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Original Article

Clinical Response To Switch From Ranibizumab To Aflibercept In Wet Age-Related Macular Degeneration

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Abstract

Introduction: *To assess whether switching from Ranibizumab to Aflibercept conferred benefit in visual acuity (VA) and central macular thickness (CMT) in patients with wet age-related macular degeneration (AMD).*

Methods: *Mean change in VA and CMT was assessed in wet AMD patients 6 months prior and 6 months after switch from Ranibizumab to Aflibercept, between July 2014 and November 2016.*

Results: *90 eyes were switched from Ranibizumab to Aflibercept. VA improved in 11 eyes, 65 reported no change and 14 showed deterioration. Improvement in VA was not statistically significant (p>0.05). CMT improved in 24 eyes, 64 showed no change and in 2 there was deterioration. This improvement was statistically significant (p<0.01). Sub-analysis into patients that had switched to Aflibercept after 6 (28 patients) or >6 (62 patients) Ranibizumab injections showed no significant difference between these groups for VA or CMT change.*

Conclusion: *Although there seemed to be an improvement in the CMT with Aflibercept, this did not translate as a statistical improvement in VA. Switching earlier to Aflibercept did not show any significant benefit in either VA or reduced CMT within the first 6 months. Our research however, requires extension as the benefits may be seen over a longer period of time. In conclusion, some patients with sub-optimal response to Ranibizumab may benefit from switching to Aflibercept.*

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Introduction

Age-related macular degeneration (AMD) is one of the most common causes of irreversible visual impairment among the elderly population in the Western World.[1,2]

AMD is divided into dry AMD (non-neovascular) and wet AMD (neovascular). Dry AMD is a form of extensive atrophy of retinal pigment epithelial and photoreceptor cells. The pathogenesis of wet AMD is strongly related to enhanced expression of Vascular Endothelial Growth Factor (VEGF) with the formation of choroidal neovascularisation (CNV). Proliferation of CNV leads to exudative leakage, hemorrhage and sub-retinal scarring. Untreated CNV leads to irreversible loss of central vision causing difficulty in performing certain daily activities like driving, reading and recognising faces.

Currently there is no effective treatment for dry AMD. However, wet AMD has been successfully treated with NICE approved intravitreal anti-VEGF injections such as Ranibizumab or Aflibercept.[3,4]

Ranibizumab is a humanized monoclonal antibody fragment that binds to and inhibits the biological activity of all isoforms of VEGF-A. Efficacy and safety of Ranibizumab in the treatment of minimally-classic and occult neovascular age-related macular degeneration was demonstrated in the MARINA study.[5] Furthermore, the efficacy of Ranibizumab in the treatment of classic and predominantly classic CNV was demonstrated in the ANCHOR study.[6]

Aflibercept is comparatively a new drug for the treatment of wet AMD. Aflibercept is a fusion protein that act as a decoy receptor. It binds to VEGF-A with higher affinity than Ranibizumab as well as VEGF-B and placental growth factor (PIGF) which also present in human CNV membranes. The effectiveness of Aflibercept in wet AMD was showed in the VIEW 1 and VIEW 2 studies.[7] NICE approved Aflibercept for the treatment of wet AMD in July 2013.

In largescale clinical trials, including VIEW1 and VIEW2, it has been shown that neither Aflibercept nor Ranibizumab had a vastly superior clinical effect on improving best corrected visual acuity (BCVA) or central macular thickness (CMT).

The current NICE guidance states that clinicians should "Be aware that no clinically significant differences in effectiveness and safety between the different anti-VEGF treatments have been seen in the trials". NICE also advises that switching between different anti-VEGF drugs should be considered only when a change in regime would be beneficial to the patient and that switching from one drug to another is unlikely to confer any significant clinical advantage.[8]

The current study designed to demonstrate the 6-month change in visual acuity (VA) and lesion activity based on OCT characteristics in a cohort of patient that switched from Ranibizumab to Aflibercept for wet AMD following sub-optimal response to Ranibizumab.

Materials and Methods

A retrospective observational study of wet AMD patients who had been switched from intravitreal injections of Ranibizumab to Aflibercept was performed at a District General Hospital in the United Kingdom. Data was obtained from the wet macular degeneration patient database between 1st July 2014 and 30th November 2016.

Approval for data collection and use was obtained from the Ophthalmology Department as well as the local Research and Development Unit. The data was managed and stored in accordance with University Health Board guidance on data protection. Ethical approval was not required as it was a retrospective analysis.

The inclusion criteria were the patients who had angiographically confirmed wet AMD and had received at least 6 injections of Ranibizumab prior to switch (Table 1). Standardised departmental protocol for Ranibizumab was intravitreal injections every 4 weeks for 3 visits, following which it is given if required (PRN), based on ocular coherence tomography. Ranibizumb was instituted as first line irrespective of the fluorescein angiographic features of the type of AMD. Access to OCT angiography was not available. Patients who had persistent lesion activity despite 6 consecutive Ranibizumab injections in the form of persistent intra-retinal or subretinal fluid were switched to Aflibercept injections. Standardised protocol for Aflibercept is intravitreal injection every 4 weeks for 3 visits, after which it is given on an as needed basis every 8 weeks. Patients who had been initiated on treatment elsewhere were excluded.

