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Management of diabetic macular edema with antiangiogenic therapy

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Evaluation of: Chun DW, Heier JS, Topping TM, Duker JS, Bankert JM. A pilot study of multiple intravitreal injections of ranibizumab in patients with center-involving clinically significant diabetic macular edema. *Ophthalmology* 113, 1706–1712 (2006).

Macular edema is the leading cause of blindness in diabetic patients. Laser photocoagulation has been the standard therapy for several decades. Recently, vascular endothelial growth factor (VEGF) has been implicated as an important factor in the occurrence of vascular permeability in this disease. Thus, anti-VEGF therapy has been used to treat this condition. The paper under evaluation offers the preliminary results of a pilot study assessing the role of intravitreal injections of ranibizumab to treat center-involving clinically significant diabetic macular edema. This study demonstrates that ranibizumab therapy has the potential to maintain or improve visual acuity and reduce retinal thickness in patients with this disorder.

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Here, we shall evaluate a paper examining the efficacy and safety of intravitreal ranibizumab in patients with diabetic macular edema (DME) [1]. Nearly half of the world's diabetic population has some degree of diabetic retinopathy [2] and DME is the most common cause of visual loss in these patients. DME usually occurs before proliferative diabetic retinopathy but may coexist with it. DME may develop at any time and may even be present at the initial diagnosis of Type 2 (non-insulin-dependent) diabetes. In the development of DME, altered autoregulation of vascular flow is a key factor. In addition to this, the integrity of the blood–retina barrier is impaired. It appears that breakdown of the inner blood–retina barrier, formed by tight junctions between endothelial cells, predominates in early DME. By contrast, breakdown of the outer blood–retina barrier, formed by tight junctions between retinal pigment epithelial cells, predominates in late DME. In addition, local production of vaso-proliferative factors, such as vascular endothelial growth factor (VEGF), also plays a role in the development of DME [3]. VEGF is a

potent inducer of permeability that is 50,000 times more potent than histamine in the microvasculature. Repeated injections of high concentrations of VEGF results in leakage of fluorescein dye from the retinal vessels. It appears that VEGF may exert its effects on retinal vascular permeability by altering tight junction proteins, such as occludin and VE-cadherin [4]. Systemic factors, such as poor diabetes control, systemic arterial hypertension, hyperlipidemia and hypoalbuminemia, may all contribute to DME.

Laser photocoagulation has been the therapy used most commonly to manage DME. The Early Treatment Diabetic Retinopathy Study (ETDRS) proved that laser treatment reduces moderate visual loss in patients with clinically significant macular edema [5]. The mechanism of action for laser photocoagulation is uncertain. With fluorescein angiography (FA), most of the leakage in eyes with focal DME appears to be caused by microaneurysms and focal burns appear to coagulate them. In eyes with diffuse DME, FA demonstrates diffuse leakage from retinal vessels, suggesting that leakage from

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microaneurysms may not be the only cause of DME formation. Laser treatment used in a grid pattern appears to be effective in reducing this diffuse DME. One theory of the mechanism by which laser treatment reduces DME is that it destroys some of the photoreceptors and retinal pigment epithelial cells, which are layers that consume most of the oxygen used by the retina. Post-treatment scarring also causes retinal thinning, which allows for better diffusion of oxygen from the choroid.

Steroids have shown efficacy in reducing vascular permeability in DME, with intravitreal triamcinolone acetonide being the most tested drug. Several studies have revealed that, in the short term, intravitreal injection of triamcinolone effectively reduces macular thickening due to diffuse DME and improves visual acuity in most cases. However, the long-term effect of this treatment and predictive factors of visual recovery remain unclear [6]. In addition, many patients develop glaucoma and cataract progression after the treatment.

Vitreous samples from patients with DME contain elevated VEGF levels [7]. Recently, experiments in animals have suggested a central role for the 165 isoform of VEGF, specifically in the pathogenesis of DME [8]. There is evidence that VEGF 165 inhibition may not only be effective in preventing diabetic blood–retina barrier breakdown but may also have the potential to reverse DME once it has occurred. Based on this, pegaptanib (Macugen[®], Eyetech, NY, USA), an aptamer that binds VEGF 165, has been evaluated in Phase I and II trials designed to explore the safety and efficacy of selective VEGF 165 blockade in patients with DME. In the Phase II trial, 172 patients were randomized to receive intravitreal pegaptanib (0.3, 1 and 3 mg) or sham injections. Subjects assigned to pegaptanib had better visual outcomes, were more likely to show reduction in central retinal thickness and were deemed less likely to require additional therapy with photocoagulation [9]. Pegaptanib has been US FDA approved for the treatment of wet age-related macular degeneration (AMD) patients.

