REVIEW ARTICLE

Changes in Macular and Peripheral Perfusion Following Anti-vascular Endothelial Growth Factor Treatment for Patients with Diabetic Retinopathy

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Abstract

Diabetic retinopathy (DR) is a common complication of diabetes mellitus. Imaging techniques such as the gold standard of fluorescein angiography (FA) and the recent advent of optical coherence tomography angiography (OCTA) have allowed for detailed visualization of the microvasculature to assess and quantify macular perfusion. The development of ultra-widefield FA (UWFA) has allowed clinicians to examine ischemia within the periphery. As our imaging and diagnostic methods continue to be refined, it is important to understand how to best utilize these technologies to characterize disease severity and determine how it can guide treatment and prognosis. With the increasing use of anti-vascular endothelial growth factor (VEGF) agents for the treatment of DR, we can characterize the changes in perfusion on the microvascular level. The focus of this review is to summarize and identify the changes in both macular and peripheral perfusion with anti-VEGF treatment for patients with DR utilizing FA, UWFA, and OCTA. There remains a need for more prospective, long-term clinical trials with controls to better understand the characterization of the retinal microvasculature using these imaging techniques. In clinical practice, physicians likely will need to utilize a multimodal imaging approach to appropriately characterize the degree and progression of ischemia in DR.

Keywords: Anti-vascular endothelial growth factor, Diabetic retinopathy, Macular perfusion, Peripheral perfusion

INTRODUCTION

Diabetic retinopathy (DR), a common complication of diabetes mellitus, is a leading cause of blindness worldwide,[1] and the number of patients with sight-threatening DR is expected to increase in our future.[2] Early detection with appropriate staging and classification of the disease can determine prognosis and guide treatment to avoid preventable complications such as vision loss. It is estimated that >90% of vision loss can be prevented.[3]

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The pathophysiology of DR involves abnormal vascular function within the retinal circulation. The hyperglycemic state in uncontrolled diabetes leads to loss of pericytes, weakening retinal capillary walls.[4] Utilizing a physics perspective with the Hagen-Poiseuille equation, the dilated vessel has increased flow and thus becomes the preferred shunt vessel, causing adjacent capillaries to become non-perfused.[5] This results in ischemia and a cascade of molecular processes, including upregulation of vascular endothelial growth factor (VEGF) in response to the hypoxia.[6] Although the exact pathogenesis has not been fully defined, VEGF mediates

breakdown of the blood-retinal barrier and angiogenesis, contributing to retinal vascular hyperpermeability.[7] Furthermore, in animal models, increased VEGF levels have been correlated with recruitment of leukocytes within the retina, suggesting that leukocyte plugging may play a critical role in vessel closure.[8,9] Intravitreal anti-VEGF therapy has thus become the standard of care for diabetic macular edema. Major clinical trials such as RISE, RIDE, VIVID, and VISTA trials have well demonstrated the use of anti-VEGF agents to improve visual outcomes for patients with DR.[10,11]

Fluorescein angiography (FA) is an important diagnostic imaging tool for characterization of disease severity in DR. Using intravenous dye injection; FA can image perfusion of the retinal vessels and show dye leakage in areas of increased vascular permeability.[12] It can evaluate the manifestations of DR such as vascular abnormalities such as microaneurysms and areas of venous beading. FA can also identify areas of retinal nonperfusion, neovascularization, and areas of leakage secondary to macular edema. Drawbacks include intravenous dye injections, which can be invasive and burdensome for the patient. The test can also cause a range of unpleasant side effects such as nausea/vomiting, urticaria, and more rarely, anaphylactic reaction.[13] Other potential drawbacks include lack of optimal visualization of the deeper retinal vessels given that these images are limited to two dimensions. There may also be limitations in the interpretation of the images due to masking by leaking and hemorrhage.