Data was assessed specifically looking at change in best corrected visual acuity and central macular thickness (CMT) six months prior and six months post switching treatment from Ranibizumab to Aflibercept.

Table 1: Inclusion and Exclusion Criteria

Inclusion Criteria	Exclusion Criteria
Treatment initiated at same hospital	Treatment initiated elsewhere
Angiographically confirmed wet AMD	Absence of 6 consecutive appointments prior to switch
At least 6 injections of Ranibizumab	Absence of 6 months appointments post-switch
Persistent fluid despite 6 consecutive injections	Any data missing over assessment period

Visual acuity was recorded using the logarithm of the minimum angle of resolution (LogMAR) letter score. Spectral domain optical coherence tomography (SD-OCT) was performed to determine the presence or absence of subretinal and intraretinal fluid and to assess the central macular thickness.

With regards to best corrected visual acuity, +/- 0.1 LogMAR was considered an improvement or deterioration respectively. A change to central macular thickness of +/- 50μ was considered as a significant change.

Our null hypothesis states that there is no significant difference in mean visual acuity or central macular thickness 6 months after switching from Ranibizumab to Aflibercept. Paired T-test was applied to the data to see whether the mean value pre-switch differed significantly from the mean value post-switch for visual acuity and central macular thickness. Sub-group analysis with respect to qualitative assessment for fluorescein angiography or OCT was not performed.

Results

A total of 387 eyes of 251 patients were switched from Ranibizumab to Aflibercept between July 2014 and November 2016. However, only 90 eyes met the criteria for inclusion in this analysis of having had treatment initiated at the same hospital, had at least 6 consecutive injections of Ranibizumab before switch to Aflibercept and 6 months post-switch follow-up data with no missed appointments. There were 33 males and 57 females. The mean number of Ranibizumab injections prior to switching over to Aflibercept was 11. VA improved in 11 eyes, 65 reported no change and 14 showed deterioration on logMAR. The change in VA was not statistically significant (p>0.05) (shown in Figure 1). CMT improved in 24 eyes, 64 showed no change and in 2 there was deterioration on OCT. The improvement

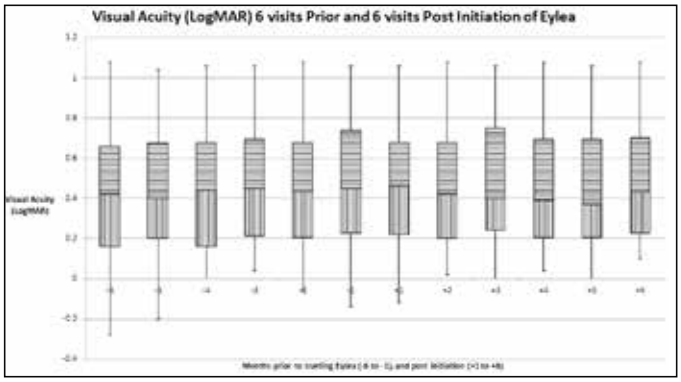

Figure 1: *Boxplots for visual acuity in LogMAR 6 visits prior to and 6 visits Post Initiation of Aflibercept. Median is shown as the junction of 2 patterns with upper and lower quartile as box, and range minimum and maximum at ends of vertical lines. Box 1 – Upper quartile of median visual acuity Box 2- Lower quartile of median visual acuity*

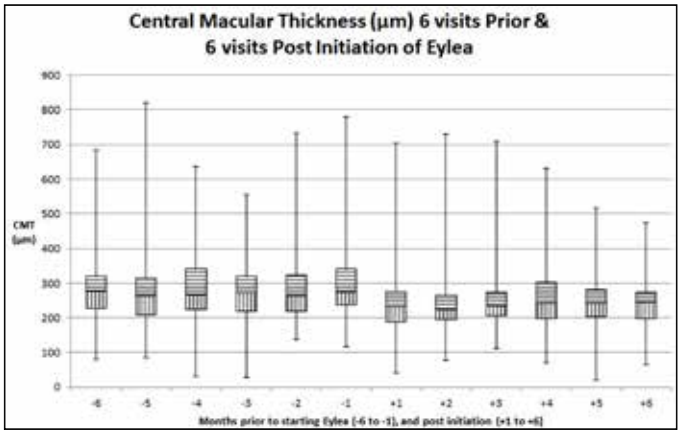

Figure 2: *Boxplots for central macular thickness in μm 6 visits Prior and 6 visits Post Initiation of Aflibercept. Median is shown as the junction of 2 patterns with upper and lower quartile as box, and range minimum and maximum at ends of vertical lines. Box 1 – Upper quartile of median central macular thickness Box 2 - Lower quartile of median central macular thickness*

in CMT was significant (p<0.01) (shown in Figure 2). Further sub-analysis split the data into patients that had switched to Aflibercept after 6 (28 patients) or >6 (62 patients) Ranibizumab injections. There was no significant difference between these groups for VA or CMT change although both groups still demonstrated a statistically significant decrease in CMT (p<0.01) post-switch.

