the corresponding author (TRF). Change

in area of capillary nonperfusion was defined in our study as a greater than or equal to 10% difference in total ischemic pixels between two time points. Patients with less than a 10% difference in ischemic pixel quantities were considered as having unchanged capillary nonperfusion. This threshold was chosen because despite the benefit provided by widefield FA to see the far periphery, blurring and artifact can occur at the edges of the image making smaller changes in pixel density difficult to fully ascribe to treatment effects. The change in area of nonperfusion as determined by this method was compared between baseline and 12-week follow-up, the scheduled injection phase of the study, as well as between 12-week follow-up and last study follow-up, the injection as needed phase of the study.

Secondary endpoints included visual acuity and central macular thickness as measured on OCT. Change was defined as a greater than 10% difference in central macular thickness as measured in microns. Comparisons of visual acuity and macular thickness were made baseline to 12-weeks follow-up, the scheduled injection portion of the study, and from 12-week follow-up to last study follow-up, the injection as needed portion of the study.

Results

Eight eyes of eight patients were included in this study, including five males and three females. Age at time of enrollment, ages ranged from 25.5 to 74.6 years old with an average age of 58.3 ± 15.2 years. Of the eight eyes, five eyes had NPDR and three eyes had PDR at the time of enrollment. Duration of follow-up ranged from 38.1 to 73.0 weeks with a mean follow-up period of 58.3 ± 10.9 weeks (Table 1). The number of injections of pegaptanib sodium received during this study ranged from three to five with a mean of 4.0 ± 0.5 injections. Within the first 36 weeks of the study period, each eye received three injections. All eyes had a minimum of two-disc areas of ischemia when totaled at baseline. Visual acuity and macular thickness baseline and final characteristics are presented in Table 2.

From the time of enrollment visit to 12-weeks follow-up, the scheduled injection period of the study, five eyes (62.5%) showed a decrease in the total area of capillary nonperfusion, three eyes (37.5%) had no change in total area of capillary nonperfusion, and zero eyes exhibited an increase in total area of capillary nonperfusion (Figure 1 and Table 1). All five eyes that experienced a decrease in total area of nonperfusion had greater than 200 ischemic pixels on their baseline FA. The three eyes that had no change in their area of nonperfusion had fewer than 200 ischemic pixels on baseline imaging.

When comparing total area of capillary nonperfusion at 12 weeks to 36 weeks, a six-month period without injections, seven eyes (87.5%) showed an increase in their total area of nonperfusion, one eye (12.5%) showed no change, and zero eyes showed a decrease. From the time of the third injection at 12 weeks (the end of scheduled injections) to the final follow-up visit, the injection as needed period, eyes received between 0 to 2 additional injections of pegaptanib sodium as needed with an average of 1 ± 0.5 additional injections. Over this injection as needed period, five eyes (62.5%) showed an increase in total area of capillary nonperfusion, two eyes (25%) showed a decrease, and one eye (12.5%) showed no change. When comparing capillary nonperfusion at enrollment to that at the time of final visit, three eyes (37.5%) had a decrease in total area of capillary nonperfusion, one eye (12.5%) had no change, and four eyes (50%) had an increase.

Table 1: Patient characteristics and ischemic changes during study period.

Patient	Age (Years)	Gender	Diagnosis	Follow-Up Length (Weeks)	Ischemia Changes: Scheduled Injection Period	Ischemia Changes: Inject As Needed Period
1	65	Male	NPDR	61	↓	↑
2	64	Male	NPDR	67	←→	←→
3	48	Female	PDR	38	↓	↑
4	25	Male	NPDR	65	↓	↑
5	65	Male	PDR	52	←→	↑
6	63	Female	NPDR	58	←→	↓
7	62	Male	PDR	73	↓	↑
8	74	Female	NPDR	52	↓	↓

Table 2: Patient baseline visual acuity and macular thickness characteristics.

