

Macular ischaemia: a contraindication for anti-VEGF treatment in retinal vascular disease?

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ABSTRACT

Anti-vascular endothelial growth factor (anti-VEGF) therapy has been shown to be effective at improving vision in patients with macular oedema due to diabetic retinopathy and vein occlusions, but blocking VEGF at least in theory could be detrimental to vascular integrity. For this reason, some patients with macular ischaemia were excluded from studies showing the effectiveness of therapy. A considerable number of patients present with mixed pathology of macular oedema and macular ischaemia and it is often impossible to determine the degree to which ischaemia accounts for decreased vision. In this review, the authors have dealt with the specific question of whether or not there is evidence to support potential worsening of the macular perfusion and visual function after anti-VEGF treatment with bevacizumab or ranibizumab for macular oedema secondary to diabetic retinopathy or retinal vein occlusions, especially if there is coexisting macular ischaemia. The authors conclude that anti-VEGF therapy rarely seems to further compromise the retinal circulation; however, worsening of macular ischaemia in the long term cannot be definitely excluded, particularly in eyes with significant ischaemia at baseline and after repeated intraocular anti-VEGF injections. The decision to offer prolonged anti-VEGF treatment in cases of significant coexisting macular ischaemia should not be based only on measurements of macular thickness; instead repeat fluorescein angiograms should be performed.

INTRODUCTION

The primary treatment of diabetic macular oedema (DMO) and macular oedema secondary to branch retinal vein occlusion (BRVO) has been laser photocoagulation, supported by the Early Treatment Diabetic Retinopathy Study (ETDRS)¹ and the Branch Retinal Vein Occlusion study.² By contrast, the results of the Central Retinal Vein Occlusion (CRVO) Study Group did not support a recommendation for laser photocoagulation for macular oedema for the population meeting the study's eligibility criteria.³ Over the last decade there has been a surge in clinical data supporting the role, safety and better visual outcome of pharmacological therapy and in particular anti-vascular endothelial growth factor (anti-VEGF) agents in place of laser therapy for both DMO and macular oedema secondary to CRVO and BRVO.^{4–14} The effect of VEGF blockade on the ocular circulation forms a small proportion of two recent reviews on the safety of anti-VEGF therapy^{15 16} and another review on the use of anti-VEGF therapy for DMO¹⁷ but in the light of further publications and trial

results, along with the increasing use of anti-VEGF therapy for macular oedema, we felt there was a need for a wider consideration of the subject.

Good visual outcomes from the current trials of anti-VEGF therapy do suggest that VEGF blockade does not induce retinal ischaemia, at least not often and in the relatively healthy retina. Often patients with more ischaemic retinas were excluded from such studies. The latest therapy to have published vision data, VEGF Trap-eye, which is probably the most potent anti-VEGF agent so far, at least at 24 weeks, did not cause significant ocular side effects. No patients given the 2 mg dose lost >15 letters compared with 9.1% in the laser group and 4.5% in the 0.5 mg group.¹⁸ Macular ischaemia may be present in eyes with potentially treatable macular oedema, and may impart a poor prognosis after both laser and/or anti-VEGF therapy.^{19 20} In the case of concomitant macular oedema and macular ischaemia it is often impossible to determine the degree to which ischaemia accounts for decreased vision.

The purpose of this review is to deal with the specific question of whether or not there is evidence that treatment with the anti-VEGF agents bevacizumab and ranibizumab can worsen macular perfusion and visual function especially when a considerable amount of macular ischaemia is present at baseline.

