Intravitreal aflibercept in neovascular age-related macular degeneration previously treated with ranibizumab

Rachel Hui Fen Lim, Bhaskar Gupta, Peter Simcock

Royal Devon and Exeter NHS Foundation Trust, Barrack Road, Exeter, EX2 5DW, United Kingdom

Correspondence to: Bhaskar Gupta. Royal Devon and Exeter NHS Foundation Trust, Barrack Road, Exeter, EX2 5DW, United Kingdom. Bhaskar.gupta@nhs.net

Received: 2016-06-01 Accepted: 2016-11-08

Abstract

- **AIM:** To report the change in visual acuity and central macular thickness (CMT) following treatment with intravitreal aflibercept injections in patients with neovascular age-related macular degeneration (nAMD) with suboptimum response to ranibizumab.
- **METHODS:** This was a retrospective study. The inclusion criteria were patients with nAMD who responded poorly to ranibizumab. Patients then received either 3 consecutive aflibercept injections followed by pro re nata (PRN) treatment or PRN alone. Primary endpoints were mean change in best-corrected visual acuity (BCVA) and CMT at 12mo. Secondary endpoints were number of injections and adverse events.
- **RESULTS:** Forty-nine eyes from 49 patients met the inclusion criteria and completed 12-month follow up on aflibercept. Thirty-eight eyes received 3 consecutive aflibercept injections followed by PRN treatment and 11 eyes received PRN injections alone. At 12mo, mean BCVA improved by one letters (logMAR 0.56±0.31 to 0.54±0.34) and mean CMT decreased from 303.9±82.1 to 259.2±108.3 µm. Four percent of eyes gained 15 letters or more, 6% lost more than 15 letters and the remaining 90% had stable BCVA. The mean number of aflibercept injections was 6. There was one case of infectious endophthalmitis.
- **CONCLUSION:** Intravitreal aflibercept in patients with nAMD with a previous suboptimal response to ranibizumab resulted in an anatomical improvement in macular appearance at 12mo without a corresponding improvement in visual acuity.
- **KEYWORDS:** aflibercept; ranibizumab; neovascular age-related macular degeneration

DOI:10.18240/ijo.2017.03.15

INTRODUCTION

Neovascular age-related macular degeneration (nAMD) leads to a rapid, progressive loss of central vision and disease activity is often lifelong[1]. Anti-vascular endothelial growth factor (anti-VEGF) inhibitors are the current gold standard therapy for nAMD. They inhibit choroidal neovascularization (CNV) and vascular leakage[2]. Ranibizumab and aflibercept are the two anti-VEGF drugs approved and licensed for intraocular administration by the National Institute for Health and Care Excellence (NICE) and used in the United Kingdom[3-4]. Ranibizumab is a recombinant, humanized, monoclonal Fab antibody fragment that neutralizes all active forms of VEGF-A. Aflibercept is a soluble VEGF receptor fusion protein which binds to all forms of VEGF-A, VEGF-B, and placental growth factor. Aflibercept has a longer half-life and higher binding affinity in comparison to ranibizumab[5]. In the CATT trial (Comparison of AMD Treatment Trial), 51.5% of patients treated with ranibizumab showed evidence of persistent fluid on time-domain optical coherence tomography (OCT) despite monthly treatment with anti-VEGF agents for 2y[6]. Such persistent fluid may limit visual improvement in these patients. A limited number of studies have investigated the effects of aflibercept on patients with retinal leakage that is resistant to either bevacizumab or ranibizumab treatments[7-13]. Most of these studies have reported short-term outcome with little to no change in visual acuity at the end of study period. The purpose of this study is to report and assess the efficacy of aflibercept at 12mo in patients who had a suboptimal response to previous treatment with ranibizumab.

SUBJECTS AND METHODS

Ethical Approval of Studies This study adhered to the principles of the Declaration of Helsinki and was approved by the Hospital Clinical Research and Audit Review Board.

Methods This was a retrospective study from the Royal Devon and Exeter NHS Foundation Trust, UK. All statistical analyses were done using statistical analysis provided with Microsoft Excel version 10. A descriptive analysis was performed and included means along with standard deviation, paired t-test was used to compare the change in means. Distribution of data for normality was checked using Anderson-Darling test. Percentages were determined for presence of morphological characteristics. The significance of any difference in means was
evaluated by parametric $t$-tests, and statistical significance was defined as $P<0.05$.

**Inclusion Criteria** 1) CNV due to age related macular degeneration confirmed on fundus fluorescein angiogram (FFA) prior to initiation of anti-VEGF therapy. 2) Suboptimal response to ranibizumab: suboptimal response was defined as persistent fluid on OCT despite 6 monthly injections of ranibizumab at the initiation of therapy or the need for more than 5 injections in any 6-month period after a loading dose of 3 injections. 3) Patients with a minimum follow up of 12mo after the initiation of aflibercept. 4) In patients with bilateral disease, the eye with worse best-corrected visual acuity (BCVA) at start of aflibercept treatment was included.

**Exclusion Criteria** CNV due to any other ocular cause and eyes with permanent structural damage to the central fovea. Structural damage was defined as foveal involving fibrosis or retinal pigment epithelial tear involving fovea. Patients were followed-up every month and logMAR visual acuity (VA) was recorded. Central macular thickness (CMT) was measured using spectral domain optical coherence tomography (SD-OCT). The decision to treat was based on presence of active disease on OCT (i.e. presence of either subretinal/intraretinal fluid or both) or evidence of fresh retinal haemorrhage on slit lamp biomicroscopy. Presence of pigment epithelial detachment (PED) alone did not qualify for treatment.