Patient	Diagnosis	Visual Acuity at Baseline	Visual Acuity at Final Visit	Macular Thickness at Baseline (Microns)	Macular Thickness at Final Visit (Microns)
1	NPDR	20/200	20/250	669	562
2	NPDR	20/320	20/320	745	702
3	PDR	20/40	20/50	305	389
4	NPDR	20/50	20/40	443	304
5	PDR	20/250	20/200	527	555
6	NPDR	20/160	20/80	629	351
7	PDR	20/250	20/400	531	248
8	NPDR	20/250	20/250	161	158

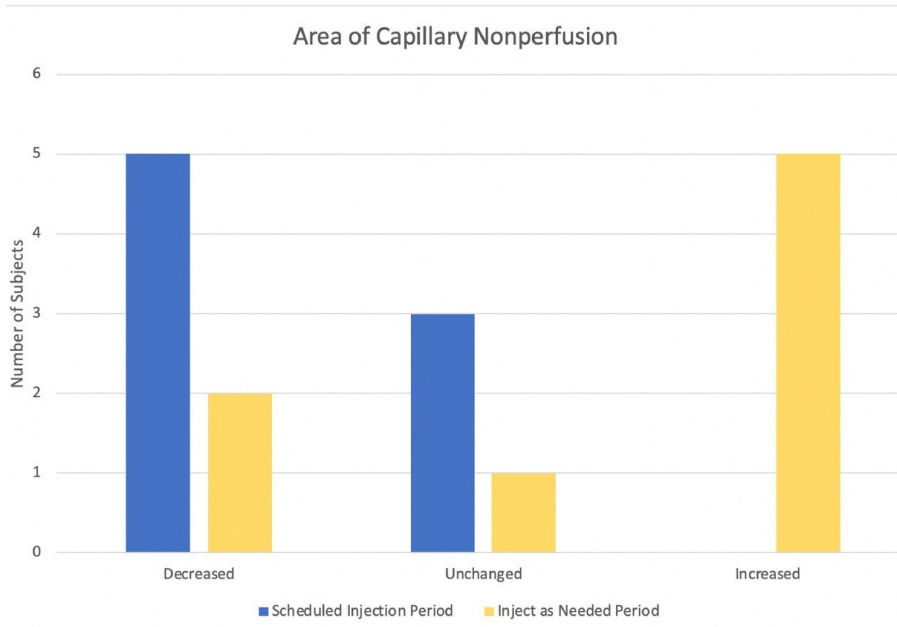

Figure 1: Changes in capillary nonperfusion over study period.

