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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NS Sharma, JM Ong and J-L Ooi

Medical Retina, Cambridge University Hospitals NHS Trust, Addenbrooke's Hospital, Cambridge, UK
E-mail: neilsss@hotmail.com

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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

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J Hanhart[1,2] and I Chowers[2]

[1]Department of Ophthalmology, Shaare Zedek Medical Center, Jerusalem, Israel
[2]Department of Ophthalmology, Hadassah-Hebrew University Medical Center, Jerusalem, Israel
E-mail: chowers@hadassah.org.il

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Sir,

Is accelerated corneal cross-linking for keratoconus the way forward? Yes or No

While I congratulate the Journal for encouraging such interesting debates and the authors for their hard work in presenting their points of view, I feel it is necessary to point out two inaccuracies presented and repeated in both articles.[1,2]

The first is equating the degree, depth, and safety of cross-linking to the depth of the demarcation line. There is currently no evidence to support this direct correlation. The so-called stromal demarcation line, first described by Seiler and Hafezi,[3] can be easily delineated by anterior segment optical coherence tomography, has been shown to possibly be shallower in older patients and those with more severe ectatic disease.[4] It has been found to be thicker centrally and thinner peripherally[5] and possibly related to an increased density of the extracellular matrix.[6] Although a deeper demarcation line has been associated with a larger decrease in corneal thickness,[7] its depth has not been shown to be correlated to either visual or keratometric changes at 6 months post-operatively.[4] It may simply represent natural wound healing responses rather than delineate the true area between cross-linked and uncross-linked tissue. Clearly a lot more research is required to ascertain the true nature of this demarcation line and its relationship with the actual cross-linking process.

Finally, in both articles it is stated that keratoconus in its early stages is a posterior corneal disease. Although posterior corneal curvature changes can indeed be detected before anterior alterations in sub-clinical disease, this is almost certainly due to the epithelium masking early anterior changes. This has been elegantly demonstrated by Reinstein *et al*[8] using high-resolution ultrasound.

Conflict of interest

The author declares no conflict of interest.

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DPS O'Brart

Department of Ophthalmology, Guy's and St Thomas NHS Foundation Trust, London, UK
E-mail: davidobrart@aol.com

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