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**Full Title**

Visual Acuity Improvement when Switching from Ranibizumab to Aflibercept is Not Sustained

**Abbreviated Title**

Transient Benefit with Anti-VEGF Switch

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**Key Words**

Aflibercept; age-related macular degeneration; choroidal neovascularization; ranibizumab; tachyphylaxis; vascular endothelial growth factor

**Summary Statement**

Transient improvement in visual acuity occurs when patients undergoing chronic ranibizumab are switched to aflibercept therapy for treatment of neovascular age-related macular degeneration.

**ABSTRACT**

**Purpose:** To assess whether visual benefits exist in switching to aflibercept in patients who have been chronically treated with ranibizumab for neovascular age-related macular degeneration (nvAMD).

**Methods:** We performed a multicenter, national electronic medical record database study. Patients undergoing 6 continuous monthly ranibizumab injections and then switched to continuous aflibercept were matched to patients on continuous ranibizumab therapy. Matching was performed in a 2:1 ratio and based on visual acuity (VA) 6 months prior to and at the time of the switch, and the number of prior ranibizumab injections.

**Results:** Patients who were switched to aflibercept demonstrated transiently significant improvement in VA that peaked at an increase of 0.9 ETDRS letters three months after the switch while control patients continued on ranibizumab treatment showed a steady decline in VA. VA differences between the groups were significant ( $p < 0.05$ ) at two, three, and five months after the switch. Beginning at four months after the switch, the switch group showed a VA decline similar to the control group.

**Conclusion:** Transient, non-sustained improvement in VA occurs when switching between anti-vascular endothelial growth factor (anti-VEGF) agents, which may have implications in treating patients on chronic maintenance therapy on one anti-VEGF medication.

## **INTRODUCTION**

Age-related macular degeneration (AMD), the leading cause of blindness in North Americans and Europeans of age 50 years and over,<sup>1,2</sup> currently affects approximately 6.5% of Americans aged 40 years and older.<sup>3</sup> This blinding eye disease is classified into two types of pathologies. Non-neovascular AMD is characterized by drusen formation, which damages photoreceptors and contributes to the geographic atrophy of the macula. Approximately 85-90% of people with AMD have the non-neovascular form. Neovascular AMD (nvAMD) is characterized by choroidal neovascularization (CNV) and responsible for 80-90% of AMD cases of blindness.<sup>4</sup>

The current treatment method of nvAMD consists of intravitreal inhibitors of vascular endothelial growth factor (VEGF), a key player in CNV pathogenesis. The pivotal trials, Anti-VEGF antibody for the Treatment of Predominantly Classical Choroidal Neovascularization in AMD (ANCHOR) and Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab In the Treatment of Neovascular AMD (MARINA), have shown the efficacy of ranibizumab over photodynamic therapy or sham injections.<sup>5,6</sup> Comparison of AMD Treatment Trials (CATT) study has demonstrated no inferiority between fixed monthly dosing of ranibizumab and bevacizumab in treatment naïve patients.<sup>7</sup> However, no trial has assessed the effect of cross-over between anti-VEGF agents.

Today, clinicians encounter more than one anti-VEGF choice in treating patients with nvAMD. The contributing factors toward choosing one agent over the rest include cost, frequency of dosing, physician's preference, patients' insurance status, and other literature findings.<sup>8,9</sup> Tachyphylaxis, the acutely progressive weakening of a pharmacological response due to long-term or repeated exposure to a drug,<sup>10</sup> has been previously described in patients with nvAMD and several studies of small sample size have reported conflicting results with some showing possible clinical benefits of switching between anti-VEGF agents but others with no significant advantage.<sup>11,12</sup> (Add all the new references here) However, no large study has determined the clinical significance and duration of possible tachyphylaxis in patients undergoing chronic

intravitreal anti-VEGF injections for AMD, which has important clinical implications since many patients are maintained on chronic monotherapy.

In the United Kingdom, ranibizumab was used exclusively to treat exudative AMD in the National Health Service (NHS) until aflibercept was approved in 2012. A significant portion of patients were switched from ranibizumab to aflibercept dosing at this time, providing us with rich clinical data with outcomes on the patients who continued ranibizumab vs. those who switched. The purpose of this study was to compare the visual outcomes of patients who switched from ranibizumab to aflibercept with those who continued ranibizumab therapy.