The recent advent of optical coherence tomography angiography (OCTA) has allowed for noninvasive visualization of structural features and retinal vascular mapping. OCTA allows for precise and detailed visualization of retinal and choroidal blood vessels at each retinal capillary layer. This imaging modality can visualize abnormalities in the capillary flow density and microaneurysms within the deep capillary layer that was unable to be visualized on FA.[14-16]

As our imaging and diagnostic methods continue to be refined, it is important to understand how to best utilize these technologies to characterize disease severity and determine how it guides treatment and prognosis. With the increasing use of anti-VEGF injections for the treatment of diabetic macular edema (DME), there are still relatively few studies that have examined the changes on a microvascular level in patients with DR from the use of anti-VEGF agents. The focus of this review is to summarize and identify changes in macular and peripheral perfusion following anti-VEGF treatment for patients with DR.

Table 1: Studies examining retinal perfusion and presumed impact of anti-VEGF therapy

Study	Presumed impact of anti-VEGF on change in macular or peripheral perfusion as measured by FA or OCTA	Pertinent findings
Post hoc analysis of RISE/RIDE studies (Reddy *et al.*, Campochiaro *et al.*)	Neutral	Percentage of patients with MNP was stable in anti-VEGF treatment arms through study period of 24 months, while percentage of patients with MNP increased in sham arm through the study period.
Feucht *et al.*	Negative	FAZ area increased 6–8 weeks after single anti-VEGF injection
Erol *et al.*	Negative	FAZ area increased after 3 anti-VEGF injections
Subanalysis of RESTORE study (Karst *et al.*)	Neutral	FAZ area unchanged and capillary loss not worsened significantly throughout the study period of 36 months
Subanalysis of Bolt study (Michaelides *et al.*)	Neutral	FAZ area without significant change after 4 months of anti-VEGF therapy
Ghasemi Falavarjani *et al.*	Neutral	No change in retinal capillary density in SCP or DCP after single anti-VEGF injection. No change in FAZ area after single anti-VEGF injection.
Gill *et al.*	Positive	FAZ area decreased between visits (note: Not all patients received anti-VEGF in this study).
Levin *et al.*	Positive	Reperfusion demonstrated in areas of nonperfusion with anti-VEGF therapy
PERMEATE study (Ehlers *et al.*)	Positive	Ischemic index decreased after 12 months of anti-VEGF treatment (note: Patients had either RVO or DME in this study)
Bonnin *et al.*	Neutral	No reperfusion noted after 3 months of anti-VEGF treatment

VEGF: Vascular endothelial growth factor, OCTA: Optical coherence tomography angiography, FA: Fluorescein angiography, DME: Diabetic macular edema, FAZ: Foveal avascular zone, MNP: Macular nonperfusion

METHODS

A PubMed engine search was carried out using the terms "DR" with the terms "anti-VEGF," "OCTA," "ultra-wide field FA," "macular perfusion," and "peripheral perfusion." Relevant studies published in English up to November 2018 were reviewed. Case reports were excluded.

Changes in macular perfusion

The findings of the studies discussed in this review and their conclusions on the impact of the role of anti-VEGF therapy on macular or peripheral perfusion are briefly summarized in Table 1.

FA

FA has been considered the gold standard to evaluate the microvascular structure. It currently remains the most clinically available and is used to assess for nonperfusion in patients with retinal vascular diseases. It can be useful in evaluating the changes in macular perfusion with anti-VEGF agents.

