Letter to the Editor

The effect of pegaptanib (Macugen®) injection on retinal and retrobulbar blood flow in retinal Ischaemic diseases

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doi: 10.1111/aos.12603

Editor,

Pegaptanib sodium (Macugen; Eyetech Pharmaceuticals/Pfizer Inc, New York, NY, USA) is an antivascular endothelial growth factor (anti-VEGF) aptamer that specifically blocks the 165 isoform. It is currently FDA approved for treating neovascular age-related macular degeneration (Gragoudas et al. 2004). Macugen has also been shown to decrease central retinal thickness, improve visual acuity and reduce the need for additional photocoagulation in patients with diabetic macula oedema (DME) (Cunningham et al. 2005) and branch retinal vein occlusion (BRVO) (Wroblewski et al. 2010). Although the effects of anti-VEGF drugs on retinal structure appear promising, their effects on the ocular vasculature are not well studied. The mechanism of anti-VEGF treatments suggests a potential for interaction with the ocular circulation. To the best of our knowledge, we report for the first time the effects of Macugen on retrobulbar and retinal haemodynamics.

This was a prospective, open-label case series involving patients with macular oedema caused by DM or branch RVO. Patients were diagnosed at the ophthalmology clinics of the Indiana University School of Medicine. All study procedures conformed to the tenets of the Declaration of Helsinki and were approved by the University Institutional Review Board. Subjects were informed that Macugen is FDA approved for AMD but is being utilized as an off-label indication in DME and BRVO. Primary outcome measures were the changes in both retrobulbar and retinal circulation (measured by colour Doppler imaging and Heidelberg Retinal Flowmetry, respectively), as well as the change in macular thickness as measured by optical coherence tomography (OCT). Eight patients were enrolled in the study (mean age 58.5 ($\pm$16.2) years, five female). Six were diagnosed with macular oedema due to diabetic maculopathy and two due to BRVO. After baseline measurements were taken, the injections were performed every 6 weeks for three injection cycles. Measurements were taken at each visit prior to injection. Patients were given an additional injection at 18 weeks if there was residual macular oedema (OCT thickness >250 μm) after the first three injections.

Macugen caused a statistically significant reduction in blood flow velocity of the central retinal artery (CRA) after the 3rd injection as compared to preinjection (Table 1). The drug did not significantly affect velocity or resistance index in the ophthalmic artery or short posterior ciliary arteries. Baseline values of superior and inferior mean retinal capillary blow flow were 450.9 and 451.7 and after the third Macugen injection were 525.5 and 406.9, respectively; this was not a statistically significant alteration ($p = 0.094$ and 0.37, respectively). Visual acuity was not statistically significantly altered after each study visit. Macular thickness showed a trend of reduction in every OCT parameter at nearly every visit; however, only one visit and parameter (macular outer inferior region thickness after first injection) reached statistical significance.

Our data suggest that Macugen injections may reduce CRA blood flow velocities with repeated treatments as part of a cumulative effect. A single injection of another anti-VEGF treatment, bevacizumab, has been shown to decrease blood flow velocity in all retrobulbar arteries (Bonnin et al. 2010). A larger study with accompanying

Table 1. Colour doppler imaging of the retrobulbar blood vessels.

	Baseline mean (SD)	Post inj 1 mean (SD)	Post inj 2 mean (SD)	Post inj 3 mean (SD)	*T*-test post inj 1 versus base	*T*-test post inj 2 versus base	*T*-test post inj 3 versus base	*T*-test post versus pre-inj 2	*T*-test post versus pre-inj 3
OA PSV	19.7 (8.9)	21 (4.3)	24.4 (7.9)	24.7 (9.6)	0.99	0.18	0.33	0.28	0.71
OA EDV	4.5 (1.6)	5.8 (1.6)	5.9 (1.7)	5.6 (3.0)	0.21	0.08	0.33	0.92	0.86
OA RI	0.75 (0.05)	0.68 (0.09)	0.76 (0.05)	0.78 (0.06)	0.19	0.7	0.93	0.24	0.268
CRA PSV	6.6 (2.0)	7.7 (2.6)	8.1 (2.4)	6.9 (1.9)	0.22	0.18	0.6	0.44	0.02*
CRA EDV	2.4 (0.8)	2.6 (0.4)	2.7 (0.5)	2.0 (0.6)	0.49	0.13	1	0.83	0.01*
CRA RI	0.63 (0.07)	0.64 (0.1)	0.66 (0.05)	0.7 (0.06)	0.73	0.79	0.37	0.36	0.11
TPCA PSV	8.3 (1.7)	7.0 (1.4)	8.3 (1.1)	7.9 (1.6)	0.095	0.15	0.25	0.03	1
TPCA EDV	3.2 (0.8)	3.2 (1.6)	3.1 (0.7)	2.7 (0.5)	0.9	0.37	0.72	0.84	0.37
TPCA RI	0.6 (0.05)	0.63 (0.07)	0.63 (0.07)	0.66 (0.05)	0.6	0.5	0.93	0.85	0.38
NPCA PSV	8.1 (1.8)	6.9 (0.5)	7.5 (0.7)	7.2 (1.5)	0.35	0.61	0.82	0.24	0.64
NPCA EDV	3.2 (0.6)	2.4 (0.4)	2.5 (0.3)	2.3 (0.4)	0.1	0.63	0.26	0.82	0.48
NPCA RI	0.6 (0.05)	0.65 (0.06)	0.67 (0.04)	0.67 (0.04)	0.18	0.32	0.23	0.76	0.64

OA, ophthalmic artery; CRA, central retinal artery; TPCA, temporal short posterior ciliary arteries; NPCA, nasal short posterior ciliary artery; PSV, peak systolic velocities (cm/s); EDV, end diastolic velocities (cm/s); RI, vascular resistance index.
* statistically significant.

controls may help elucidate the presence or absence of any cumulative effects of Macugen in these other retrobulbar blood vessels.

In our analysis, retinal capillary blood flow was not altered by Macugen. Another pilot study found a significant decrease in the retinal arteriolar diameter after each intravitreal injection of ranibizumab (Papadopoulou et al. 2009). Taken together with our results, this suggests that anti-VEGF injections may reduce blood supply to the retina; however, data are not consistent, and the potential effects in patients with macular oedema both secondary to DR and BRVO require further verification.

Our study is limited by small sample size and lack of a control group. Therefore, a period effect cannot be ruled out from the current findings. Additionally, vessel diameter was not examined in the study. In conclusion, Macugen caused a significant reduction in CRA blood flow velocity after repeated treatments, although the other retrobulbar and retinal vessels did not show significant haemodynamic changes.

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