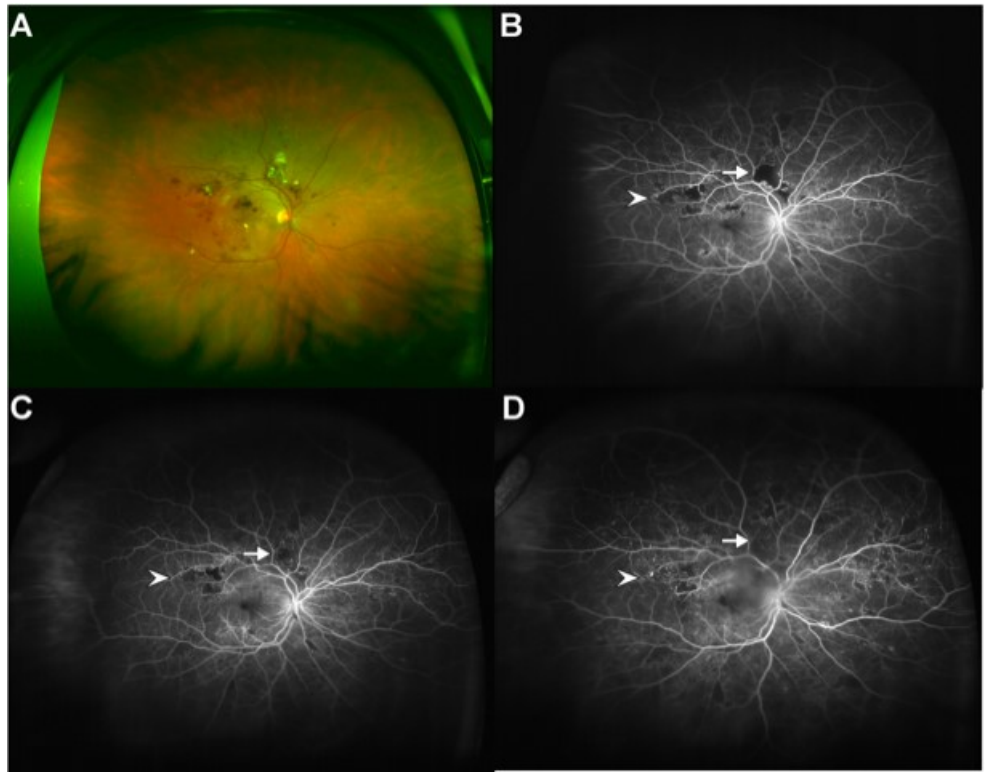

Figure 2: Images show a reduction in total area of capillary nonperfusion during scheduled injection period and recurrence of nonperfusion during injection as needed period in a patient with diabetic retinopathy. **A:** Baseline fundus photograph of a 65-year-old patient with diabetic retinopathy demonstrating multiple dot, dot blot, and flame hemorrhages with circinate exudates in the fovea. **B:** Baseline widefield fluorescein angiography shows many areas of hypofluorescence, the majority of which are areas of capillary nonperfusion with a few areas representing hemorrhage. **C:** Repeat widefield fluorescein angiography at 12-week follow-up after scheduled injection of pegaptanib sodium demonstrates focal areas of reperfusion which appear to occur at the pre-capillary arteriolar as well as capillary level. **D:** widefield fluorescein angiography at 36-week follow-up after a six-month hiatus from anti-VEGF shows increased ischemia.

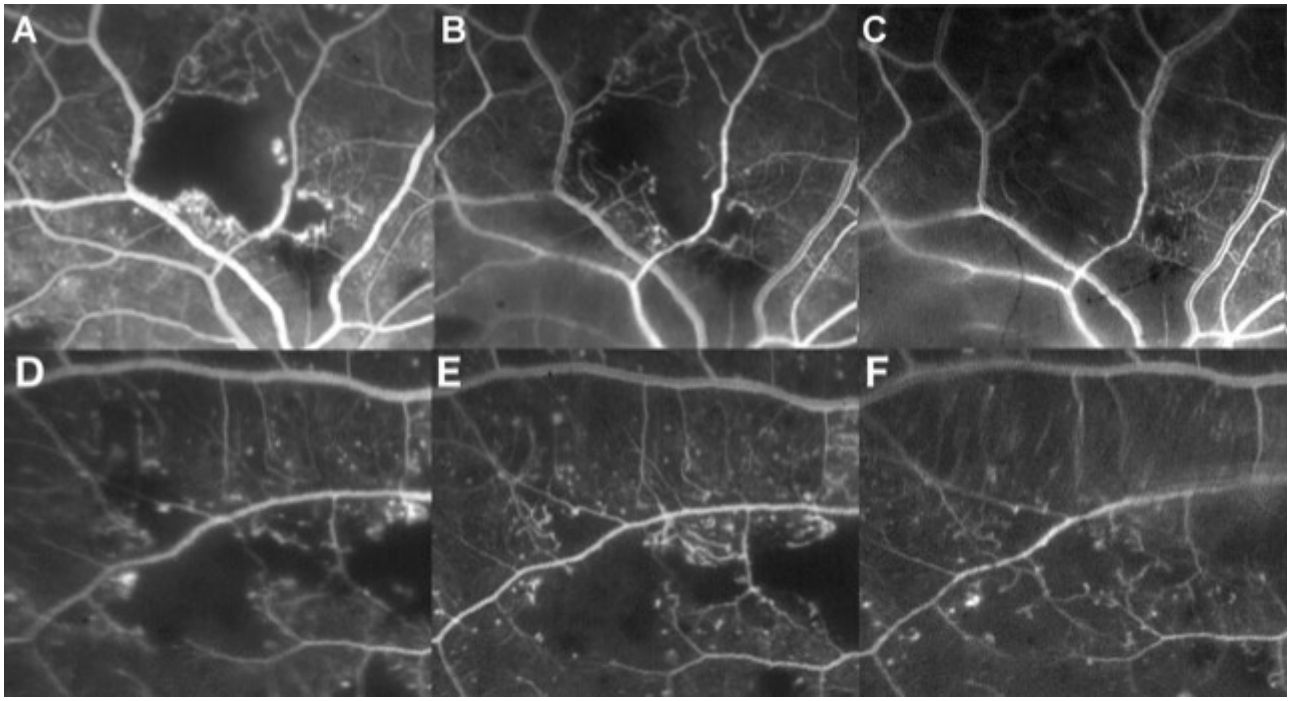

Figure 3: Images highlight two areas of capillary nonperfusion. **A-C:** Area of capillary nonperfusion corresponding to arrows in Figure 2 shows increasing pre-capillary arteriolar perfusion from baseline (**A**) to 12-week follow-up (**B**), with more diffuse leakage obscuring increasing ischemia at 36-week follow-up (**C**). Second area of nonperfusion in the superior macula corresponding to arrowheads in Figure 2 improves from baseline (**D**) to 12-week follow-up (**E**) and also at 36-week follow-up (**F**) with increase perfusion of pre-capillary arterioles.