METHOD

A Medline/PubMed search of the English language literature was conducted. In addition manual reference checks were performed on bibliographies from included articles until no new references were found. The search items used were diabetic retinopathy (DR), macular oedema, central retinal vein occlusion, branch retinal vein occlusion, macular ischaemia, vascular endothelial growth factor, retinal ischaemia, VEGF inhibitors, bevacizumab and ranibizumab in various combinations and in US and UK spelling. In particular, articles which were considered clinically significant included:

1. Articles focusing on the possible protective role of VEGF in retinal ischaemic conditions.
2. Randomised studies about the efficacy and safety of anti-VEGF agents ranibizumab and bevacizumab in DMO or macular oedema secondary to retinal vein occlusion (RVO), which established anti-VEGF treatment as an officially approved treatment for these conditions in many countries. The authors commented on these studies regarding whether eyes with macular ischaemia at baseline were included and whether fundus fluorescein angiography (FFA) based follow-up information of

the macular perfusion after anti-VEGF treatment was provided.

3. Non-randomised studies providing FFA-based assessment of the effect of ranibizumab and/or bevacizumab treatment on retinal/macular perfusion in eyes with DMO or macular oedema secondary to RVO with or without macular ischaemia at baseline.
4. Case reports of severe ocular ischaemic complications attributed to intraocular administration of the above anti-VEGF agents.

DETERMINING THE SEVERITY OF MACULAR ISCHAEMIA

FFA is the standard method for assessing macular ischaemia. The ETDRS provided a complex qualitative grading scheme of macular perfusion with evaluation of size and outline of the foveal avascular zone (FAZ) as well as capillary loss.²¹ Efforts to provide a quantitative assessment of the FAZ and perifoveal intercapillary area were made but these measurements have not been standardised yet.²² Additionally there is significant overlap of the size and surface of the FAZ between normal and abnormal individuals. As a result, grading of macular ischaemia lacks uniformity among published reports.

VEGF: IMPACT ON RETINAL VASCULATURE AND ROLE IN RETINAL ISCHAEMIA

Angiogenesis, the dynamic process whereby endothelial cells lead to new vessel formation, is essential for the development of human tissues and wound healing. VEGF has been identified as the main regulator of angiogenesis in the eye for physiological and pathological processes.²³ Under physiological conditions the human retina contains little VEGF, but VEGF expression increases under hypoxic conditions and is upregulated in ischaemic retinopathies such as DR.^{24 25} Abnormal high levels of VEGF have been found in intraocular fluid of patients with DMO²⁶ and macular oedema secondary to RVO.²⁷ Several forms of VEGF have been identified: VEGF-A, VEGF-B, VEGF-C, VEGF-D, VEGF-E and placental growth factor, all of which are derived from the same gene family.²⁸ The family of VEGF-A appears to be involved in vascular proliferation and has drawn a great deal of attention. Within this family alternative exon splicing results in four principal isoforms (VEGF 121, 165, 189 and 206).

VEGF induces endothelial proliferation and migration consistent with clinical findings of microaneurysm formation and neovascularisation.²⁹ VEGF also induces hyperpermeability of retinal capillaries resulting in macular oedema by disruptive effects on the endothelial zona occludens, induction of fenestrations in endothelial cells, fragmentation of endothelium and degenerative changes in endothelial basement membranes.^{30–34} However, VEGF has a protective role against apoptotic neuroretinal cell death in ischaemic retinal conditions.³⁵ It is well established that increasing blood flow to neuronal tissues can enhance neuroprotection.³⁶ VEGF cannot only increase volumetric blood flow but it seems to have an additional direct neuroprotective effect on retinal neurons.³⁵ Various studies suggest that VEGF-A along with other hypoxia-inducible proteins are upregulated by ischaemic preconditioning, a brief ischaemic episode that protects various tissues, including neurons, against subsequent prolonged ischaemic damage and VEGF blockade significantly reduces or even abolishes the neuroprotective effects of this phenomenon.^{35 37}

