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Intravitreal bevacizumab (Avastin) for the treatment of choroidal neovascularization in age-related macular degeneration: results from 118 cases

Several vascular endothelial growth factor inhibitors have recently been studied as treatments for neovascular AMD.[1 2] Pegaptanib sodium improved visual acuity in 6% of patients at one year;[1] Ranibizumab 0.5 mg improved vision by three lines in 33% of patients at one year.[2] Michels *et al*.[3] initially reported the use of intravenous bevacizumab for the treatment of choroidal neovascularization (CNV), and others have found visual improvement and reduction in macular thickness with intravitreal bevacizumab.[4–8] We present the results from 118 cases treated with intravitreal bevacizumab based at a single centre.

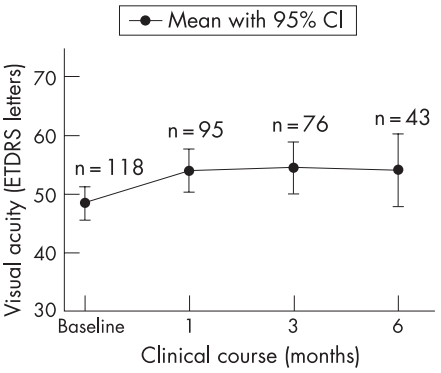

Figure 1 Graph showing change in mean visual acuity (derived Early Treatment Diabetic Retinopathy Study (ETDRS) letters) after intravitreal bevacizumab treatment.

Methods

A retrospective review of 115 consecutive patients (118 eyes) based at Southampton Eye Unit, treated with intravitreal bevacizumab for CNV was performed. Lesions of all types irrespective of size or location that were either ineligible for photodynamic therapy (PDT) under the National Health Service (including minimally classic and occult CNV) or those not responding to PDT (classic or predominantly classic CNV with recurrent or persistent CNV activity) were included in the study (table 1). All patients underwent visual acuity testing (best corrected Snellen), slitlamp examination and fundus fluorescein angiography. Central macular thickness (CMT) was assessed using Stratus optical coherence tomography (Carl Zeiss Meditec, USA).

After discussion about the off-label nature of treatment and the potential risks, informed consent was obtained from all patients. Intravitreal bevacizumab 1.25 mg was injected via the pars plana under sterile conditions; topical antibiotics were given for five days postoperatively. Patients were followed up at 2–4 weeks and then at 1-month intervals; Repeat injections were offered in the event of persistent lesion activity (indicated by persistent intraretinal/subretinal fluid or fibrovascular pigment epithelial detachment). All patients were monitored for any systemic and ocular adverse events. Blood pressure was measured before and 4–6 weeks after treatment.

Snellen visual acuity was converted to a standard logarithm of the minimum angle of resolution scale and ETDRS letter score for statistical analysis.[6] The Mann–Whitney test was used to compare the mean visual acuity and CMT, before and after treatment.

Table 1 Baseline characteristics

Demographic details	Numbers
Age, mean (range)	78.7 (50–93)
Male : female	46 : 69
Lesion subtypes (n = 118)	
Classic CNV	10
Predominantly classic CNV	10
Minimally classic CNV	15
Occult CNV	74
Peripapillary CNV*	3
Unknown/unclassified	6
Average baseline visual acuity	
Snellen acuity	6/30
ETDRS letters (mean ± SD)	48.5 ± 15.6
LogMAR vision (mean ± SD)	0.73 ± 0.31
CMT (mean ± SD)	346.3 ± 79.3 μm

CMT, Central macular thickness; CNV, choroidal neovascularization; ETDRS, Early Treatment Diabetic Retinopathy Study; logMAR, logarithm of the minimum angle of resolution; SD, standard deviation.
*With or without subfoveal extension.

Results

Demographic details and lesion subtypes are detailed in table 1. Thirty-six eyes had received other modalities of treatments (including PDT and periocular/intravitreal steroids) before intravitreal bevacizumab. At baseline, the mean ETDRS score was 48.5 ± 15.6 (Snellen equivalent 6/30). The mean CMT was 346.3 ± 79.3 μm (n = 57). In total, 219 injections were given. The mean number of injections per patient was 1.86; mean follow-up was 4.6 months (range 1–9 months).

At one month (n = 95), the mean ETDRS score improved to 54 ± 17.9 (Snellen equivalent 6/24; $p = 0.05$). At three months (n = 76), the score improved further to 54.5 ± 19.2 ($p = 0.01$). This improvement in vision was maintained at 5–6 months (n = 43), although was not statistically significant ($p = 0.09$), with a mean score of 54.1 ± 20.0. The change in visual acuity after intravitreal bevacizumab is depicted in fig 1.

