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EDITORIAL

Peripheral photocoagulation not the answer for DMO

Eye (2023) 37:3302–3303; https://doi.org/10.1038/s41433-023-02596-8

Vascular endothelial cell growth factor-A (VEGF-A) plays a major role in diabetic macular oedema (DMO) and intraocular injections of proteins that block VEGF-A are highly efficacious [1–3]. However, observational trials have shown that visual outcomes for DMO patients treated in clinical practice are substantially worse than visual outcomes obtained in clinical trials, and injection frequencies are lower [4]. This suggests that high treatment burden is an impediment to good outcomes and new treatments that reduce the burden of frequent clinic visits and injections are needed. In this issue of Eye, Cornish et al. [5] tested the hypothesis that targeted scatter photocoagulation to peripheral areas of retinal ischemia reduces the frequency of injections needed to control DMO. There is good rationale for this hypothesis because retinal ischemia increases levels of VEGF-A in the eye, and scatter photocoagulation of peripheral ischemic retina results in reduction of VEGF-A levels [6]. The study suggested that the hypothesis is incorrect, because the frequency of anti-VEGF-A injections required to control DMO was similar in patients who had targeted scatter photocoagulation compared with those who did not. These results are consistent with previous studies [7, 8] which also found that targeted scatter photocoagulation did not reduce the frequency of anti-VEGF-A injections needed to control DMO and maintain vision. One caveat is that areas of peripheral retina that may not look ischemic because there is no closure of large vessels, may still be ischemic because of closure of small vessels and poor perfusion that is not visualized on wide angle fluorescein angiograms. Such areas of retina would not be treated by the targeted photocoagulation protocols and are likely to contribute to increased production of VEGF-A. Thus, Cornish et al. and the two prior studies [7, 8] conclusively show that targeted scatter photocoagulation does not reduce anti-VEGF-A injection burden in DMO, but they do not rule out the possibility that complete peripheral scatter photocoagulation does so. However, complete peripheral scatter photocoagulation did not reduce anti-VEGF-A injection frequency needed to control edema and maintain vision in another ischemic retinopathy, central retinal vein occlusion [9], and thus it is reasonable to assume that even more complete scatter photocoagulation would not provide benefit in DMO.

Why is it that in ischemic retinopathies, anti-VEGF-A injections provide effective treatment for retinal neovascularization and macular edema, while scatter photocoagulation provides benefit for retinal neovascularization, but not macular edema? Scatter photocoagulation can cause macular edema by a mechanism that is probably unrelated to VEGF-A [10, 11] and perhaps this masks any beneficial effects it might have by reducing total VEGF-A levels in the eye. Another possibility is that local production of VEGF-A in ischemic posterior retina in and around the macula is a major contributor to macular edema, and reduction of total VEGF-A levels by ablation of ischemic peripheral retina is not sufficient to overcome local effects. There is indirect evidence suggesting that this may be the case. The mechanism by which focal/grid laser in the macula reduces DMO [12] or edema in branch retinal vein occlusion [13] is not known, but one hypothesis is that it reduces hypoxia in the macula which in turn would reduce local VEGF-A production. However, since visual outcomes with focal/grid laser are inferior to those seen with anti-VEGF-A injections in eyes of patients with DMO [14, 15], focal/grid laser is generally not used to reduce anti-VEGF-A treatment burden. Whether focal/grid laser is considered in the eyes of DMO patients poorly responsive to anti-VEGF injections or other treatments is separate issue.

While scatter photocoagulation or focal/grid laser in the macula are not effective strategies to reduce anti-VEGF-A treatment burden while maintaining optimal visual outcomes in DMO, promising data have been obtained with other approaches. Angiopoietin 2 enhances retinal vessel sensitivity to VEGF-A and contributes to excessive permeability in DMO [16]. The YOSEMITE and RHINE trials showed that faricimab, a bispecific antibody that blocks VEGF-A and angiopoietin 2, controls edema and maintains vision in a substantial number of DMO patients with injections every 3 or 4 months [17]. The PAGODA trial has shown that in patients with DMO, implantation of the port delivery system with ranibizumab with refill/exchanges every 6 months maintains vision and controls edema as well as monthly injections of ranibizumab [18]. Sustained delivery of VEGF receptor tyrosine kinase inhibitors and gene therapy to express anti-VEGF proteins have shown encouraging preliminary data in patients with neovascular AMD and may have potential to reduce treatment burden with good visual outcomes in DMO.

Thus, while scatter photocoagulation is not the answer, other approaches show great promise to maintain good vision with reduced treatment burden in patients with DMO and thereby fill a major unmet need in clinical practice.

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Received: 5 May 2023 Revised: 9 May 2023 Accepted: 17 May 2023
Published online: 5 June 2023

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ACKNOWLEDGEMENTS

Grant Support: Aerpio, Ashvattha, Genentech, Inc./Roche, Graybug, Mallinckrodt, Oxford Biomedica, Regeneron, Regenixbio, Sanofi Genzyme.

COMPETING INTERESTS

Consultant: Aerpio, Allegro Ophthalmics, AsclepiX, Ashvattha, Bausch + Lomb, Catawba Research, Celanese, Clearside Biomedical, Cove, CureVac, Exegenesis Bio, Exonate, Graybug, Merck, Novartis, Perfuse, Wave Life Sciences; Financial support—Aerpio, Ashvattha, Genentech, Inc./Roche, Graybug, Mallinckrodt, Oxford Biomedica, Regeneron, Regenixbio, Sanofi Genzyme. Consultant for which institution receives payment: Genentech, Inc./Roche. Stock Options: Allegro Ophthalmics, Cove.

ADDITIONAL INFORMATION

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