

When to change course: timing of treatment change in the management of diabetic macular edema

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Provenance: This is a Guest Editorial commissioned by Section Editor Weihong Yu, MD (Department of Ophthalmology, Peking Union Medical College Hospital, Chinese Academy of Medical Science, Beijing, China).

Comment on: Ciulla TA, Hussain RM, Ciulla LM, *et al.* Ranibizumab for diabetic macular edema refractory to multiple prior treatments. *Retina* 2016;36:1292-7.

Submitted Nov 01, 2016. Accepted for publication Nov 02, 2016.

doi: 10.3978/j.issn.1000-4432.2017.01.04

View this article at: <http://dx.doi.org/10.3978/j.issn.1000-4432.2017.01.04>

Diabetes mellitus currently affects at least 1 in 40 persons worldwide, and is expected to affect 1 in 20 people by 2030 (1). Among those affected, approximately one-quarter have diabetic retinopathy (2) and a similar number will go on to develop vision-threatening diabetic macular edema (DME) within 15 years of their initial diagnosis of diabetes (3). Consequently, the growing prevalence of diabetes resulted in the World Health Organization adding diabetic retinopathy to their list of priority eye diseases for which safe and effective treatment is available.

The discovery of vascular endothelial growth factor (VEGF) as a key mediator in the development of retinal neovascularization and macular edema in diabetic retinopathy was a turning point in the field of ophthalmology, leading to the development of new treatment paradigms beyond conventional focal and grid laser. Contemporary management of DME now includes intravitreal triamcinolone, intravitreal dexamethasone implants (Ozurdex, Allergan Inc., Irvine, CA, USA), the anti-VEGF monoclonal antibodies bevacizumab (Avastin, Genentech USA Inc., South San Francisco, CA, USA) and ranibizumab (Lucentis, Genentech USA Inc.), and more recently the VEGF receptor decoy aflibercept (Eylea, Regeneron Pharmaceuticals Inc., Tarrytown, NY, USA), as discussed in (4) and references therein.

Ciulla and colleagues (5) recently reported on their experience with intravitreal ranibizumab for management of refractory DME in eyes previously managed with focal

laser, intravitreal steroids, or bevacizumab. They found that switching to ranibizumab resulted in both anatomical and visual improvement with central subfield foveal thickness (CSFT) decreasing from 384 to 335 μm , and visual improvement from 20/110 to 20/90, after an average of six ranibizumab injections over 48 weeks. Ciulla *et al.* use the term “refractory” as meaning persistent DME for at least 6 months despite two prior treatments. This work suggests an alternative treatment avenue in ranibizumab for patients that do not appear to respond to other treatments. Whether these patients were adequately treated prior to being labelled refractory, however, is questionable. While the patients in Ciulla and coworkers’ study (5) received only 3.4 injections with bevacizumab prior to commencement of ranibizumab, we know from recent work by the Diabetic Retinopathy Clinical Research Network (DCDR.net) consortium using Protocol T that the maximal response of DME to bevacizumab requires an average of ten injections (6) over a year, with fewer than 2% of patients receiving less than four injections before achieving an optimal response.

Recent work from Bressler *et al.* (7) indicates that approximately 20%, 45%, and 60% of patients with persistent macular edema present at 6 months despite treatment with ranibizumab became responsive to therapy with visual and anatomical improvement after 1-, 2-, and 3-year visits, respectively. This suggests that a substantial proportion of DME requires continued anti-VEGF treatment over several years before substantial

improvement occurs. The reduction of DME seen by Ciulla and colleagues (5) after commencing their ranibizumab regime may represent a similar delay in response rather than failure of previous treatment with bevacizumab. Indeed, the authors acknowledged the need for randomized trials to determine whether switching from bevacizumab to ranibizumab or aflibercept is superior to continued use of bevacizumab for persistent DME (5). That said, work from Do and others (8) from the VISTA and VIVID trials indicates that, at least in the case of aflibercept, significant visual and anatomic improvement occurs regardless of whether an eye was previously treated with bevacizumab. As suggested by Ciulla and coworkers, the same may hold true for ranibizumab (5). Taken together, the adequate use of early and intensive anti-VEGF treatment, regardless of the specific agent, remains a key message yet to be widely appreciated.

Use of intravitreal steroids as an alternative to anti-VEGF and laser treatments from DME gained more traction with the completion of the Macular Edema: Assessment of Implantable Dexamethasone in Diabetes (MEAD) registration trials (9,10). A recently published randomized trial comparing the dexamethasone implant with ranibizumab showed 7–17% and 4–26% of patients gaining more than 15 ETDRS letters of vision after treatment with dexamethasone and ranibizumab, respectively, over the 1-year trial period (11). Improvement in macular edema occurred largely in the first half of the year in dexamethasone treated eyes and in the second half for ranibizumab treated eyes (11). We speculate that eyes in Ciulla and coworkers' study (5) that did poorly with intravitreal dexamethasone may represent largely VEGF-dependent DME rather than the non-VEGF inflammatory edema at which steroids are targeted (12).

In contemporary ophthalmic practice the decision to commence ranibizumab or aflibercept is often driven by economic considerations as much as, if not more than, medical indications. In the United States, off-label bevacizumab repackaged by compounding pharmacies is currently about US \$60 per dose, while ranibizumab and aflibercept are US \$1,200 and \$1,800, respectively. Despite the higher efficacy of aflibercept and ranibizumab for management of DME, they are not as cost-effective as bevacizumab (13). It follows that the marginal visual acuity gain of four ETDRS letters noted by Ciulla *et al.* (5) may be difficult to justify from an economic standpoint.

While more affordable purpose-built anti-VEGF injectables including the newly introduced conbercept

appear promising (14–16), its availability in international markets remains limited and its efficacy less well characterized. Next-generation therapies including integrin peptides (17), squalamine (18), and Tie-2 agonists (19) may offer alternative options for management of DME, though for now it seems that the clinician must continue to balance the use of evidence-based medicine with the financial and lifestyle limitations of their patients to achieve a beneficial outcome. We must also be mindful that anti-VEGF agents are used differently when managing DME compared to age-related macular degeneration, and the use of early intensive therapy with a view to continued treatment before labeling patients as refractory is likely necessary to achieve the best results.

Acknowledgements

None.

Footnote

Conflicts of Interest: Dr. Cheung serves as a speaker and advisory board member for Bayer, Novartis, Allergan and has received research grants from Bayer and Novartis. The other author has no conflicts of interest to declare.

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Cite this article as: Fenner BJ, Cheung CM. When to change course: timing of treatment change in the management of diabetic macular edema. *Yan Ke Xue Bao* 2017;32(1):16-18. doi: 10.3978/j.issn.1000-4432.2017.01.04