In CRVO restoration of venous flow is considered to occur either by recanalisation or by the development of collateral

vessels at the optic nerve head. Similarly, reperfusion of non-perfused retinal areas has been documented in cases of DR.³⁸ In a retrospective study where repeat FFAs of patients with DR were reviewed during a mean follow-up period of 2 years (range 1–12 years), reperfusion of occluded capillary beds was observed in 65 (69%) of the 94 eyes studied. Reperfusion was characterised by recanalisation in only 22 (34%) of the 65 eyes, whereas intraretinal neovascularisation was the main mechanism of reperfusion in 54 (83%) of the 65 eyes. Moreover, the former took place in small non-perfused areas, while the latter in larger non-perfused areas.³⁸ In another study, intraretinal neovascularisation was again the main mechanism of reperfusion of diabetic ischaemic retina, and was observed in 39 out of 60 eyes studied.³⁹ VEGF has been shown to carry the capacity to promote formation of collateral vessels, which is essential for recovery after ischaemic events and may play a key role for the phenomenon of retinal reperfusion.^{40 41} In a study of six patients with CRVO treated with repeated intravitreal bevacizumab injections, no collateral vessels developed after a mean follow-up of 12 months.⁴² It has been suggested that, as in cerebral ischaemia, a core of irreversible retinal infarction is surrounded by a zone of hypoxic but still viable tissue (the ‘penumbra’) in retinal ischaemic conditions. The ‘penumbral’ neurons may eventually escape infarction and recover their function if reperfusion occurs. Impairment of mechanisms of reperfusion may subsequently result in irreversible damage of hypoxic but still viable retina.⁴³

VEGF inhibition has also been shown to induce retinal arteriolar vasoconstriction in eyes with neovascular age-related macular degeneration.^{44 45} If this is also true in eyes with DR or RVO, then VEGF blockade-induced vasoconstriction in an already compromised macular capillary bed could further increase hypoxic damage with a potentially devastating effect on macular function and visual outcome.

The choroid is considered as a vital source of retinal oxygenation in the presence of inner retinal capillary closure.⁴⁵ Concerns over circulation disturbances in the choriocapillaris have been raised as intravitreal bevacizumab has been shown to reduce choriocapillaris endothelial cell fenestration in primate eyes.^{46 47} Thus, the effect of anti-VEGF treatment in the choriocapillaris bed might further disturb the oxygen supply to ischaemic retina.

Bevacizumab and ranibizumab induce non-selective blockade of all VEGF isoforms and are the most commonly used anti-VEGF agents for treatment of DMO and macular oedema secondary to RVO. As these agents are non-selective VEGF inhibitors blocking all isoforms of VEGF, they may downregulate normal physiological functions of VEGF. Indeed, a significant decrease of VEGF below physiological levels was detected in the intraocular fluid of eyes with DMO after intravitreal anti-VEGF therapy and this reduction was prolonged by consecutive injections.⁴⁸ Similarly, a substantial decrease of VEGF below physiological levels under a loading dose of consecutive monthly retreatments was observed in eyes with macular oedema secondary to RVO.²⁷ Anti-VEGF treatment is an effective treatment in reducing macular oedema and improving visual acuity but prolonged therapy with repeat injections is often necessary.^{4–8 13 14} The possibility exists that VEGF inhibition may help preserve or even improve vision in the short term by reducing macular oedema but this may be at the long-term expense of increased neuroretinal apoptosis and/or capillary dropout in a macula with an already compromised blood supply.

Suppression of VEGF in the setting of coexisting macular ischaemia could, in summary, worsen visual function by:

1. Further increase in macular capillary drop-out.
2. Attenuating the direct neuroprotective effect of VEGF in conditions of retinal hypoxia.
3. Impairment of the development of collateral vessel circulation in cases of RVO.
4. Impairment of reperfusion of occluded capillary bed, by downregulating intraretinal neovascularisation in the long term, in cases of DR.
5. Vasoconstriction of the remaining normal retinal capillaries resulting in further reduction of blood supply to retinal neurons, which are already undergoing hypoxic stress.
6. Circulation disturbances in the choriocapillaris.