Figure 2A shows a baseline fundus photograph of a 65-year-old patient (Patient #1 in Table 1) with NPDR demonstrating multiple dot, dot blot, and flame hemorrhages with circinate exudates in the fovea. Baseline widefield FA shows many areas of hypofluorescence, the majority of which are areas of capillary nonperfusion with a few areas representing hemorrhage (Figure 2B). Repeat widefield FA at 12-week follow-up (Figure 2C) after scheduled injection of pegaptanib sodium demonstrates multiple areas of reperfusion which appear to occur at the precapillary arteriolar as well as capillary level, while, widefield FA at 36-week follow-up (Figure 2D) after a six-month hiatus from anti-VEGF shows increased nonperfusion.

In Figure 3, two areas of capillary nonperfusion are highlighted. An area of capillary nonperfusion superior to the optic disc shows increasing pre-capillary arteriolar perfusion from baseline (3A) to 12-week (3B), with more diffuse leakage obscuring increasing ischemia at 36-week follow-up visit (3C). Interestingly, one area in the superior macula at baseline (3D) improves not only at 12 weeks (especially superotemporally) but also at 36 weeks follow-up with increased perfusion of pre-capillary arterioles.

When comparing the secondary endpoint of macular thickness, four eyes (50%) showed a decrease in central macular thickness, three eyes (37.5%) showed no change, and one eye (12.5%) showed an increase during the scheduled injection portion of the study. Visual acuity over this period improved by at least one line in five eyes (62.5%), one eye (12.5%) showed no change, and two eyes (25%) showed a decline of at least one line. When comparing macular thickness during the injection as needed portion of the study, three eyes (37.5%) showed a decrease in foveal thickness, three eyes (37.5%) showed no change, and one eye (25%) showed an increase. Comparing visual acuity over this period, three eyes (37.5%) had an improvement of at least one line, one eye (12.5%) showed no change, and four eyes (50%) showed a decline of at least one line. Over the course of the entire study from baseline to final visit, three eyes (37.5%) had at least one line of improvement, four eyes (50%) showed a decline of at least one line, and one eye (12.5%) showed no change.

Discussion

To our knowledge, this is the first study to demonstrate that VEGF suppression with pegaptanib sodium, a VEGF-165 antagonist, can halt, and in many cases, reverse capillary nonperfusion in diabetic eye disease. Similar findings have subsequently been reported by Heier and Shah [14] in the Impact of Intravitreal Aflibercept Injections on Capillary Non-Perfusion Study (ANDROID study) presented at the 2016 meeting of the Macula Society. Heier and Shah found that in 24 eyes (15 with PDR and nine with RVO) receiving monthly aflibercept for one year or monthly injections for six months then bimonthly injections for a total period of one year, 83% had an improvement in capillary nonperfusion and 17% had worsening of their capillary nonperfusion. No statistically significant difference between those receiving twelve or nine injections was found or between those with proliferative diabetic retinopathy and retinal vein occlusion. Wykoff et al. recently evaluated changes in retinal perfusion in 466 eyes with diabetic macular edema that were randomized to laser, intravitreal aflibercept every 4 weeks, or

aflibercept every 8 weeks and found that 44.7% and 40.0% of eyes treated with aflibercept demonstrated improvement in perfusion status [15].

The key difference between our study and these studies was the use of pegaptanib sodium versus aflibercept, frequency of injections, as well as the use of widefield FA in our studied compared to standard 7-field imaging. Pegaptanib sodium acts on VEGF-165, one subtype of VEGF-A, whereas aflibercept acts a VEGF "trap" binding all forms of VEGF-A and VEGF-B. The number and frequency of injections was also greater in these subsequent studies. Levin et al. found similar rates of reperfusion (75%) in their retrospective study 16 eyes with diabetic retinopathy utilizing widefield FA [16]. Our study is unique in that we are able to show the process of reperfusion of existing capillaries over time in multiple areas of drop out (Figures 2 and 3). Our study adds to the growing literature that retinal nonperfusion, once thought to be irreversible, can be reversed through VEGF suppression. We are unaware of any published, definitive fluorescein angiographic evidence of localized capillary reperfusion in the same region of regard using pegaptanib sodium or any other anti-VEGF medication.

Consistent with the above findings, during the scheduled injection period, five eyes (62.5%) showed at least a 10% reduction in total area of capillary nonperfusion. The eyes that did not show a reduction in area of nonperfusion all remained stable and all had a minimal area of ischemia at baseline. No patients had an increase in the area of ischemia during the scheduled injection period. These results suggest that fluorescein evidence of reperfusion may be more marked in patients with greater ischemic burden at baseline. As seven of eight eyes (87.5%) developed an increased area of ischemia between week 12 and week 36 of the study, a six-month period without injections, reperfusion appears to be transient in the absence of chronic VEGF suppression.