The RIDE and RISE clinical trials demonstrated the efficacy of anti-VEGF agents for patients with DME. Reddy *et al*. performed a *post hoc* analysis of the RIDE/RISE trials to examine patients with DME with coexisting macular nonperfusion (MNP) at baseline as determined by FA. MNP in this study was measured using an overlay of the Early Treatment for DR Study (ETDRS) grid on a FA of the macula. The percentage of capillary loss in the central, inner, and outer subfields was estimated, and a software algorithm was used to convert these percentages into disc areas to quantify MNP. The study concluded that although patients with baseline MNP had worse baseline visual acuity and increased central subfield thickness, this subgroup still was able to improve significantly in terms of visual/anatomical outcomes with ranibizumab injections, with results comparable to eyes without baseline MNP (+15.06 vs. +13.4 letters, respectively, $P = 0.2$).[17] Campochiaro *et al*. also studied retinal capillary nonperfusion in patients with DME from RISE/RIDE trials, focusing on whether monthly ranibizumab injections reduced the progression of posterior retinal nonperfusion (RNP). RNP was measured by a masked grader who assessed FAs in the center, inner, and outer ETDRS subfields to measure disc areas that had angiographic characteristics such as a darker choroid or pruned appearance of adjacent arterioles. The percentage of patients in the ranibizumab arms of the study without retinal nonperfusion was relatively stable at baseline, 12 months, and 24 months, with a slight decrease seen at 36 months (71.8%, 78.1%, 75.1%, and 66.1%, respectively, for patients receiving 0.3 mg of ranibizumab; and 74.2%, 81.8%, 74.4%, and 65.5%, respectively, for patients receiving 0.5 mg of ranibizumab). However, the percentage of patients in the sham arms without retinal nonperfusion decreased from baseline compared to 12 and 24 months (73.7%, 64.5%, and 56.9, respectively) suggesting that the rate of progression of nonperfusion in the eyes of patients receiving anti-VEGF is slowed.[17,18] Campochiaro *et al*. concluded that anti-VEGF intervention can slow, though not completely prevent, retinal capillary closure in patients with DME. Patients in both the ranibizumab group and in the sham group had worsening retinal nonperfusion over time, though patients in the sham group had a faster rate of increase in retinal nonperfusion.[18]

Some studies have reported enlargement of the foveal avascular zone (FAZ), a marker of diabetic macular ischemia,[19] as measured by FA images after anti-VEGF therapy. Feucht *et al*. retrospectively examined 53 eyes with retinal vascular disease, either with branch retinal vein occlusion or DME who had received bevacizumab injections and found an enlargement of the FAZ area after approximately 6–8 weeks (+0.095 mm^2, $P < 0.001$).[20] Erol *et al*. also examined 29 patients with chronic DME and also found an increase in FAZ area after 3 months bevacizumab injections (+0.045mm^2, $P < 0.05$).[21] However, other studies within literature could not confirm this finding. Karst *et al*., who analyzed DME patients from the 24-month RESTORE study, did not find any significant increase in FAZ area with repeated ranibizumab treatment over a 36-month period. It was also noted that patients with moderate to severe capillary loss in this study did not worsen significantly over the 36-month study period.[22] Similarly, Michaelides *et al*. prospectively examined the FAZ area for 42 eyes with DME who had received three injections of bevacizumab. There was no evidence of worsening macular ischemia given no change was found in the FAZ area at 4 months.[23]

OCTA

OCTA is especially useful in its visualization of each retinal capillary layer and can provide greater detail in the deeper capillary network that may not be visualized on FA.[14-16] Studies have shown that the microvascular changes of DR such as microaneurysms and retinal nonperfused areas can be well visualized with OCTA.[16,24]

Ghasemi Falavarjani *et al*. examined 18 patients with either DME or macular edema secondary to central retinal vein occlusion to evaluate changes in the FAZ area and retinal capillary density with OCTA after a single anti-VEGF injection.[25] The authors found that retinal capillary density (both foveal and parafoveal vessel densities) in both the superficial capillary plexus (SCP) and deep capillary plexus (DCP) did not change significantly with a single anti-VEGF injection. Furthermore, they did not find any significant change in FAZ area in both the SCP and DCP before and after anti-VEGF injection.

Gill *et al*. retrospectively examined 20 eyes from 14 patients with DME to examine changes over time (mean:3.2 months)

in the FAZ. Eleven of these eyes received anti-VEGF while the others were observed; however, subgroup analyses were not performed due to small sample size. Using pseudo-automated and manual measurements of the FAZ area, there was a decrease in the size between two consecutive visits in the deep, superficial, and summated plexuses. They also noted that the largest decrease in the FAZ area was visualized within the deep plexus.[26]

Lee *et al*. retrospectively studied 51 eyes with DME who had a poor response to anti-VEGF agents and 32 eyes with DME who had a good response to anti-VEGF treatment. A good responder was defined as more than 50 μm reduction of central retinal thickness after three anti-VEGF treatments. These authors found that poor responders to anti-VEGF agents had lower flow density, larger number of microaneurysms, and a larger FAZ area within the DCP.[27] This study performed OCTAs after eyes were classified as either poor or good anti-VEGF responders; although there is no baseline OCTA before anti-VEGF intervention, this study was unique in its comparison of treatment response to the degree of damage at a microvascular level.