## **SUBJECTS & METHODS**

Anonymized data were extracted from the electronic medical record (EMR) system (Medisoft Ophthalmology, Medisoft Limited, Leeds, UK) of 20 UK. The Caldicott Guardian (responsible nominee for data protection) gave approval for anonymized data extraction. Anonymized database analyses of this type do not require full ethical permission as they are viewed as an audit or service evaluation (see <http://www.hra.nhs.uk/research-community/before-you-apply/determine-whether-your-study-is-research/>). This study was conducted in accordance with the declaration of Helsinki, and the UK's Data Protection Act. Medisoft Limited (Leeds, UK) has a structured data set for the management of nvAMD that allows the rapid pooling of the data fields collected. This data set was defined and set up before the date of first data collection into this study. Data collected at all sites included visual acuity (VA) for each eye (and the method of measurement) and treatment if required (with procedure details and complications).

### *Data Variables*

Study eyes were identified with the diagnosis of nvAMD undergoing ranibizumab therapy. In this report, the 'best-measured VA' was the best VA with refraction or habitual correction and/or pinhole as measured on an Early Treatment Diabetic Retinopathy Study (ETDRS) chart and

expressed as ETDRS letters, which is the mandated way of collecting VA in the UK for anti-VEGF treated patients. All analyses were performed using ETDRS letters. Data variables also extracted included age, gender, site of treatment, dates of assessment visits, and dates of intravitreal therapy.

### *Matching*

Figure 1 outlines the treatment sequence of patients in the switched and continuous ranibizumab groups. Patient eyes that were treated with at least 1 year of therapy since the initiation of therapy for nvAMD, at least 6 monthly, continuous ranibizumab therapy, and treated with at least 3 aflibercept injections after switching from ranibizumab were identified. These patient eyes were then matched to control eyes that were treated with at least 1 year of therapy since the initiation of therapy for nvAMD, at least 6 monthly, continuous ranibizumab therapy, and treated with at least 3 additional ranibizumab injections. Neither group changed therapies after initially switching to aflibercept or remaining on ranibizumab for the remainder of the study. The matching ratio was fixed in a 2:1 ratio and the criteria for matching were the number of prior ranibizumab injections at the time of the switch within 5 injections, the visual acuity at the time of the switch within 5 ETDRS letters, and the visual acuity at 6 months prior to the switch within 5 ETDRS letters. The matching was performed using a pseudorandom number generator and a total of 100,000 random permutations were tested to identify the matching that yielded in the highest number of patients matched.

### *Imputations*

The visual acuities were imputed using last observation carried forward and the relative visual acuity difference for each patient eye was calculated with the reference being the visual acuity at the time of switching. The mean visual acuities for each month for 6 months prior and 6 months after switching were evaluated.

### *Statistical Analyses*

A generalized linear model was used to evaluate the difference in relative VA at each month after switching between the groups adjusted for age at the time of switching, the number of ranibizumab injections at the time of switching, and the visual acuities at 6 months prior and at the time of switching. All analyses were performed using Ruby (<http://www.ruby-lang.org>) and R (<http://www.r-project.org>).

## **RESULTS**

A total of 1,344 patients treated with intravitreal ranibizumab injections were included in the study. A total of 448 patients were switched from ranibizumab to aflibercept and 896 patients were matched with continued ranibizumab injections. Table 1 shows the baseline demographic characteristics of the patients.

Six months prior to the switch, the VA of the control and switch groups was 1.3 ETDRS letters and 1.7 letters higher than at the time of the switch, respectively (Figure 2). Two months after the switch, the switch group demonstrated improvement from 0 to 0.74 letters, while the control group resulted in 0.71 letters of VA loss. Six months after the switch, VA for the control and switch groups had declined to -1.3 and -0.75 letters, respectively. On multivariate analysis, the relative visual acuity in the switch group was significantly higher ( $p < 0.05$ ) than the control group at months 2, 3 and 5 after the switch (Table 1, Figure 3).