CLINICAL DATA

Data from prospective, randomised studies

The BOLT study is the only prospective, randomised trial where a detailed, FFA-based, quantitative, statistical evaluation of macular perfusion before and after anti-VEGF treatment was provided. In this prospective randomised trial of intravitreal bevacizumab or laser therapy in the management of DMO no evidence of worsening of macular ischaemia was observed in both groups of the study at 4 months and no patients were withdrawn from the trial because of worsening of macular ischaemia.⁴⁹ At 12 months, 10 patients of the bevacizumab group had a 1-step progression of perifoveal capillary loss (from grade present to grade moderate as defined by the study) and 11 patients of the same group had an improvement of perifoveal capillary loss from grade moderate to grade present.⁵⁰ However, patients with severe capillary loss according to ETDRS criteria or a FAZ of $>1,000\ \mu\text{m}$ at baseline were not included in this study.^{49 50} Three patients of the bevacizumab group progressed to grade severe perifoveal capillary loss at 12 months. In summary, no statistically significant worsening of macular perfusion status was evident, but as the authors note, clinically significant adverse effects are unlikely to be seen with relatively small numbers of patients.

In the RESOLVE study presence of retinal ischaemia $>500\ \mu\text{m}$ which was located $<500\ \mu\text{m}$ from the centre of the macula was an exclusion criterion.⁵ In the DRCR net study FFAs were not required, so the authors of this study state that it could not be determined whether there were cases of development or progression of macular ischaemia.⁶ In the 24-month results of the READ-2 study no specific evaluation of macular perfusion status based on FFAs is reported.⁸ The investigators of the RESTORE study report that ranibizumab treatment did not negatively influence the visual acuity outcome or the progression of macular ischaemia at 12 months in the subgroups with or without retinal ischaemia. However, no details of the severity of macular ischaemia at baseline were given.⁴ In the BRAVO study patients with capillary non-perfusion of >10 disc diameters were excluded.¹¹ Similarly, in the CRUISE study only 2 out of 392 patients included had >10 disc diameters retinal ischaemia.¹² In both BRAVO and CRUISE studies presence of relative afferent pupillary defect was an exclusion criterion. At 12 months worsening of macular ischaemia was not reported as an adverse event, but as the authors state elsewhere, detailed evaluation of the FFAs of both studies is needed to definitely answer this question.⁵¹ Moreover based on the exclusion criteria of both studies it is likely that only a small number of eyes with a significant amount of macular ischaemia were included. In a small prospective randomised trial of anti-VEGF treatment for macular oedema secondary to BRVO (20 eyes) and CRVO (20 eyes), the presence of macular oedema for over a year and extensive closure of perifoveal capillaries were the two baseline

characteristics predicting poor visual outcome at 24 months.⁵² The lack of detailed FFA follow-up data from prospective, randomised studies including eyes with significant macular ischaemia treated with bevacizumab or ranibizumab precludes any meta-analysis of the effect of this treatment on macular perfusion status in the setting of coexisting macular oedema and macular ischaemia.

Data from non-randomised studies

In a retrospective review of visual outcome after intravitreal bevacizumab therapy in DMO concomitant macular ischaemia had a negative impact upon visual outcome. Out of 18 eyes with an enlarged FAZ of $>1000\ \mu\text{m}$, or a broken capillary ring at the border of the FAZ, with a distinct area of capillary non-perfusion within one disc diameter of the foveal centre (classified as ischaemic eyes), 9 (50%) eyes experienced a visual acuity loss of ≥ 1 line and 4 (22%) eyes experienced a visual acuity loss of ≥ 3 lines on the ETDRS chart at 3 months.²⁰ Overall 72% of ischaemic eyes lost ≥ 1 lines on the ETDRS chart in this study at 3 months. However, it remains unclear if the above mentioned visual acuity loss in the ischaemic group would have happened even without anti-VEGF treatment, merely as a part of the natural history of macular ischaemia. In the ETDRS study only 90 out of 1243 eyes (7%) presented with moderate or severe capillary loss at baseline, among which only 28 eyes (2.25%) had severe capillary loss.⁵³ Although macular ischaemia is known to progress with advancing stages of DR,^{22 54 55} this progression seems to occur over the long term according to ETDRS data.⁵³ This implies that changes of macular perfusion and/or visual acuity observed shortly after anti-VEGF treatment could probably be considered to be treatment related.