At final follow-up, 104 eyes (88%) had stable or improved vision. Although stable vision (gain or loss of <15 letters) was noted in 77 (65.2%) eyes, 27 eyes (22.8%) achieved more than 15 letters improvement. Fourteen eyes (11.9%) lost more than 15 letters of vision. Classic and predominantly classic CNV groups showed a greater improvement in vision, whereas the occult CNV group showed the least visual improvement after treatment.

There was a statistically significant reduction in CMT after intravitreal bevacizumab. The mean CMT (n = 57) reduced from 346.3 ± 79.3 μm at baseline to 259.6 ± 67.6 μm at final follow-up ($p<0.0001$). The change in macular thickness did not show any correlation with the change in visual acuity ($p = 0.2$).

One patient, non-compliant to postoperative antibiotics, developed endophthalmitis positive for *Staphylococcus aureus* and requiring vitrectomy. One patient developed a retinal pigment epithelial rip two weeks after treatment. No patient had thromboembolism or any other systemic adverse events. The average systolic pressures before and after treatment were 147.9 and 146.4 mm Hg ($p = 0.8$), whereas the corresponding diastolic pressures were 80.6 and 77.0 mm Hg, respectively ($p = 0.24$).

Comment

In this retrospective review of eyes with neovascular AMD, visual acuity improved by more than 15 ETDRS letters in 27 eyes (22.8%) and stabilised in a further 77 eyes (65.2%) after intravitreal bevacizumab. Only 14 eyes (11.9%) lost 15 letters or more of vision. The mean visual acuity improved from a Snellen equivalent of 6/30 to 6/24 at one month, and this improvement was maintained at six months. The mean macular thickness decreased by 87 μm, with a reduction in intraretinal and subretinal fluid and pigment epithelial detachment. Many patients had not responded satisfactorily to other forms of treatment such as PDT and periocular/intravitreal steroids. The reduction in macular thickness was not always

associated with visual improvement. The final visual outcome could have been influenced by other factors such as the type, duration and stage of CNV, time of intervention, presence of macular scarring and retinal atrophy.

Our results are comparable to other recent studies.[4 6 7] Spaide *et al.*,[4] in a series of 266 patients, found visual improvement in a third at one month. Nearly 6% had worse visual acuity and 80% of patients had a reduction in optical coherence tomography measurements at one month. Rich *et al.*[6] observed improvements in visual acuity and macular thickness at one week, which continued to month three. At month three, mean visual acuity had improved from 20/160 to 20/125 and mean macular thickness had decreased by 99.6 μm.

We encountered no significant bevacizumab-related systemic side effects. The only ocular adverse events included a case of infectious endophthalmitis in a non-compliant patient and one retinal pigment epithelial rip. These patients had poor visual outcome. Other recent studies also found no serious drug-related ocular or systemic adverse events.[4 6–9]

This study was a non-randomized retrospective study with short-term follow-up. The study included a wide range of patients with various types and stages of CNV, some with previous treatments. The use of Snellen acuity measurements also means that direct comparison with previously published data is difficult. Despite these limitations it clearly demonstrates the efficacy and short-term safety of bevacizumab in the treatment of CNV and confirms the findings of previous studies. These preliminary results suggest that intravitreal bevacizumab is clinically effective in the management of neovascular AMD. Further studies are warranted to establish the long-term safety and efficacy of bevacizumab, and the optimal dosage for different lesions.

K C Madhusudhana, S R Hannan, C P R Williams, S V Goverdhan, C Rennie, A J Lotery, A J Luff, R S B Newsom

Southampton Eye Unit, Southampton University Hospitals NHS Trust, Southampton, UK

Correspondence to: Dr Richard S B Newsom, Southampton Eye Unit, Tremona Road, Southampton S016 6YD, UK; Richard.Newsom@suht.swest.nhs.uk

doi: 10.1136/bjo.2006.108639

Accepted 23 February 2007

Competing interests: None.