## **DISCUSSION**

Our study demonstrates that when patients are switched from ranibizumab to aflibercept injections, a statistically significant but transient improvement in VA occurs at two, three and five months after the switch. Following the transient improvement, a decline in VA occurs four to six

months after the switch, similar to the control group. Even at month 2 and 3, the difference in letters read were 1.5 and 1.3, which is not deemed to be clinically relevant when compared with the non-inferiority limit of 5 letters set in the CATT study.<sup>7</sup>

Several hypotheses could explain our study findings. First, aflibercept may be superior to ranibizumab in inhibiting VEGF-A, given that aflibercept has a binding affinity that is nearly 140 times that of ranibizumab.<sup>14</sup> In addition, Stewart and Rosenfeld predicted that the intraocular biological activity of aflibercept at 10 weeks after a single injection is comparable to ranibizumab activity at 30 days, based on a mathematical model that assumes the molecular mass of an antibody is proportional to its intravitreal half-life.<sup>14</sup> Thus, aflibercept may be more effective for longer durations compared to ranibizumab. However, the VEGF Trap-Eye: Investigation of Efficacy and Safety in Wet AMD Trials (VIEW 1, VIEW 2) did not demonstrate superiority of aflibercept in preventing moderate visual acuity loss over ranibizumab after 1 year of treatment.<sup>15</sup>

On the other hand, tachyphylaxis may have developed during the long-term use of ranibizumab prior to the switch. Tachyphylaxis occurs when cells acutely respond to drug treatment by downregulating signaling pathways downstream from their receptors to return to homeostasis.<sup>16</sup> The patients who were switched to aflibercept may have shown improvement in vision due to the use of a novel biological agent rather than its superiority. This explanation is substantiated by the transient, rather than long-term nature of VA improvement observed in patients who switched to aflibercept, as shown in a retrospective case series conducted by Slean *et al*.<sup>17</sup> In this study, a total of 80 nvAMD eyes were initially treated with an average of 20.71 injections of bevacizumab and/or ranibizumab and then switched to aflibercept. The median central macular thickness (CMT) improved transiently from 317  $\mu\text{m}$  to 285  $\mu\text{m}$  after the switch. However, CMT later worsened to a median of 296  $\mu\text{m}$  after continuous aflibercept treatments. Interestingly, after a total average of 7.2 aflibercept injections, 21 eyes (19 patients) were switched back to

either ranibizumab or bevacizumab due to recurrent fluid or VA decline. After the switch, the eyes demonstrated transient improvement in CMT (283  $\mu\text{m}$ ) again. Even though fluid followed a similar trend throughout the transitions, median VA showed little apparent change. Slean *et al* concluded that nvAMD eyes with recurrent fluid may demonstrate a therapeutic response to periodically rotating anti-VEGF agents.<sup>17</sup>

Prior smaller studies have similarly investigated whether tachyphylaxis occurs during anti-VEGF treatments. In a review of the literatures on the treatment of refractive nvAMD to bevacizumab and/or ranibizumab,<sup>1</sup> five small studies of 26 to 65 patients showed statistically significant visual acuity improvement (p-value <0.05) ranging from 0.5 to 6.9 ETDRS letters and 0.09 to 0.1 logMAR at 6 months after the switch to aflibercept.<sup>2,3,4-6</sup> Additional studies reported visual acuity improvement ranging from 0.01 to 0.29 logMAR and 0.2 to 2.5 ETDRS letters but none of these changes were statistically significant.<sup>7, 8, 9-12</sup> Thus, the majority of the studies have shown either non clinically and/or statistically significant difference in visual benefit at 6 months after switching to aflibercept, comparable to our study results.

Forooghian *et al* conducted a retrospective review focusing on OCT outcome measures of 59 patients with nvAMD and reported tachyphylaxis in 6 eyes (5 patients) after 31 to 128 weeks of bevacizumab treatment.<sup>13</sup> Tachyphylaxis was defined as a loss of therapeutic response 3 to 5 weeks after bevacizumab administration in an eye that had previously demonstrated a therapeutic response in the same time interval within the treatment period. Patients were treated with intravitreal bevacizumab as needed based on the intra- or subretinal fluid on spectral domain optical coherence tomography (OCT) and followed every 4 weeks for 14 months. In another study, Gasperini *et al*<sup>18</sup> identified 10 eyes that were initially treated with bevacizumab and then switched to ranibizumab, and 16 eyes that were initially treated with ranibizumab and switched to bevacizumab, with a mean follow-up period of 13 months (range 6-28). A total of 21

out of 26 eyes with nvAMD demonstrated a transient improvement in therapeutic responses after switching treatments, which was similar to the results of our study.