Bevacizumab (Avastin[®], Genentech, CA, USA) is a humanized recombinant antibody that binds all isoforms of VEGF. It has been FDA approved for the treatment of metastatic colorectal cancer. There are recent reports of intravitreal bevacizumab being well tolerated in the short term and showing promise in the treatment of diabetic retinopathy [10].

Ranibizumab (Lucentis[®], Genentech, CA, USA) is a smaller modified binding site derived from the same murine antibody as bevacizumab and it was developed to diffuse more efficiently through the retina after intraocular injection. It has been FDA approved recently for the treatment of wet AMD.

The paper under evaluation explores the potential role of intravitreal injections of ranibizumab in patients with DME.

Methods & results

This study was an open-label, single-center, dose-escalating pilot study. The authors enrolled ten patients; five patients were assigned to a low dose of ranibizumab (0.3 mg) and five patients to a high dose (0.5 mg). Patients received intravitreal injections of ranibizumab on day 0, month 1 and month 2 and

were evaluated for adverse reactions on days 3 and 7. Monthly observation visits occurred until month 6. Eye examinations, including measurement of best-corrected visual acuity (BCVA), occurred at all visits. Optical coherence tomography (OCT) and stereoscopic color fundus photography were performed at baseline and at each monthly follow-up visit to determine retinal thickness. FA was performed at baseline and at months 3 and 6 to determine macular leakage. The primary end points of the study were the incidence and severity of systemic and ocular adverse events. Secondary end points included change from baseline to months 3 and 6 in BCVA using the ETDRS chart and change from baseline to months 3 and 6 in the retina, as assessed by color fundus photography, FA and OCT.

Patient selection criteria included: aged 18 years or below, a history of diabetes mellitus with stereo fundus photographic evidence of center-involving clinically significant DME in the study eye within 28 days of the start of the study, BCVA between 20/63 and 20/400 in the study eye and 20/400 or better in the fellow eye and eyes considered clinically acceptable to defer laser photocoagulation for at least 4 months. Eyes treated previously with intraocular steroids or vitreoretinal surgery were excluded.

During the study, no systemic adverse events were reported. A total of five ocular adverse events occurred. In both the low- and high-dose groups, there were two reports of mild inflammation (fewer than ten cells observed by slit-lamp examination) that resolved in a period of 1–6 weeks without treatment. There was one report of moderate inflammation (10–50 cells) in the high-dose group that resolved after topical prednisolone administered four-times daily for 1 week followed by rapid tapering. None of these adverse events led to withdrawal from the study.

At month 3, the mean BCVA in the study eye for both treatment groups improved over baseline. The low-dose group gained a mean of 12 letters and the high-dose group gained a mean of 7.8 letters. At month 6, the low-dose group gained a mean of 8.8 letters and the high-dose group gained a mean of 0.8 letters.

After treatment, mean retinal thickness of the study eye, as determined by OCT, was reduced in both groups. At month 3, mean reduction was 45.3 μm in the low-dose group and 197.8 μm in the high-dose group. At month 6, mean reduction was 74.0 μm in the low-dose group and 223.4 μm in the high-dose group.

Discussion & significance

This pilot study is the first to demonstrate the safety and efficacy of repeated intravitreal injections of ranibizumab in the treatment of DME. No systemic adverse events were reported and the ocular adverse events consisted of mild-to-moderate intraocular inflammation. Overall, visual acuity improved in both groups of patients. Although the gains appeared to diminish from the 3- to the 6-month visit in both groups, they were more likely to be sustained in the low-dose group. The authors state that, with only five patients per group, no

conclusions can be drawn from this finding. Moreover, better baseline visual acuity was present in the high-dose group with greater baseline central retinal thickness as well. Overall, central retinal thickness decreased in both groups of patients, with a trend towards a greater decrease in the high-dose group. The authors state that, although the small number of patients precludes definitive conclusions, this trend suggests that the higher dose may be more effective in achieving an antipermeability effect.

Expert commentary & conclusion

Laser therapy has been the gold standard in the management of DME for 20 years [5]. Currently, a pharmacological approach is gaining popularity. Intravitreal steroids, mainly triamcinolone acetonide, are being used as primary treatment or as treatment for cases that have failed after laser therapy. Nevertheless, recurrences are common and there is a high rate of adverse events, such as glaucoma and cataract progression [6].

There is growing evidence that VEGF plays an important role in the development of DME [3]. This supports the idea of treating this disorder with anti-VEGF therapy, notwithstanding the fact that we do not know whether a selective blockade is better than a nonselective one. Intravitreal injections of pegaptanib (Macugen) have been tested in different clinical trials, with promising results [9]. This aptamer selectively blocks the VEGF 165 isoform, which is presumably the isoform most related to the pathology [8].