Our literature search found one study of the visual outcomes of anti-VEGF treatment, which only included eyes with DMO associated with severe capillary loss.⁵⁶ In this open labelled, non-randomised study, 10 eyes of 10 consecutive patients with DMO and severe capillary loss, as assessed by FFAs according to ETDRS criteria, received treatment with intravitreal bevacizumab. Six eyes had severe non-proliferative DR and four eyes had proliferative DR. All eyes had received previous mild or full scatter pan-retinal photocoagulation. The final study visit was performed at week 54 (± 2). At 54 weeks a mean improvement in best-corrected visual acuity of 2.28 ETDRS lines was observed, which was statistically significant. A last visit evaluation of repeat FFA demonstrated no noticeable qualitative change in the macular perfusion status. However, these results should be interpreted with caution due to the small number of eyes involved in the study. Kook *et al*⁵⁷ reported the long-term effect of intravitreal bevacizumab in patients with chronic (>12 months duration) diffuse DMO. 56 (44%) out of 126 eyes studied had a FAZ $>800\ \mu\text{m}$, which was classified as marked macular ischaemia. Fifty-nine eyes completed a follow-up of 12 months. The authors state that no deterioration or improvement of the FAZ was noticed on follow-up, but no precise statistical analysis of the FAZ diameter was provided. At 12 months there was a significant increase of visual acuity in the whole patient group, but again no separate statistical evaluation of the results of the treatment in eyes with and without marked ischaemia was provided. However, the authors do state that visual acuity change and retinal thickness change in optical coherence tomography did not correlate with the diameter of the FAZ. They conclude that the different functional results of their study compared with the more favourable results of other studies were probably due to inclusion of many cases with marked macular ischaemia.

During a prospective study, which included 22 patients treated with intravitreal ranibizumab for CRVO, confluent areas of non-perfusion in the retinal periphery ranging in size from 16 to 242 disc areas were detected in all of the patients.⁵⁸ The imaging of the retina was performed using wide-field fluorescein angiography. Interestingly, eyes which would have been classified as perfused based on the CRVO Study imaging criteria, were found to have confluent areas of peripheral non-perfusion after intravitreal anti-VEGF therapy, and surprisingly these areas did not differ significantly from the confluent areas of non-perfusion of eyes, which would have been classified as non-perfused according to the CRVO Study imaging criteria. The patients had a mean of 16.1 injections over a mean follow-up of 28.5 months. No correlation between the number of anti-VEGF injections and any measure of non-perfusion including largest diameter of the FAZ and the area of peripheral non-perfusion was evident. Based on this the author concluded that it is unlikely that the anti-VEGF injections caused the peripheral non-perfusion and that the peripheral vascular obliteration was likely the result of interplay among retinal vascular endothelial cells, elements formed in the blood, growth factors and cytokines. However, this assumption is controversial. As mentioned above, a substantial and prolonged decrease of VEGF below physiological levels was observed in eyes with macular oedema secondary to RVO after anti-VEGF therapy.²⁷ In addition, baseline levels of VEGF correlate negatively with the duration of CRVO. The fact that lower levels of VEGF are found with longer disease implies that VEGF levels tend to decrease as a part of the natural course. Moreover the complete lack of perfusion in the retinal periphery is likely to have resulted in infarction of the retina and consequently to less surviving tissue able to produce VEGF in the long term, as mentioned by the author himself.⁵⁸ Based on the above observations, it could be assumed that suppression of VEGF during an initial critical ischaemic period may result in changing/worsening of the retinal perfusion status. After that critical period, the VEGF levels are anyway very low (as a result of the natural course of the disease, progressive death of tissue capable of producing VEGF and/or prolonged anti-VEGF therapy), so that further anti-VEGF injections will not change an already established retinal perfusion status. This way the number of further intravitreal injections would not correlate with the measurement of non-perfusion.