Changes in peripheral perfusion

FA

The invention of UWFA has allowed for further visualization of the retina to 200°, compared to the typical 75° as seen by the seven standard fields (7SF) angiogram.[28] Given hypotheses that DR lesions may first develop in the peripheral retina and that increased peripheral retinal lesions may also be correlated with increased severity of DR,[29,30] it is also important to assess peripheral perfusion. Although the level of peripheral ischemia using an ischemic index as a representative has been correlated with DR and DME severity,[31,32] there have been relatively few studies about the variation in peripheral perfusion after intravitreal injections of anti-VEGF.

Levin *et al*. retrospectively studied 16 eyes of 15 patients with DR and assessed UWFA images pre- and post-anti-VEGF injection for reperfusion. In this study, reperfusion was qualitatively assessed by visual comparison of pre- and post-injection images on UWFA. It was quantitatively measured using ImageJ software; each image was binarized (so that perfused areas appeared white on black background) and the areas of white pixels were compared between pre- and post-injection images. However, only selected areas were assessed for reperfusion in each image, as the whole area was unable to be quantified given artifacts in the images. The authors found that 12 of the 16 eyes demonstrated reperfusion, both qualitatively and quantitatively, on UWFA following anti-VEGF therapy in areas of the retina that had been non-perfused pre-injection.[33] As mentioned previously, RISE/RIDE studies had reported delayed rates progression of nonperfusion with ranibizumab; however, RISE/RIDE had not measured for reperfusion in the study, and reperfusion outside the 7SF zone would not have been captured within that study.

The PERMEATE study by Ehlers *et al*. prospectively examined 30 patients with either DME or RVO to quantify changes in leakage index using UWFA.[34] Leakage index was detected using an automated segmentation and detection algorithm using processed early phase and late phase images as described in an earlier study.[35] The authors found a significant decrease in leakage index (3.4–0.5%, $P < 0.0001$) after 12 months of intravitreal anti-VEGF therapy.[34]

Bonnin *et al*. retrospectively studied 18 eyes of 14 patients with DR after 3 months of anti-VEGF therapy to examine for retinal reperfusion as measured by UWFA. The authors in this study noted that although there was a regression in capillary leakage, no reperfusion of arterioles or venules in the initially nonperfused areas or a decrease in nonperfused areas was noted after treatment. Nonperfusion was not specifically quantified in this study; graders analyzed UWFA images side-by-side at baseline and at 3 months and compared for disappearance or reappearance of arterioles or venules. Although no small vessel reperfusion was observed in this study, the authors note that patients did have an improvement in DR severity score as based on fundus photos, suggesting that patients may show improvement in DR severity without retinal reperfusion.[36,37]

DISCUSSION

Although the effectiveness of anti-VEGF therapy for DME has been well demonstrated, the role of FA/UWFA and OCTA for characterization of ischemia in DR needs to be further refined. Understanding how DR affects both macular and peripheral perfusion and how it is altered by anti-VEGF intervention is important to guide management and determine visual prognosis.

Studies utilizing FA to examine macular perfusion after anti-VEGF intervention has provided some conflicting data. Studies describing an increase in FAZ area after anti-VEGF therapy had relatively short follow-up periods,[20,21] with concerns for risk of worsening macular perfusion. Larger analyses with longer follow-up periods from the RESTORE[22] study and the RISE/RIDE[10,11] studies suggest that anti-VEGF treatment does not increase the risk of further malperfusion.