A nonselective blockade of VEGF isoforms is more efficacious in the treatment of choroidal neovascularization secondary to AMD. Ranibizumab (Lucentis) is an antibody fragment that binds all VEGF isoforms with high affinity. Although the underlying process producing choroidal neovascularization and

DME is not the same, there might be several affinities. This is why there is evidence to support the idea that the use of intravitreal ranibizumab for DME could be equally beneficial.

This evaluated paper is the first one to demonstrate the safety and efficacy of intravitreal injections of ranibizumab in the management of DME. However, there are limitations that must be recognized. It is a pilot study with only ten recruited patients; five per group. With such a limited sample, it is not possible to draw significant conclusions. Also, a 6-month follow-up is not long enough to draw any conclusions in a disorder such as DME. However, the visual and anatomical results obtained in this study are sufficiently promising to encourage exploration of this treatment modality in large, randomized clinical trials. In addition, this study suggests the potential for application in other diseases where macular edema plays a key role, such as retinal vein occlusion.

Five-year view

Over the next 5 years, we will continue to see progress in the field of DME treatment with antiangiogenic therapy. Certainly, the real influence of VEGF and other growth factors in the development and progression of DME will be determined with more precision. It is probable that laser therapy will be used less commonly in favor of antiangiogenic therapy. Moreover, several routes of administration are currently under evaluation to reduce the number of reinjections that are needed to stabilize the maculopathy. Nevertheless, we should not forget that DME is a multifactorial disorder and medical control of the systemic disease still plays an essential role. Also, genetic studies can be useful for developing preventive strategies in high-risk patients. Surgical management of DME will probably not be the gold standard. However, it could be considered in selected cases with relevant vitreomacular tractions.

Key issues

- Macular edema is the leading cause of blindness in diabetic patients.
- Vascular endothelial growth factor (VEGF) has been implicated as an important factor in the occurrence of vascular permeability in diabetic macular edema (DME).
- Ranibizumab is a fragment of a humanized recombinant antibody that binds all isoforms of VEGF, blocking its action.
- In a pilot study, repeated intravitreal injections of ranibizumab have demonstrated efficacy and safety in the management of DME.

References

Papers of special note have been highlighted as:

- of interest
- of considerable interest

- 1 Chun DW, Heier JS, Topping TM, Duker JS, Bankert JM. A pilot study of multiple intravitreal injections of ranibizumab in patients with center-involving clinically significant diabetic macular edema. *Ophthalmology* 113, 1706–1712 (2006).
- 2 Aiello LP. Angiogenic pathways in diabetic retinopathy. *N. Engl. J. Med.* 353, 839–841 (2005).
- 3 Funatsu H, Yamashita H, Nakamura S *et al.* Vitreous levels of pigment epithelium-derived factor and vascular endothelial growth factor are related to diabetic macular edema. *Ophthalmology* 113, 294–301 (2006).
- 4 Antonetti DA, Barber AJ, Khin S *et al.* Vascular permeability in experimental diabetes is associated with reduced endothelial occluding content: vascular endothelial growth factor decreases occluding in retinal endothelial cells. *Diabetes* 47, 1953–1959 (1998).
- 5 Early Treatment Diabetic Retinopathy Study Research Group. Photocoagulation for diabetic macular edema. ETDRS Report Number 1. *Arch. Ophthalmol.* 103, 1796–1806 (1985).

- Provides evidence to support the use of laser therapy in the management of DME.

- 6 Audren F, Erginay A, Haouchine B *et al.* Intravitreal triamcinolone acetonide for diffuse diabetic macular edema: 6-month results of a prospective controlled trial. *Acta Ophthalmol. Scand.* 84, 624–630 (2006).
- 7 Brooks HL Jr, Caballero S Jr, Newell CK *et al.* Vitreous levels of vascular endothelial growth factor and stromal-derived factor 1 in patients with diabetic retinopathy and cystoid macular edema before and after intraocular injection of triamcinolone. *Arch. Ophthalmol.* 122, 1801–1807 (2004).
- 8 Ishida S, Usui T, Yamashiro K *et al.* VEGF 164 is proinflammatory in the diabetic retina. *Invest. Ophthalmol. Vis. Sci.* 44, 2155–2162 (2003).
- 9 Macugen Diabetic Retinopathy Study Group. A Phase II randomized double-masked trial of pegaptanib, an anti-vascular endothelial growth factor aptamer, for diabetic macular edema. *Ophthalmology* 112, 1747–1757 (2005).
- 10 Avery RL, Pearlman J, Pieramici DJ *et al.* Intravitreal bevacizumab (Avastin) in the treatment of proliferative diabetic retinopathy. *Ophthalmology* 113, 1695–1705 (2006).

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