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ORIGINAL ARTICLE

Clinical experience of switching anti-VEGF therapy from ranibizumab to aflibercept in age-related choroidal neovascularization

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ABSTRACT

Purpose: To report the response of participants switching from ranibizumab to aflibercept treatment for neovascular age-related macular degeneration (nAMD) requiring further anti-vascular endothelial growth factor treatment.

Methods: In this retrospective case review of 68 participants treated in a single hospital, all participants, prior to switching, received ranibizumab injections only. Best-corrected visual acuity (BCVA), clinical examination, and optical coherence tomography (OCT) were performed at each visit. Active nAMD was defined as persistent intraretinal or subretinal fluid on OCT. Participants had their first aflibercept injection at baseline and 2 more injections at 2 monthly intervals. Afterwards, they were followed up every 6-8 weeks and given injections as needed. The main outcome measures were visual acuity and the OCT central retinal thickness (CRT), average thickness (AT), and total macular volume (TMV).

Results: The BCVA at baseline visit was 0.57 ± 0.33 log MAR and the final BCVA was 0.54 ± 0.37 log MAR ($p = 0.215$). The CRT mean change was -75.6 ± 85.6 ($p = 0.001$), the AT mean change was -24.2 ± 27.2 ($p = 0.001$), and TMV mean change was -0.69 ± 0.78 ($p = 0.001$). There were no significant ophthalmic complications related to treatments.

Conclusions: Intravitreal aflibercept improved anatomic outcomes (as measured by OCT) in eyes with nAMD that were previously treated with intravitreal ranibizumab and were still active. There was no statistically significant difference in logMAR visual acuity in participants who switched to aflibercept with a follow-up of at least 6 months.

Keywords: Aflibercept, Anti-VEGF, Intravitreal therapy, Neovascular age-related macular degeneration, Ranibizumab

Introduction

Age-related macular degeneration associated with neovascularization is one of the leading causes of visual loss in adults aged over 60 years (1). Current preferred treatment is intravitreal administration of anti-vascular endothelial growth factor (VEGF) treatment agents. The 2 most commonly used agents in the United Kingdom are ranibizumab (Lucentis; Genentech, Inc., South San Francisco, CA, USA) and aflibercept (Eylea; Regeneron, Tarrytown, NY, USA), approved by the National Institute of Health and Care Excellence. Bevacizumab (Avastin; Genentech, Inc.), another anti-VEGF agent, is used as an off-label treatment in the public sector in the United Kingdom. Numerous studies, among them CATT (2) and VIEW 1 and 2 (3), have shown the efficacy of the above agents in maintaining visual acuity in neovascular age-related macular degeneration (nAMD). Aflibercept has the advantage of potential dosing every 2 months, while ranibizumab and bevacizumab are instead given monthly, if a treat and extend regimen is not applied. The burden of monthly hospital visits and potential treatments has increased exponentially across the United Kingdom and has put a strain on both patients and hospital resources. For that reason, some institutions have switched to aflibercept and longer follow-up periods. Several studies have shown that when switching from ranibizumab to aflibercept, optical coherence tomography (OCT) anatomical parameters improve, although visual acuity results are equivocal. The purpose of this study was to evaluate the response of patients switching from ranibizumab to aflibercept due to a change in institutional policy in patients with nAMD requiring further anti-VEGF treatment. This was done irrespective of the response of these eyes to ranibizumab in the period before switching, aiming to reduce the total num-

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TABLE I - Summary of data before and after switching to aflibercept

	At baseline, before switching (ranibizumab only)	After switching (aflibercept only)
Follow-up range, mo	14-38	6-12
No. of injections, mean ± SD	9.95 ± 8.48	3.54 ± 1.11
BCVA, logMAR, mean ± SD	0.57 ± 0.33	0.54 ± 0.37
OCT, average thickness, µm, mean ± SD	276.8 ± 30	252. 6 ± 28.3
OCT, central thickness, µm, mean ± SD	322.3 ± 85.2	246.7 ± 63.4
OCT, total volume, mean ± SD	7.83 ± 0.85	7.14 ± 0.8

BCVA = best-corrected visual acuity; OCT = optical coherence tomography.

ber of appointments and treatments. If nAMD was defined as still active, patients were offered the opportunity to switch to aflibercept and were included in the study.

Methods

This was a retrospective study of patients with active nAMD switching from ranibizumab to aflibercept injections. All patients were treated and followed up in Moorfields Eye Clinic at Croydon University Hospital, London, UK. Only one eye of any bilateral patient was included (first eye to be treated). All participants had fluorescein angiography and spectral-domain OCT performed for diagnosis (indocyanine green angiography was performed in selected cases to exclude polypoidal vasculopathy). All participants, prior to switching, had received treatment with ranibizumab injections only, on a PRN basis after the first 3 monthly loading injections of ranibizumab. Every patient was treated for the last time with ranibizumab 4 to 5 weeks before the first aflibercept injection. Active nAMD was defined as persistent intraretinal or subretinal fluid on OCT (3DOCT-2000; Topcon, Tokyo, Japan) during monthly follow-up visits. When switching, participants had their first aflibercept injection at the baseline visit and then 2 more injections at 2 monthly intervals (3 injections in the first 3 months). They were subsequently followed up every 6-8 weeks and given injections on a PRN basis, until the conclusion of their follow-up (final visit). Best-corrected visual acuity (BCVA), intraocular pressure check, and dilated fundus biomicroscopy were performed at every visit. The study adhered to the tenets of the Declaration of Helsinki. All patients provided informed written consent before commencement of treatment.