Our study demonstrates that intravitreal injection of pegaptanib sodium can halt and reverse capillary nonperfusion in patients with diabetic retinopathy. It is important to note that at a given timepoint the total area of ischemia was decreased due to reperfusion of certain capillary beds while others remained ischemic. This implies that not all nonperfused tissue can be salvaged by anti-VEGF therapy. While these areas of capillary nonperfusion are outside of the fovea and do not directly affect visual acuity, the ability to halt or reverse capillary nonperfusion may have some benefits for patients with diabetic eye disease. As mentioned earlier, reversal or stabilization of retinal ischemia may be one mechanism for the prevention or postponement of clinical sequelae of VEGF overexpression such as macular edema and proliferative disease, especially in patients at high risk of progression with severe NPDR. Reversing capillary nonperfusion may also impact other components of functional vision. For example, Arend et al. [17] demonstrated that even before edema and proliferative disease arise, diabetic patients have decreased contrast sensitivity that correlates with the amount of capillary dropout. Loss of contrast sensitivity has important consequences for patients as it has been associated with issues in mobility, reading, facial recognition, finding objects, and driving [18].

The advantage of pan-VEGF inhibition offered by ranibizumab, bevacizumab, and aflibercept have made these drugs the standard of care for macular edema and neovascular disease, however, the use of pegaptanib sodium still has a role to play in specific cases. A study of 50 eyes in Japan with ranibizumab-resistance exudative age-related macular degeneration treated with pegaptanib sodium found complete resolution of exudative changes in 54% of these eyes and reduction of exudative changes in 42% [19]. These effects were hypothesized to be due to tachyphylaxis to ranibizumab, which has been demonstrated in previous studies [20,21]. In diabetic retinopathy, VEGF-165 has been implicated in animal studies to be involved in the breakdown of blood-retina barrier with re-establishment of the blood-retina barrier following pegaptanib administration [22,23]. Our results in a small series of patients treated early on with pegaptanib found similar reperfusion rates as those treated with pan-VEGF inhibitors, perhaps highlighting that VEGF-165 plays a larger role in comparison to other VEGF isoforms in precipitating capillary dropout in diabetic retinopathy.

Regarding our secondary outcomes, macular edema did improve or remain the same in the majority of eyes during both the scheduled and injection as needed period of the study. These results are in line with the well-established benefit of VEGF suppression in treating macular edema. Some eyes did experience improvement or stabilization in visual acuity. However, over the course of the entire study period, five of eight eyes (62.5%) experienced a decline in visual acuity. This was likely due to a combination of progression of their underlying disease and chronicity of edema prior to enrollment.

Advantages of our study include duration of follow-up with repeated widefield fluorescein angiograms and prospective design. There are a number of limitations as well. We had no control group of eyes with capillary nonperfusion that were followed over a similar time period without injection. One large study of the natural history of capillary nonperfusion in diabetic retinopathy found that reperfusion occurred in 69% of eyes over a mean follow-up period of two years, however, this study defined reperfusion as being due to recanalization or neovascularization [24]. Only 34% of eyes experienced reperfusion due to recanalization and this study was limited as it did not utilize widefield fluorescein angiography. Our study in conjunction with evidence from Heier and Shah, Levin et al., and Wykoff et al. imply a treatment effect beyond that of reperfusion due to natural history. Second, our results cannot be extrapolated to patients with more longstanding retinal ischemia. Finally, we had a small number of subjects with diabetic retinopathy of varying severity underlying their capillary nonperfusion. Early Widefield FA platforms had the inherent limitation of blurring and artifact at the edges of the captured image, however, we mitigated this limitation by having a large threshold for defining change (greater than 10% difference) and only making categorical comparisons between individual patients.

Growing evidence suggests that VEGF inhibition can influence capillary nonperfusion in diabetic retinopathy. Our study provides photographic evidence of reperfusion following treatment with pegaptanib sodium. Further investigation is warranted to see if capillary reperfusion offers any functional benefits for patients.

Conflicts of Interest

Neither author has any conflicts of interest to report.

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Author Contributions Statement

Asad F. Durrani contributed to data acquisition and research execution, data analysis and interpretation, and manuscript preparation.

Thomas R. Friberg contributed to research design, data acquisition and research execution, data analysis and interpretation, and manuscript preparation.

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