

Effects on the Contralateral Eye After Intravitreal Bevacizumab and Ranibizumab Injections: A Case Report

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Abstract

Introduction: We report a case in which intravitreal bevacizumab and ranibizumab appeared to have effects in the contralateral, uninjected eye. **Clinical Picture:** An 83-year-old man with macular oedema from branch retinal vein occlusion (BRVO) in the right eye developed neovascular macular degeneration in the left eye. Intravitreal bevacizumab in the left eye improved macular oedema in the right eye temporarily before it recurred. Subsequently, intravitreal ranibizumab in the left eye also resulted in significant reduction of macular oedema in the right eye. **Outcome:** Vision and macular oedema in the right eye improved. **Conclusion:** Bevacizumab and ranibizumab may have therapeutic effects in the uninjected eye, possibly because they may escape from the eye into the systemic circulation.

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Key words: Side effects, Uninjected eye

Introduction

Vascular endothelial growth factor (VEGF) is recognised as an important mediator in the pathogenesis of age-related macular degeneration (AMD) and retinal neovascularisation. Anti-VEGF therapies such as pegaptanib (Macugen, EyeTech/OSI Pharmaceuticals) and ranibizumab (Lucentis, Genentech) are Food and Drug Administration (FDA)-approved in the US for the treatment of neovascular AMD. Bevacizumab (Avastin, Genentech) has also been widely used as an effective, low-cost, off-label alternative.

While pegaptanib and ranibizumab are produced exclusively for intravitreal injections, bevacizumab was originally approved as a systemic treatment for colon carcinoma. Bevacizumab is known to increase the risk of thromboembolic events when infused intravenously. However, even when administered intravitreally at much lower concentrations, bevacizumab may have a therapeutic effect on the uninjected eye.¹ One possible mechanism for this effect is that intravitreal bevacizumab may be able to escape from the eye into the systemic circulation, where it may inhibit VEGF in the other eye.² In a recent press release from the Safety Assessment of Intravitreal Lucentis for

AMD (SAILOR) trial of open-label intravitreal ranibizumab for neovascular AMD, a slight increased risk of strokes was reported in patients receiving the 0.5-mg dose versus the 0.3-mg dose (1.2% versus 0.3%, $P = 0.02$).³ Similarly, the ANCHOR and MARINA 1-year pooled results showed a slight increase in the rate of strokes and myocardial infarctions in patients receiving 0.5-mg injections versus sham injections, although the risk was not statistically significant.⁴ If verified, this phenomenon may have a similar mechanism. However, an effect of ranibizumab on the uninjected fellow eye has not yet been described in the literature.

Case Report

An 83-year-old Caucasian man with a history of hypertension, diabetes mellitus type II, and hypercholesterolaemia presented with decreased vision in the inferior visual field of the right eye (OD). His best corrected visual acuity (BCVA) was 20/40 OD and 20/20 left eye (OS), with only trace nuclear sclerosis in both eyes (OU). He was diagnosed with a superotemporal branch retinal vein occlusion (BRVO) associated with mild macular oedema OD. Two months later, he complained of sudden vision loss OD. BCVA was count fingers at 5 feet due to dense

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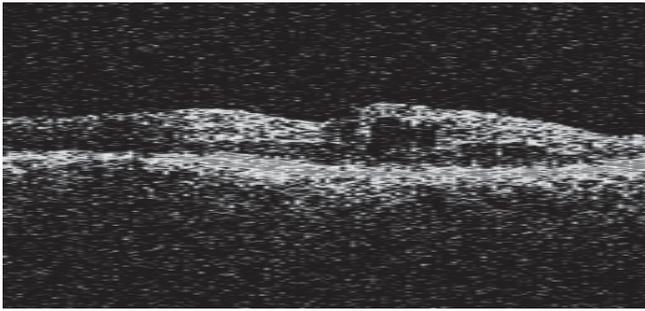


Fig. 1. A fast macula OCT scan of the right eye showing cystic macular oedema superior to the fovea due to branch retinal vein occlusion, before ranibizumab injection in the left eye.

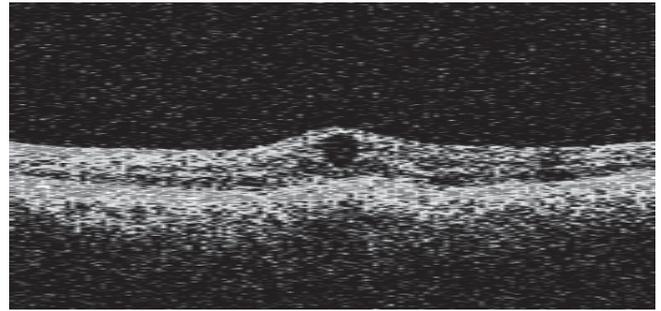


Fig. 2. A fast macula OCT scan of the left eye showing pigment epithelial elevation secondary to neovascular macular degeneration, before ranibizumab injection.

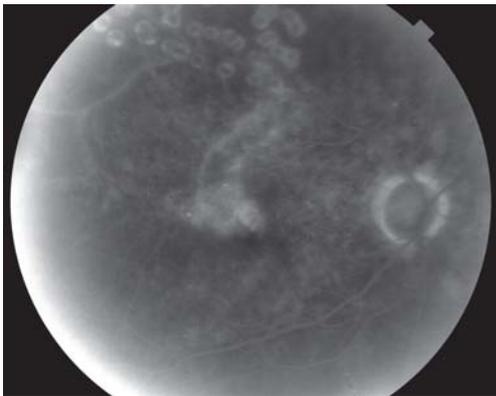


Fig. 3. Leakage of dye in the macula and along the superior arcade in the right eye.