Statistical analysis was performed with SPSS 12.0.1 (SPSS Inc., Chicago, IL, USA) software. Paired *t* tests were used to compare the differences in means between baseline and final visits for BCVA and OCT parameters. The OCT parameters studied were central retinal thickness (CRT), average thickness (AT), and total macular volume (TMV). Each scan at the macular area, where the parameters were derived, had a size of 6 6 mm. A p value of less than 0.05 was considered to be statistically significant. All results are presented as values ± standard deviations (SD). In cases when patients did not attend a scheduled visit, the last observation was carried forward for analysis.

Results

Sixty-eight eyes (36 right eyes, 53%; 32 left eyes, 47%) of 68 participants (45 female, 66%; 23 male, 34%) were included in the study. Mean age was 80.7 ± 8.3 years. Range of follow-up before baseline visit (when patients received ranibizumab injections only) was 14 to 38 months. The average number of ranibizumab injections before switching (at baseline) was 9.95 ± 8.48. Ranibizumab BCVA and OCT parameters at baseline prior to aflibercept being commenced are presented in Table I. After switching, range of follow-up was 6-12 months (mean 9.7 months, SD ± 2.2 months). Mean number of aflibercept injections was 3.54 ± 1.11. Final visit data are also presented in Table I. The BCVA at baseline visit was 0.57 ± 0.33 logMAR, equivalent to 20/75 Snellen. Final BCVA was 0.54 ± 0.37 logMAR, equivalent to 20/68 Snellen. Paired *t* test comparison of BCVAs between baseline and final visits was not statistically significant (p = 0.215, 2-tailed). The OCT CRT mean change was -75.6 ± 85.6, the AT mean change was -24.2 ± 27.2, and TMV mean change was -0.69 ± 0.78. Paired *t* tests for OCT parameters at baseline and final visits were as follows: (1) for CRT, p = 0.001, 95% confidence interval (CI) was 54.9-96.35; (2) for AT, p = 0.001, 95% CI was 17.64-30.79; (3) for TMV, p = 0.001, 95% CI was 0.5-0.87. There were no significant ophthalmic complications such as endophthalmitis, intravitreal haemorrhage, retinal detachment, or induced cataract during the whole follow-up period (either with ranibizumab or aflibercept injections). No systemic side effects were reported in any participant during the same period, due to the above treatments.

Discussion

Aflibercept previously has been shown to be effective in treatment-naive patients with nAMD. Several studies have also suggested that it can reduce persistent retinal fluid in patients when switched from ranibizumab (4-18). Our results show that intravitreal aflibercept improves anatomic outcomes (as measured by OCT) in eyes with nAMD that were previously treated with intravitreal ranibizumab and were still active. There was no statistically significant change in logMAR visual acuity in these eyes with a follow-up of at least 6 months. Some studies have found some improvement in

visual acuity (1 Snellen line) in patients switched from ranibizumab to aflibercept (8, 9, 14, 16), although most included participants switched due to treatment resistance, i.e., no satisfactory response to ranibizumab. Other studies have shown similar results to ours. Most aforementioned studies (including ours) share the limitation of being small and retrospective. A strength of this study was the real-life clinical data and the lack of any selection bias, as the patient population that was studied included all patients with active nAMD, as per the institutional policy change.

Anatomic improvement observed on OCT after switching treatment may have various possible explanations. There is a possibility that previous ranibizumab treatment resulted in pharmacologic tachyphylaxis (19, 20), whereby there was a gradually decreasing therapeutic benefit from prolonged use, so aflibercept treatment was effective in reducing residual fluid after patients were desensitized to ranibizumab. Although it cannot be proven, this may have happened in our series, because all patients in our study had responded to ranibizumab treatment (albeit at varying degrees) initially, but eventually were still active at the time when they were switched to aflibercept.

The cumulative duration of anti-VEGF treatment (at least 12 months of ranibizumab treatment before switching) can also be a possible explanation for the improved anatomic outcomes. Another explanation could be that aflibercept is a more potent agent, since it binds all isoforms of VEGF-A (most important for angiogenesis) and VEGF-B, with a higher binding affinity than either ranibizumab or bevacizumab. It also binds placenta growth factor, unlike bevacizumab and ranibizumab (21).

This study provides evidence that aflibercept can improve anatomic outcomes successfully in patients with active nAMD who are switched from previous ranibizumab therapy and that the effect is maintained with 2-monthly treatment intervals. Less frequent injections carry reduced risk for treatment-related complications. It also reduces significantly the monthly burden of appointments and treatment on patients and care providers. Longer-term follow-up is required to validate these results in clinical practice.

Disclosures

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