Conflict of interest

The authors declare no conflict of interest.

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Eye (2015) **29,** 290–291; doi:10.1038/eye.2014.249; published online 21 November 2014

Sir,
Re: 'Fellow eye effect of unilateral intravitreal bevacizumab injection in eyes with diabetic macular edema'

We read with interest the article 'Fellow eye effect of unilateral intravitreal bevacizumab injection in eyes with diabetic macular edema'.[1] The authors report improvement in the non-injected eye of patients that received unilateral bevacizumab for diabetic macular oedema. A previous study also reported a significant difference in the mean macular thickness of the fellow eye treated with unilateral intravitreal bevacizumab for diabetic macular oedema, but no difference in the fellow eye of those receiving unilateral ranibizumab.[2]

We report a case of a significant improvement in macular thickness of the non-injected eye of a patient receiving unilateral ranibizumab for diabetic macular oedema. To our knowledge, this effect has not previously been reported.

An 81-year-old man with type II diabetes was referred with bilateral diabetic macular oedema. Best-corrected visual acuity was 6/30 in each eye. Baseline OCT scans showed a right central retinal thickness (CRT) of 607 μm and left CRT of 798 μm (Figures 1 and 2). Fundus fluorescein angiography demonstrated leaking microaneurysms close to the fovea. The patient elected to initially have ranibizumab therapy only in the right eye. No treatment was performed to the left eye, and there was no significant change to his diabetic medications or glycaemic control. Following three loading phase injections to the right eye, follow-up OCT scanning demonstrated a significant improvement in the macular oedema in both eyes, with the CRT measuring 185 and 157 μm, respectively (Figures 3 and 4). Unfortunately,

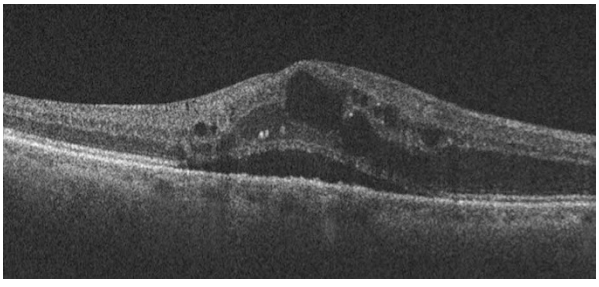

Figure 1 Pretreatment OCT of right eye showing diabetic macular oedema.

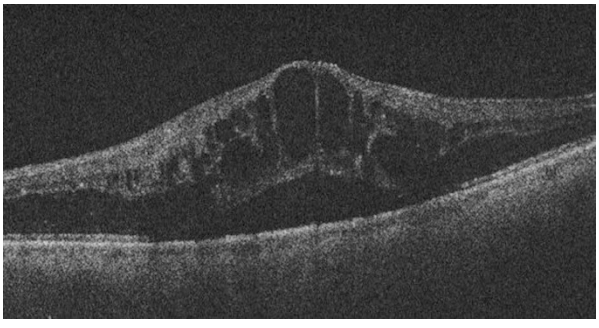

Figure 2 OCT of left eye showing diabetic macular oedema.

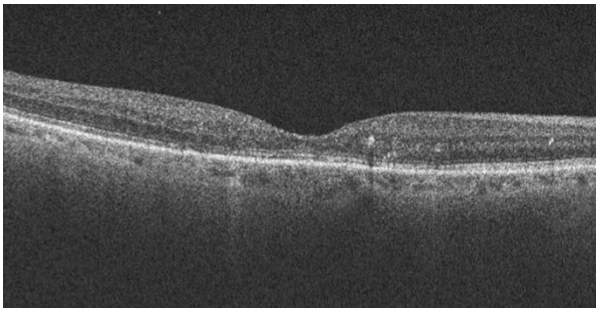

Figure 3 OCT of the right eye demonstrating improved macular oedema following three loading ranibizumab injections.