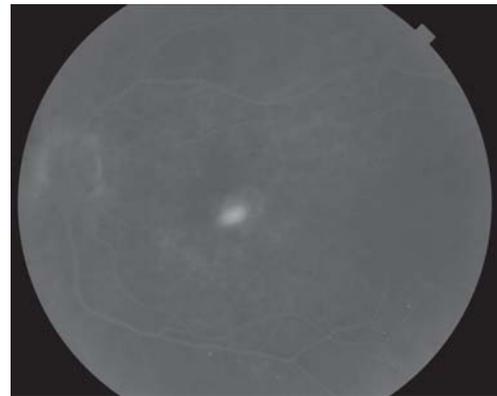


Fig. 4. Leakage from choroidal neovascular membrane in the left eye.

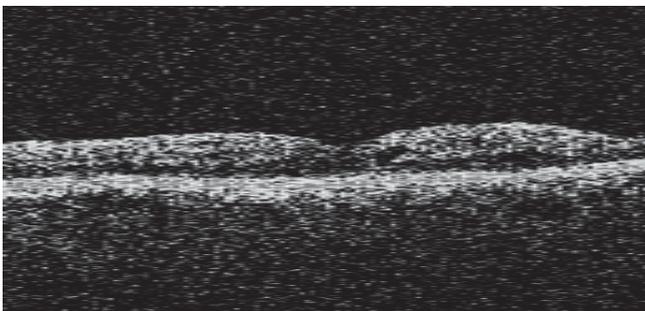


Fig. 5. After ranibizumab injection in the left eye, the right eye showed significant reduction of cystic macular oedema on OCT.

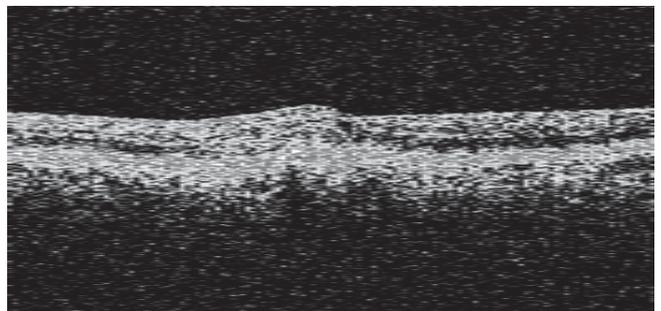


Fig. 6. Pigment epithelial elevation and retinal oedema in the left eye also improved after ranibizumab injection.

vitreous haemorrhage. With no improvement over the next 3 weeks, the patient elected to have vitrectomy and endolaser. Six weeks after surgery, BCVA was 20/70 OD with trace nuclear sclerosis, but he also noted metamorphopsia OS with a BCVA of 20/30. Optical coherence tomography (OCT) of the right eye revealed cystic macular oedema with a foveal central subfield (FCS) thickness of 305 microns. The left eye had a thin layer of subretinal fluid and FCS thickness of 270 microns. Fluorescein angiography confirmed leakage from telangiectatic vessels in the

distribution of the superotemporal vein and a branch supplying the macula, as well as accumulation of dye in the right macula. A choroidal neovascular (CNV) membrane was identified in the left eye. The patient elected to have intravitreal bevacizumab therapy (1.25 mg) in the left eye. Six weeks later, his BCVA was 20/50 in the right eye and 20/25 in the left. OCT of the right eye showed reduction of retinal oedema with FCS of 259 microns. The patient was lost to follow-up until 11 weeks later, when his BCVA was 20/60 OD and 20/40 OS. FCS was 305 microns OD (with

re-accumulation of oedema) and 261 microns OS. The patient declined further treatment but returned 3 weeks later. His BCVA remained 20/60 OD but dropped to 20/50 OS. The FCS was 335 microns OD (Fig. 1) and 337 microns OS (Fig. 2). Fluorescein angiography again showed macular leakage in the distribution of the superotemporal branch vein OD (Fig. 3) and persistent leakage from CNV OS (Fig. 4). The patient elected to begin ranibizumab therapy in the left eye. A month after 2 ranibizumab injections 4 weeks apart in the left eye, his BCVA was 20/80 OU, with a progressing nuclear sclerotic cataract noted in the right eye and an evolving subretinal fibrotic scar in the left. FCS decreased to 239 microns on the right with significant reduction of retinal oedema (Fig. 5) and 257 microns OS (Fig. 6). Two weeks after cataract extraction with intraocular lens implantation in the right eye, his BCVA improved to 20/30.

Discussion

The effectiveness of intravitreal bevacizumab on neovascular AMD and macular oedema secondary to BRVO is well documented.⁵⁻⁷ It is thought that VEGF plays an important role in the pathogenesis of both conditions.⁸ Given the effectiveness of ranibizumab in neovascular AMD⁹ and diabetic macular oedema,¹⁰ it is not surprising that it may be as effective as bevacizumab in the treatment of BRVO-related macular oedema.

The exact mechanism of how bevacizumab can affect the uninjected eye has not been elucidated. The molecule may escape into the systemic circulation. Ranibizumab, a much smaller molecule, may also possess this capability, thus accounting for the purported slightly increased risk of thromboembolic events in clinical trials.^{3,4}

The effects of bevacizumab and ranibizumab intravitreal injections are relatively short-lived. In our patient, the foveal central subfield thickness decreased in the contralateral eye with BRVO a few weeks following injection of either bevacizumab or ranibizumab, but macular oedema returned 17 weeks after bevacizumab injection, presumably because the medication had been cleared. The

temporal relationship between the intravitreal injections and the variations in central macular thickness in the contralateral eye suggests that both molecules may have anti-VEGF side effects outside of the intended treatment target.

Conflict of Interest: The authors have no proprietary interest in any of the topics discussed in this manuscript.

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