In a study of 58 eyes of 58 patients with macular oedema secondary to BRVO treated with intravitreal bevacizumab, three of 37 eyes without capillary non-perfusion prior to therapy developed capillary non-perfusion only 1 month after therapy. In the same study a not statistically significant increase in the area of non-perfusion was observed in eyes, which had macular non-perfusion at baseline. Increase of non-perfusion area of more than 1 disc diameter was observed only in one eye.⁵⁹ The incidence of worsening of macular perfusion status was very low. However, it is of notice that worsening of macular ischaemia was still observed in patients, who received only one intravitreal bevacizumab injection and only 1 month after therapy. The presence of macular ischaemia was a negative prognostic factor after anti-VEGF therapy for macular oedema due to BRVO in a retrospective review, where 14 out of 17 eyes with macular ischaemia either gained <5 ETDRS letters or had visual acuity deterioration after treatment. By contrast, 25 out of 33 eyes without macular ischaemia gained >5 ETDRS letters in the same study.⁶⁰

In a small case series including seven eyes of seven patients with ischaemic CRVO or hemiretinal CRVO treated with intravitreal bevacizumab for macular oedema, no obvious

change in the non-perfusion area was noticed in all the eyes at 6 months follow-up.⁶¹

Neubauer *et al* found an improvement of peripheral ischaemia in the short term (after 4 weeks) in a small series of patients receiving intravitreal bevacizumab for diffuse DMO.⁶²

A summary of imaging studies of retinal perfusion after anti-VEGF treatment in DR and RVO is given in online supplementary table 1.

Eighteen case reports of severe ocular ischaemic complications associated with anti-VEGF treatment have been described in the literature^{63–78} (online supplementary table 2). In addition, Mansour *et al*⁷⁹ reported on a collaborative multicentre retrospective case series of eight patients who were documented to have retinal vascular events after intravitreal bevacizumab injection (online supplementary table 2). These patients had severe ocular and systemic risk factors for retinal vascular events and in four of them an increased intraocular pressure between 28–32 mm Hg was documented post-injection. Mansour *et al* finally concluded that the retinal vascular adverse events in their series may be associated with one or more of the following: the underlying systemic disease, the increased intraocular pressure and/or the vasoconstrictor effect of bevacizumab.

CONCLUSIONS

No definite answer can be given to the question whether macular ischaemia is a contraindication for prolonged anti-VEGF treatment. Large multicentre studies have proven the efficacy and safety of anti-VEGF therapy for DMO and macular oedema secondary to RVO. However, worsening of macular ischaemia in the long term cannot be definitely excluded, particularly, in some eyes with significant ischaemia at baseline and after repeated intraocular anti-VEGF injections. Long-term, statistical, FFA-based evaluations of retinal perfusion before and after treatment with anti-VEGF therapy are lacking at present. If mild to moderate macular ischaemia with a considerable amount of oedema is present, it is reasonable to offer anti-VEGF therapy. For a macula undergoing a greater amount of hypoxic stress due to more severe ischaemia further compromise of blood supply might have devastating effects on vision, even if macular oedema decreases after therapy. Although grading of macular ischaemia lacks uniformity among published reports, from a clinical point of view and to enable decision making we suggest that eyes with severe capillary loss according to ETDRS criteria or a FAZ of >1000 µm should be considered as having severe ischaemia. The decision to treat such patients with anti-VEGF agents should be individualised and taken after thorough discussion about possible risks. Moreover, if prolonged anti-VEGF treatment is offered to these patients, follow-up and the decision to re-treat should not be based only on measurements of macular thickness with optical coherence tomography rather repeat FFAs should be performed.

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Contributors KM conceived the idea for the article and wrote the manuscript. KM and JT performed the literature search, reviewed the article before submission and are guarantors.

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