Intravitreal Therapy in Bilateral Neovascular Age-Related Macular Degeneration

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Running head: Bilateral treatment for neovascular AMD

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Intravitreal anti vascular endothelial growth Factor (antiVEGF) agents such as ranibizumab are established as standard treatment for neovascular age-related macular degeneration (nAMD). For statistical reasons, most clinical trials include 1 study eye per patient. Although up to 50% of patients with nAMD in one eye may develop fellow eye involvement within 5 years¹, few data are available on treatment outcomes in these second-affected eyes. Here we report such outcomes in patients with bilateral disease from the collaborative Fight Retinal Blindness! (FRB!) Project², which has designed and established an efficient web-based system to track outcomes of patients receiving treatment for nAMD in clinical practice.

We studied all patients from the FRB! database with bilateral nAMD in whom the second eye was diagnosed at least 2 months after the first eye and in whom both eyes had at least 12 months of follow-up data. The delay between diagnoses was chosen to ensure diagnoses were made independently, thereby excluding patients who may have presented initially with bilateral disease. Ethics approval was obtained from the respective Human Research Ethics Committees of participating doctors. Data collected included age and angiographic lesion criteria (lesion type and greatest linear dimension [GLD] in μm) at commencement of treatment (index visit); best visual acuity (VA) score (with and without spectacles or pin hole) was recorded in LogMAR letters at each visit as well as treatment given. Data are presented as mean and interquartile range (Q1 and Q3).

Of the total cohort of 1992 patients in the FRB! database, 28% had bilateral disease, which is similar to previous studies³. First and second eyes had been diagnosed with nAMD at least 2 months apart with at least 12 month follow-up data in 176 participants which formed the analysis set. Sixty-two percent of participants were female. Mean age at diagnosis of the first-affected eye was 78.6 (74 and 83) years and mean VA in first eyes was 49.7 (40 and 64) logMAR letters. Mean GLD in first eyes was 2840 μm (1500 and 3500). Median time to diagnosis of the second eye was 427 days after the first eye. At their index visit, second eyes

had a mean VA of 61.2 (54 and 75) logMAR letters and a mean GLD of 2250µm (1000 and 2880). Twelve months after commencing intravitreal anti VEGF treatment with ranibizumab, first eyes had a mean VA of 56.9 (54 and 60) logMAR letters (mean 7.2 letter improvement compared to index visit, $P<0.001$, paired t-test), while second eyes had a mean VA of 65 (63 and 67) logMAR letters (mean 3.8 letters improvement compared to index visit, $P<0.001$, paired t-test). Although a greater mean change was observed in first eyes, their 12 month mean VA was still less than that of the second eye group at their index visit (Figure 1). In the first eye group a mean of 6.3 (4 and 8) injections were administered within the first 12 months, while second eyes received a mean of 7.3 (5 and 9) injections (difference of 0.9 injections, $p<0.001$).

Choroidal neovascular (CNV) lesions were diagnosed by the treating physician as either occult, minimally classic, predominantly classic, retinal angiomatous proliferation; all other lesion types were combined into a single category. Overall, 64% of patients had the same lesion type in each eye (Cohen kappa=0.48) indicating fair to good concordance of lesion type between first and second affected eyes.

The present study evaluated characteristics and outcomes in a large cohort of patients in whom both eyes were diagnosed and treated for nAMD with intravitreal ranibizumab. The within-patient, paired data allows a close examination of characteristics at diagnosis and 12 month outcomes without extraneous variation as both eyes belonged to the same patient and were treated in the same practice. Second-affected eyes had smaller lesions and better vision when they started treatment. They had slightly more injections than first affected eyes over the first 12 months of their treatment (mean 7.3 vs. 6.3) and had better VA after 12 months of treatment than first-affected eyes, even though first-affected eyes had a greater mean VA improvement. This provides strong evidence that earlier diagnosis and treatment of nAMD leads to better outcomes⁴.

The fact that the mean VA of the first-affected eye group was 11 logMAR letters lower than the second-affected group at the index visit was expected. A recent analysis of approximately 1200 eyes with nAMD from patients treated in the United Kingdom found a 10 letter difference at presentation between first and second-affected eyes⁵. A slow decline in VA in one eye may go unnoticed if the other eye still has good vision and that patients are likely to seek help more quickly when the better (second) eye is affected. It is also likely that second eye involvement would be detected earlier during the regular visits required for treatment of the first-affected eye. This is reflected by the better vision and smaller lesion size of second-affected eyes that we observed. The better VA at the index visit seems to be the main reason for better outcomes after 12 months of treatment since mean VA improvement of the first-affected eye group was significantly greater than that of the second-affected group. The relatively greater improvement in first eyes is most likely due to ceiling effects in the second affected eye which had higher starting VA.

We also observed concordance of CNV lesion types developing in the first- and second-affected eyes. This may be attributed to various factors, most likely genetic, although some discordance observed suggests that environmental factors may also contribute to lesion type.

Although not addressed in RCTs, second eye involvement is common. Hence, patient education that second eye involvement may occur and regular checks of the second eye during busy clinics in which the first-affected eye is being treated are strongly recommended in order to pick up changes early and institute treatments promptly.

Figure 1

Figure 1: Fitted LOESS lines to 12 month longitudinal visual acuity outcomes for 176 eyes diagnosed first and their fellow 'second' eyes. Individual visual acuity readings are shown as dots. Panel A shows data for first eyes, Panel B for second eyes

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