Our study differs from previous studies due to a substantially larger sample size in a real-world clinical setting. The largest of prior studies included 109 patients,<sup>13</sup> much smaller than our cohort. No other study has performed significant matching on patient eyes based on VA at six months prior to the switch and at the time of switch, as well as the number of ranibizumab injections at the time of switch, which provides significantly more detailed comparison between two groups. In addition, while past studies only included the patients who were treatment refractory to bevacizumab and/or ranibizumab, our study patients were switched to aflibercept as en-bloc, which addresses the question of how patients respond to aflibercept on chronic ranibizumab therapy regardless of their response.

There are several limitations to our study. We are unable to assess superiority between the two anti-VEGF drugs due to the lack of data from patients who switched from aflibercept to ranibizumab. Given that aflibercept was FDA-approved only five years ago, we have not enrolled a significant number of patients who were initiated on aflibercept and then switched to ranibizumab treatment. This lack of data prevents us from determining whether this improvement is truly due to tachyphylaxis, although the transient nature of the improvement followed by a decline in vision for patients in both groups is suggestive of tachyphylaxis.

Alternatively, the transient improvement may be due to the increase in frequency of injections that occur at the time of the switching. The cohort effect may have biased on the results of our study; an inherent difference between patients who were treated with ranibizumab in the early 2000's may exist compared to patients who were treated in more recent years.

Despite these limitations, our study demonstrates that switching patients from ranibizumab to aflibercept injections had a clinically not significant yet statistically significant transient

improvement in vision. Intravitreal anti-VEGFs will continue to be the primary treatment for nvAMD for North Americans and Europeans. Future research on nvAMD should continue to explore anti-VEGF drug efficacy and the possible consequence of tachyphylaxis in order to optimize the treatment for this presently incurable disease.

### **CONFLICTS OF INTEREST**

Dr. Tufail has served on Advisory Boards for the following companies: Allergan, Bayer, Genentech, GlaxoSmithKline, Novartis, Roche. All other authors have no financial disclosures.

R. Johnston is the Medical Director of Medisoft Limited, which developed the electronic medical record from which data were extracted.

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## **TABLES**

Table 1. Baseline Characteristics of Two Treatment Groups.

	<b>Continuous ranibizumab (n = 896)</b>	<b>Ranibizumab to aflibercept (n = 448)</b>	<b>p-value</b>
<b>Right eyes, n (%)</b>	453 (50.6)	235 (52.5)	0.525
<b>Age, mean (SD)</b>	79.3 (7.5)	78.8 (7.7)	0.259
<b>Visual acuity 6 months prior to switch, mean (SD)</b>	61.5 (14.7)	61.7 (14.9)	0.815
<b>Visual acuity at the time of switch, mean (SD)</b>	60.1 (14.0)	59.9 (14.3)	0.827
<b>Number of ranibizumab injections at the time of switching, mean (SD)</b>	20.0 (7.1)	21.0 (7.7)	0.020

SD, standard deviation.

Table 2. Multivariate Regression Analysis on Change in Visual Acuity.

Month	Change in visual acuity		
	Beta	95% CI	p-value
1	0.566	-0.125, 1.258	0.187
2	1.376	0.636, 2.116	<0.001
3	1.227	0.464, 1.991	0.002
4	0.147	-0.684, 0.978	0.729
5	0.885	0.033, 1.738	0.042
6	0.441	-0.507, 1.389	0.362

CI, confidence interval.

## **FIGURE LEGENDS**

**Fig. 1.** Patient treatment sequence. The flow chart illustrates the treatment sequence for patients in the switched and continuous ranibizumab groups. Both had a minimum of 1 year of intravitreal therapy, a minimum of 6 months of ranibizumab therapy, a minimum of 3 subsequent injections following the point of switch, and continued the post-switch therapy for the duration of the study period. nvAMD, Neovascular Age-related Macular degeneration.

**Fig. 2.** Change in visual acuity. The graph illustrates a comparison of visual acuity (relative Early Treatment Diabetic Retinopathy Study (ETDRS) letters) over time (months) between the switch group and the continuous ranibizumab group. Negative months indicate time before the switch. Error bars ( $\pm$  SD).

**Fig. 3.** Visual acuity differences. The graph illustrates the statistical significance of visual acuity differences between the switch group and the continuous ranibizumab group by month following the switch. The dotted line indicates significance at  $p = 0.05$ .

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