Discussion

The present study retrospectively assessed the mean BCVA and mean CMT as independent outcome measures 6 months prior and 6 months post switch from Ranibizumab to Aflibercept. There was no statistically significant improvement in BCVA. However, the majority of eyes (72%) maintained visual acuity gained during Ranibizumab treatment. Meanwhile, there was a small but statistically significant improvement in CMT. The subgroup analysis showed no significant difference in either VA or CMT outcome if patients had been on Ranibizumab for a longer period prior to switching as compared to earlier.

Studies have shown that Aflibercept is as effective as Ranibizumab with regard to visual outcome in wet AMD. VIEW clinical studies demonstrated that intravitreal Aflibercept injection every 8 weeks, following 3 initial monthly injections, was non-inferior to monthly Ranibizumab.[5] Literature shows limited data on the outcome of switching from Ranibizumab to Aflibercept in persistently active wet AMD. However, the results of our study are in line with other similar studies which described statistically significant improvement in anatomy but only a limited improvement in vision.[9,10]

Wykoff et al (2014) reported a prospective result of 46 patients who had previously been on long term Ranibizumab and were switched to Aflibercept. The mean number of previous Ranibizumab injections was 76. They reported significant improvement in mean CRT from baseline (p=0.018) but visual acuity remained stable. However, they used Ranibizumab in a higher dose of 2 mg as compared to the NICE approved dose of 0.5 mg. Therefore, replicating their study in a UK setting was not possible.

Nixon et al (2017) prospectively evaluated visual function and anatomic outcomes in a cohort of 49 eyes of 40 randomly selected patients with wet AMD who had been switched to Aflibercept from Ranibizumab. Mean number of injections prior to switch were 28, ranging from 3 to 86 injections. They assessed VA, contrast sensitivity, CMT and visual function indices. At 12 weeks after switch, mean contrast sensitivity improved from 1.32 log units at baseline to 1.40 log units but VA remained stable throughout. At week 12, there was a statistically significant decrease of 22μm in mean central retinal thickness (CRT) from 354 μm at baseline to 332 μm (P=0.004). There was no relationship between VA measurements and change in CRT. Direct comparison between these two studies is limited due to its short follow-up, differences in patient selection and the exact dosage of Ranibizumab is not mentioned in the latter study.

Several factors need to be considered when evaluating the actual effect of visual outcome after switching from Ranibizumab to Aflibercept. Although there was no significant improvement in BCVA, a small percentage of 12% did improve by 5 or more log MAR letters, but this was counteracted by a slightly higher percentage of 16% that lost 5 or more log MAR letters. Published literature has shown that in long-term treatment with anti-VEGF, after an initial gain and plateau, mean VA tends to decline over time due to structural changes, such as scar formation or development of geographic atrophy.[11,12]

The current study is associated with some limitations. The sample size of the switch cohort, similar to previous studies, was relatively small. The age demographics of the patients were such that many patients missed one or more of their follow-up appointments thereby excluding them from the analysis. Therefore only 90 of the 251 switch patients attended all their scheduled visits. The follow-up of patients was limited at 6 months. Therefore, the possibility of improvement of visual acuity with long term follow-up cannot be excluded. The VA was the only parameter used to assess the visual outcome. Thus, other vision related parameters such as contrast sensitivity and vision-related functional benefits had not been assessed. Ranibizumab was administered in all patients irrespective of the type of AMD.

No sub-group analysis was done due to small sample sizes. Qualitative analysis or OCT was not performed and there was no access to OCA angiography. Hence, conducting a larger study evaluating multiple measures of visual function is warranted. The outcome of switching to another drug is difficult to evaluate in retrospective nature without a control group.

In conclusion, this observation suggests that switching to Aflibercept treatment may benefit in a certain group of recalcitrant wet AMD patients, while maintaining prior visual gains. The lack of significant visual gains may indicate that those who do not benefit significantly initially may be due to structural changes in the retina or photoreceptor or RPE atrophy. This cohort of patients would not benefit visually with any treatment. It might be useful to see whether switching earlier, perhaps if there is sub-optimal response after the initial three loading injections and a longer follow-up gives different results. The evolution of treatment strategies for neovascular AMD is of paramount importance in recognizing alternative treatment options and therefore to enhance benefit to our patients.

Author Contributions

Ms Chandni Gupta and Dr Yasmin Levene were involved in the design of the study, data collection and analysis. Dr Bhagya Weerasinghe and Mr Jai Shankar were involved in writing up the article. Ms Chandni Gupta and Mr Jai Shankar presented this as a poster at the EuRetina Congress at Budapest, Hungary in February 2018.

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