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Viewpoint

The demonstration that VEGF-A is a critical stimulus in retinal/choroidal vascular diseases and the development of intravitreal injections of potent VEGF-A antagonists as a therapy have greatly benefited millions of patients (1, 2). However, compared with outcomes in clinical trials, those in clinical practice have been substantially worse because of difficulties maintaining sufficient frequency of injections (3). This unmet medical need has motivated development of a variety of new approaches to providing sustained suppression of VEGF. However, some clinicians and investigators are concerned that sustained suppression of VEGF may cause retinal damage and loss of vision. One reason for this concern is that conditional deletion of murine *Vegfa* in retinal pigmented epithelium (RPE) or retina results in retinal damage (4, 5). Complete elimination of a gene product is a valuable experimental technique that can demonstrate autocrine and paracrine activities of the gene product, but it is difficult to mimic by delivery of an antagonist of that gene product. Transgenic expression of a potent VEGF-A- and -B-binding protein using the strong, retina-specific rhodopsin promoter for up to seven months caused no reduction in electroretinographic (ERG) retinal function and no retinal damage in mice (6). In nonhuman primates, intravitreal adenoassociated virus delivery of the VEGF-neutralizing protein sFLT01 (a modified version of soluble Flt1) resulted in aqueous humor levels of sFLT01 of 59 [...]

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the VEGF-neutralizing protein sFLT01 (a modified version of soluble Flt1) resulted in aqueous humor levels of sFLT01 of 59 to 528 ng/ml (median 100 ng/ml) for at least 12 months, the longest time point tested (7). If retinal levels of sFLT01 had been measured, they would have been far higher than the levels measured in aqueous humor, and there was no reduction in ERG amplitudes measured every three months or histopathologic signs of retinal damage at 12 months.

A second source of concern is a study that suggested that systemic injection of an adenoviral vector expressing sFlt1 caused severe retinal damage in mice (8). The levels of sFlt1 in the eyes of mice were not measured after intravenous injection of an adenoviral vector expressing sFlt1, but were likely a small fraction of the levels of sFLT01 measured in the eyes of primates after intraocular injection of AAV2.sFLT01, which caused no decrease in retinal function or retinal damage. Thus, any retinal degeneration in mice after intravenous injection of Ad.sFlt1 is not attributable to reduced VEGF signaling in the retina.

A third cause of concern is the suggestion that the presence of VEGF receptor 2 (VEGFR2) on retinal neurons indicates that VEGF signaling is required for survival of those neurons. However, in mice, frequent administration of VEGFR kinase inhibitors, intraocular injections of a potent anti-

VEGFR2 antibody, or targeted deletion of *Vegfr2* in retinal neurons failed to cause any damage to retinal neurons (9–11). VEGFR2 on retinal neurons modulates vascular patterning, not neuronal survival (11).

A fourth cause of concern is the suggestion by authors of a manuscript describing clinical trial results, that frequent intraocular injection of either of two VEGF-targeting antibodies, ranibizumab or bevacizumab, may cause macular atrophy (12). There were four treatment groups in that study: (a) monthly injections of ranibizumab, (b) monthly injections of bevacizumab, (c) injections of ranibizumab as needed (prn) guided by OCT findings, and (d) injections of bevacizumab prn. The mean number of injections given over two years was 22.5 in the monthly injection groups and 13.1 in the prn groups. Patients in each monthly injection group had superior visual outcomes compared with the corresponding prn group, but also had more new-onset hypopigmented spots in the macula judged to be macular atrophy (designated geographic atrophy [GA]). It was concluded that, “Although monthly injections may result in slightly better visual outcomes at 2 years, the increased risk of GA development may offset this benefit long term.” Macular atrophy was ascertained by the presence of hypopigmented spots on fundus photographs, and more new hypopigmented spots were seen in each monthly injection group than in the corresponding prn group. The association of more new-onset hypopigmented spots with more frequent injections was replicated in another study, which lends credence to the observation (13), but not the interpretation, because fundus photographs are inaccurate for identification of macular atrophy without OCT confirmation of cell loss and it is not appropriate to assume causality from association.

While the ascertainment tool was poor and the assumption of causality was inappropriate, let us assume that the observation of more frequent new hypopigmented spots in monthly injection groups is an indi-

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Table 1. Summary of long-term follow-up data for patients treated with intraocular injections of a VEGF-neutralizing protein

Time points	Baseline	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Branch RVO							
Number of patients (n)	50.0	50.0	50.0	43.0	27.0	21.0	20.0
Mean BCVA	52 (20/100)	66 (20/50)	65 (20/50)	65 (20/50)	64 (20/50)	64 (20/50)	64 (20/50)
Mean no. of injections/year	NA	8.2	5.7	3.9	1.5	1.9	1.5
Mean total no. of injections	NA	8.2	13.9	17.8	19.3	21.2	22.7
Central RVO							
Number of patients (n)	40.0	40.0	38.0	35.0	29.0	27.0	20.0
Mean BCVA	48 (20/100)	61 (20/63)	61 (20/63)	62 (20/63)	60 (20/63)	59 (20/63)	59 (20/63)
Mean no. of injections/year	NA	8.6	5.7	4.5	4.3	3.8	3.1
Mean total no. of injections	NA	8.6	14.3	18.8	23.1	26.9	30