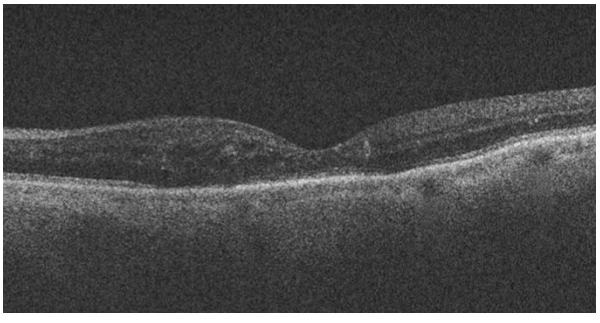

Figure 4 OCT of the left (non-injected) eye showing improved macular oedema following three loading injections to the right eye.

there was no significant corresponding improvement in vision, representing likely underlying macular ischaemia.

There have been previous case reports of two patients achieving a beneficial effect in both eyes from the unilateral injection of ranibizumab for uveitis-related macular oedema,[3] and a case of bilateral beneficial effect of both unilateral ranibizumab and bevacizumab in a patient with branch retinal vein occlusion.[4]

Our case suggests that unilateral ranibizumab can have an effect on the fellow non-injected eye in a patient with diabetic macular oedema. This is contrary to previous reports, which indicate that such an effect is only seen with bevacizumab. We suggest clinicians be aware of this possible effect to determine whether there are further similar cases.

Conflict of interest

The authors declare no conflict of interest.

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Eye (2015) **29,** 291–292; doi:10.1038/eye.2014.265; published online 14 November 2014

Sir,
Fellow eye effect of unilateral intravitreal anti-VEGF injections in eyes with diabetic macular edema

We thank Sharma *et al*[1] for reporting a case of significant bilateral reduction in macular thickness following unilateral ranibizumab therapy for diabetic macular edema (DME). This case corroborates our feeling (based on our research and experience in the clinic) that all available anti-VEGF compounds likely have an effect on the fellow eye to some extent. Most probably, the characteristics of that contralateral effect depend, among other parameters, on the precise molecular structure of the injected drug.

Ranibizumab and bevacizumab differ in their molecular weight, structure, and pharmacokinetics.[2] Ranibizumab is a 48-kDa antigen-binding fragment, which lacks a fragment crystallizable (Fc) region and is rapidly cleared from the systemic circulation.[3] Our retrospective study suggests clinically meaningful contralateral effect in more than a quarter of patients treated with bevacizumab, a 150-kDa monoclonal antibody containing an Fc region.[4] Contralateral effect might be more frequently observed with bevacizumab than ranibizumab due to the Fc region-dependent active transport of bevacizumab to the systemic circulation. In accordance with that, results from the IVAN study, conducted in AMD patients, underlines the difference in pharmacokinetics between bevacizumab and ranibizumab: the decrease in serum-free VEGF from baseline at 12 months is significantly greater with bevacizumab compared with ranibizumab.[5] Yet, some of our patients treated with ranibizumab for DME also demonstrated a fellow eye effect (unpublished observations). As highlighted by the case presented by Sharma *et al*,[1] systemic passage of ranibizumab may well result in effect on the fellow eye. Interestingly, such a contralateral influence of ranibizumab has been described in conditions in which inflammation has a pivotal role (uveitis, retinal vein occlusion, and diabetes-related macular edema).

Another point that certainly merits to be closely observed is the potential contralateral effect of intravitreally injected aflibercept, a 110-kDa fusion protein that, like bevacizumab and unlike ranibizumab, contains an Fc region.

Contralateral effects are important as unilateral injections may suffice to treat bilateral edema in certain patients. This phenomenon also underscores potential systemic effects of intravitreal injection of anti-VEGF compounds. Taken together, the case presented by Sharma *et al*, combined with our findings on bevacizumab, and other reports on the subject suggest that the incidence, extent, and consequences of such fellow eye effect should be carefully evaluated in a prospective trial.

Conflict of interest

JH declares no conflict of interest. IC served as an advisor/consultant for Novartis, Bayer, Allergan, and LycoRed; has received grants for clinical research from ISF.

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