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British family with early-onset Fuchs' endothelial corneal dystrophy associated with p.L450W mutation in the *COL8A2* gene

Endothelial dystrophies produce characteristic morphological and functional abnormalities of the cornea. The most prevalent is Fuchs' endothelial corneal dystrophy (FECD), which is characterized by bilateral primary cornea guttata and a reduced endothelial cell density that can result in corneal oedema, discomfort, and blurred vision. Histology shows a thickened Descemet's membrane with focal posterior excrescences and endothelial cell loss. The onset of FECD is typically in the fifth decade of life,[1] but an early-onset variant has been described that shows phenotypic differences from the more common late-onset disease.[2 3] A genome-wide search of a three-generation family with early-onset FECD identified a locus on chromosome 1p34.3–p32.[2] Within this locus a pathogenic mutation p.Q455K was found in the *COL8A2* gene in this and two additional pedigrees.[2] Gottsch *et al*[4] recently reported a novel mutation p.L450W in a separate family with early-onset FECD.

Case report

A white British family with early-onset FECD (fig 1) was identified. Patient I:1 (79 years) had been told he exhibited endothelial pathology when he was 23 years old. At the age of 75 years he had a left penetrating keratoplasty with cataract extraction and intraocular lens implantation. Cornea guttata were present in the right eye. Patient II:1 (53 years) experienced visual deterioration in her mid-twenties as a result of bilateral corneal oedema. A right penetrating graft was performed at age 34 years and a left penetrating keratoplasty was performed at age 41 years. Patient II:2 (55 years) was asymptomatic, but non-contact specular microscopy showed endothelial pleomorphism and cornea guttata located both centrally and within the borders of endothelial cells (fig 2A). Patient III:1 (18 years) was documented to have endothelial changes at 9 years of age but still has a corrected acuity of 6/6. Histology of the cornea from patient I:1 showed thickening of Descemet's membrane without cornea guttata (fig 2B).

Using eight primer pairs the coding region of the *COL8A2* gene was sequenced and a previously reported heterozygous point mutation leading to p.L450W substitution[4] was identified in family member I:1. The mutation was subsequently confirmed by direct sequencing in two other affected family members (fig 1). Individual III:1 has not yet been tested for this change.

Comment

Mutations in the *COL8A2* gene account for only a small proportion (less than 5%)[2] of late-onset FECD, but are associated with early onset disease.[2 4] We describe the phenotype of early-onset FECD in a white British family, which is caused by a point mutation (resulting in p.L450W substitution) in *COL8A2*. The age of onset, slit-lamp biomicroscopy findings, and endothelial imaging are similar to the phenotype of a family originally described by Magovern *et al.*[3] in 1979, in which the p.L450W change was subsequently reported.[4 5] The phenotype, the early age of onset with endothelial changes detected as early as the first decade, the presence of apparently intracellular guttae on specular microscopy, and the absence of excrescences on Descemet's membrane on histology are the noteworthy clinical features of the present pedigree. The relationship between the early and late-onset variants of FECD is, at present, uncertain.[6]

In conclusion, the identification of the p.L450W substitution in a second pedigree suggests that codon 450 in the *COL8A2* sequence might be a mutation hotspot. The possibility also exists that the two families share a common ancestor. Unfortunately, no information on other first-degree relatives of patient I:1 is available.

Acknowledgements

The authors are grateful to the family members who kindly agreed to take part in this study. The authors also thank Dr George Meligonis for performing cornea histology. The study was supported by the Special Trustees of Moorfields Eye Hospital.

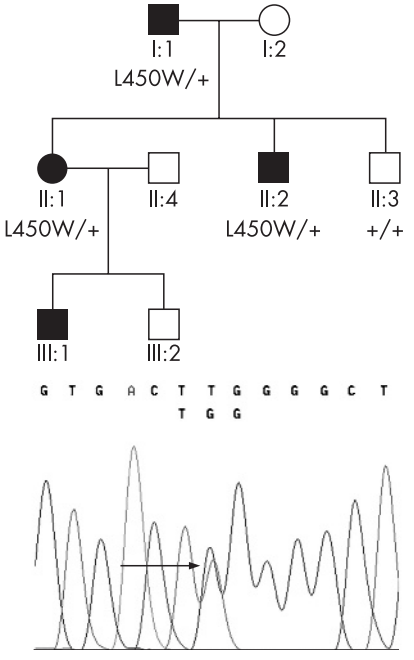

Figure 1 Fuchs' endothelial corneal dystrophy pedigree and mutation segregation. Affected patients are shown as filled symbols. Heterozygous individuals (I:1, II:1 and II:2) carry the c.1349 T>G transversion mutation resulting in a p.L450W change in the *COL8A2* gene, which is indicated by an arrow in the electropherogram. This change was not seen in the unaffected individual (II:3).