How exactly VEGF promotes the closure of retinal vessels still needs to be elucidated. As suggested by Levin *et al*., treatment with anti-VEGF may promote reperfusion of previously nonperfused areas, suggesting that ischemic areas have salvageable tissue that indeed has the potential to reperfuse.[33] For the eyes that do not show reperfusion, it

can be hypothesized that these areas are either irreversibly infarcted or may require a higher or more frequent dose of anti-VEGF therapy. It has been well established that anti-VEGF agents have antiangiogenic and antipermeability effects, though exactly the mechanism for potential reperfusion is not completely understood. Possible mechanisms include the restoration of pericytes and normalization of the basement membrane, allowing for the retinal microvasculature to regrow.[38] Furthermore, VEGF suppression reduces leukostasis, allowing for potential reopening of vessels.[9] Alternatively, findings from Bonnin *et al*. argue that retinal reperfusion does not occur and is not even necessary to have a reduction of DR severity.[36]

Given the discrepancies in these studies (Table 1), it is important to remain cognizant that nonperfusion as detected by FA is variable in the exact criteria for grading.[36] Some studies measure retinal nonperfusion in the unit of disc areas, so subtle areas of retinal nonperfusion or reperfusion may be missed.[38] Different methods have been used to quantify nonperfusion. For example, some studies used binarized images to measure these areas,[33] while other studies looked for angiographic characteristics such as a darker choroid or pruned appearance of adjacent arterioles to identify nonperfused areas.[17,18] Quantification of leakage or ischemic areas is often manually quantified, through automated methods are in development for objective quantification purposes.[35] The inconsistencies in how nonperfusion are measured by FA allows room for subjective assessment.

At present, it is unclear if there is a change in vessel density as measured by OCTA with the anti-VEGF intervention (Table 1). Most of these studies mentioned in this review had relatively short-term follow-ups, some with only after one anti-VEGF injection. Changes from anti-VEGF in the FAZ area or the vascular density may occur after chronic treatment and are likely not seen in these studies with short study periods. It is also uncertain if the presence of intraretinal fluid alters the anatomy of the FAZ in eyes with DME.[26] Furthermore, FAZ was measured using a variety of methods throughout the studies noted (for example, automated vs. manual methods). Some drawbacks with OCTA include some limited detection of deeper layers of choroidal blood flow, especially in areas with evidence of retinal pigment epithelium atrophy.[39] Furthermore, it is difficult to determine if findings visualized are attributed to the natural course of the disease itself versus a potential side effect of anti-VEGF agents, especially for the studies with shorter follow-up periods.

FA/UWFA and OCTA are distinct imaging modalities with their particular advantages. Both can appropriately identify areas of ischemia qualitatively and quantitatively, such as microaneurysms and measuring changes in the FAZ or areas of capillary nonperfusion. FA continues to remain the gold standard for assessment of ischemia in patients with DR and has been studied extensively in clinical trials. UWFA is unique in allowing for assessment of the retinal periphery, especially given hypotheses that peripheral perfusion is correlated with the disease status of DR. OCTA provides more detail on the microvasculature within the capillary plexuses as well as quantification of the FAZ and vessel density, although how exactly to interpret the findings will need be further studied given concerns for imaging artifacts.[39]

Given that FA/UWFA is an invasive and burdensome procedure for patients and that OCTA can provide better discrimination and increased sensitivity of the macular microvasculature, it is possible that OCTA will replace FA in the foreseeable future, especially as there are improvements in scanning speeds, the field of view, and resolution of the images.[40] However, before this, there will need to be more prospective, longer-term clinical trials with controls to validate this imaging modality and understand the characterization of the retinal microvasculature utilizing OCTA.

As there continue to be advances in our imaging tools for DR, it is imperative that we gain a better understanding of the progression of DR with anti-VEGF intervention on a microvascular level. Given the burden and cost of anti-VEGF injections for patients, it is important to identify factors with our imaging modalities that can help guide and predict treatment response to anti-VEGF agents. In clinical practice, physicians will need to utilize a multimodal imaging approach with both FA/UWFA and OCTA to best characterize the degree of ischemia in DR.

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