Mean change from BCVA, mean number of injections per year, and total number of injections are from a prospective follow-up study of patients with branch or central RVO treated with anti-VEGF agents (14). BCVA is shown in Early Treatment Diabetic Retinopathy Study letter score and Snellen equivalent in parentheses.

cation of more new-onset macular atrophy. It is important to recognize that macular atrophy is part of the natural history of AMD and occurs in the absence of anti-VEGF injections, so susceptibility to macular atrophy is part of the disease process. A long-term prospective follow-up of 50 patients with branch vein occlusion and 40 patients with central retinal vein occlusion (RVO) treated with anti-VEGF injections for several years showed that patients did not develop macular atrophy unless there was persistent, recurrent edema causing retinal damage (14). There was a marked improvement from baseline best-corrected visual acuity (BCVA) during the first year of anti-VEGF treatment in both groups of patients (Table 1). After 3 years, when data were available for 86% of patients, approximately 18 injections had been given in each group with maintenance of visual benefits and no sign of macular atrophy. Similarly, patients with diabetic macular edema (DME) treated with frequent anti-VEGF injections to control edema do not develop macular atrophy if edema is well controlled, but can show thinning of the macula if there is retinal damage from persistent/recurrent edema.

The lack of any evidence of retinal damage from frequent anti-VEGF injections in patients with DME or RVO suggests that suppression of VEGF does not directly damage retinal neurons and that any new-onset macular atrophy in patients with NVAMD treated with anti-VEGF agents is likely to be due to interaction between the disease process and VEGF

suppression. In patients with NVAMD, careful evaluation of fluorescein angiograms and OCT scans from the time of diagnosis of choroidal neovascularization throughout the entire course of anti-VEGF injections showed that when OCT-confirmed macular atrophy developed, it often occurred in areas previously occupied by choroidal neovascularization (most often type 1 choroidal neovascularization that is located beneath the RPE) that regressed (15). This suggests that, in some instances, choroidal neovascularization may be adaptive and improve oxygen delivery to hypoxic RPE and outer retina and that if it regresses, hypoxia is increased, resulting in atrophy of RPE and photoreceptors in that location. It is possible that a higher frequency of anti-VEGF injections increases the likelihood of regression of choroidal neovascularization, but a subsequent study by many of the same authors who initially suggested that injection frequency is a risk factor for macular atrophy concluded that, "Atrophy progression was most strongly correlated with age, which suggests that baseline disease characteristics may be more predictive of MA progression than cumulative anti-VEGF treatment" (16).

It is intellectually stimulating to debate differences in interpretation of data that lead to different conclusions, but progress in medicine depends upon accumulation of new data that resolve such differences. We are entering a new era of sustained suppression of VEGF that should provide resolution of this controversy. The first data available are from the LADDER clin-

ical trial investigating sustained delivery of ranibizumab in patients with NVAMD (17). Implantation of a refillable reservoir containing 10, 40, or 100 mg/ml ranibizumab was compared to monthly injections of 0.5 mg ranibizumab. The median time to first refill was 8.7, 13.0, and 15.0 months in the 10, 40, and 100 mg/ml implant groups, demonstrating prolonged dose-dependent periods of quiescence. These patients were previously treated and at baseline had already experienced improvement in vision from prior anti-VEGF injections; the mean changes from BCVA at the 9-month primary end point were -3.2, -0.5, and +5.0 letters in the 10, 40, and 100 mg/ml implant groups and +3.9 letter in the monthly injection group. This dose-related improvement in BCVA in previously treated patients who had good baseline vision suggests against retinal damage from sustained suppression of VEGF, and while future studies will carefully scrutinize OCTs for any evidence of dose-related macular atrophy, ophthalmoscopic examinations showed no evidence of retinal toxicity.

This initial experience with sustained suppression of VEGF is encouraging, but we cannot yet lay to rest all concerns of potential long-term adverse effects. Over the next few years, data will become available from a variety of clinical trials testing multiple strategies to achieve sustained suppression of VEGF, including the LADDER extension trial (ClinicalTrials.gov NCT03683251), a trial testing the effects of sustained intraocular delivery of a VEGFR tyrosine kinase inhibitor (ClinicalTrials.

gov NCT03249740), and a trial testing subretinal injection of an AAV8 vector expressing an anti-VEGF antibody fragment (ClinicalTrials.gov NCT03066258). These data should clearly delineate the benefits and risks of sustained suppression of VEGF signaling in the retina. Based upon the data presented above, it is my opinion that the benefits will far outweigh any risks, resulting in a new paradigm that will greatly improve outcomes for retinal and choroidal vascular diseases, the most prevalent causes of severe vision loss throughout the world.

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