Intravitreal injections were administered according to the Royal Devon and Exeter NHS Foundation Trust protocol by nurse practitioners. Injections were given using a 31-gauge needle with a dose 2 mg of aflibercept.

**Study Endpoints**

**Primary outcomes** 1) Mean change in BCVA at 12mo, and the percentage of patients who lost or gained more than 15 letters. 2) Mean change in CMT at 12mo.

**Secondary outcomes** 1) Number of aflibercept injections given by 12mo. 2) Any ocular and systemic adverse events.

**RESULTS**

**Patient Baseline Characteristics** Forty-nine patients (49 eyes) were included for analysis in the study. Mean age was 78.6±9.4y (range 52-93), and 21 patients (43%) were male. Mean duration between first diagnosis of nAMD to initiation of treatment with aflibercept was 35.58±17.70mo (range 6-67mo). Two patients had bilateral disease. The mean number of ranibizumab injections before switching to aflibercept was 16. Eighty-eight percent of patients (43 eyes) had ranibizumab monotherapy and 8% (4 eyes) received ranibizumab and bevacizumab prior to the study. Two eyes (4%) received sub-Tenon’s triamcinolone and photodynamic therapy prior to commencing ranibizumab. The study eyes were divided into 2 groups depending on treatment regimen: Group A ($n=38$): loading doses of 3 monthly intravitreal aflibercept followed by a pro re nata (PRN) injections; Group B ($n=11$): patient’s received PRN treatment.

**Visual Outcome** Mean baseline logMAR BCVA at the commencement of aflibercept injection was 0.56±0.31 (Table 1) which improved to 0.54±0.34 (0-1.06) at week 52 and was not statistically significant ($t$-test, $P=0.087$). Two eyes (4%) improved by more than 15 letters, three eyes (6%) lost more than 15 letters and the remaining 44 eyes (90%, ±15 letters) had stable vision. No significant difference was observed in visual behaviour between the 2 treatment arms (Figure 1).

**Anatomic Changes** The mean baseline CMT was 303.9±82.1 µm which decreased by 44.7 µm to 259.2±108.3 µm at 12mo (Table 1). The greatest reduction in CMT of 56.3 µm was observed at month 1 (from 304 to 248 µm). Thirty-six eyes (73%) had a stable CMT (±100 µm compared with baseline). Nine eyes (18%) showed an improvement in CMT (CMT decreased by >100 µm) and 4 eyes (8%) showed an increase of CMT of more than 100 µm. These changes were not statistically significant and there was no difference noted in the 2 treatment arms (Figures 1 and 2, $t$-test, $P=0.14$).

**Number of Injections Required** Patients received an average of 6 aflibercept injections over the course of 12mo (injection range 2-10).

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Baseline mean</th>
<th>Final mean at 12mo</th>
<th>Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Best corrected visual acuity</td>
<td>0.56±0.31 (0-1.18)</td>
<td>0.54±0.34 (0-1.06)</td>
<td>Improve by 0.02 (-0.32 to +0.7)</td>
</tr>
<tr>
<td>Central macular thickness (µm)</td>
<td>303.9±82.1 (153-672)</td>
<td>259.2±108.3 (116-862)</td>
<td>Improve by -44.7 (-292 to +190)</td>
</tr>
</tbody>
</table>

Figure 1 Change in mean visual acuity following treatment with intravitreal aflibercept.

<table>
<thead>
<tr>
<th>Month</th>
<th>LogMAR BCVA</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0.70</td>
</tr>
<tr>
<td>1</td>
<td>0.65</td>
</tr>
<tr>
<td>2</td>
<td>0.60</td>
</tr>
<tr>
<td>3</td>
<td>0.55</td>
</tr>
<tr>
<td>4</td>
<td>0.50</td>
</tr>
<tr>
<td>5</td>
<td>0.45</td>
</tr>
<tr>
<td>6</td>
<td>0.40</td>
</tr>
</tbody>
</table>

Table 1 Change in BCVA and change in CMT at month 0 and month 12 following treatment with aflibercept.
for visual gain. However Miki et al to the photoreceptors may have resulted in limited potential.
aflibercept, and one theory is that permanent structural damage
relatively prolonged periods of time prior to being switched to
showed no signs of disease activity after very few injections.
the group selected for treatment with aflibercept were by
death in monkey models.
ranibizumab, led to individual retinal pigment epithelium cell
on the contrary, reported that intravitreal aflibercept, and not
MARINA studies, which may have influenced their outcome
standard" of monthly injection as seen in pivotal Anchor and
subsequent PRN injection treatments rather than the "gold
improved to 0.94.
This study demonstrates an improvement in anatomical out-
with intravitreal aflibercept in patients who demonstrated a
sub-optimal response to intravitreal ranibizumab.
The improved anatomical outcome did not translate to a
significant improvement in VA in the patients in this study.
Patients prior to changing to aflibercept had been treated with
a course of 3 consecutive ranibizumab injections with
subsequent PRN injection treatments rather than the "gold
standard" of monthly injection as seen in pivotal Anchor and
MARINA studies, which may have influenced their outcome
with ranibizumab treatment\textsuperscript{[15-16]} A small proportion of patients
showed no signs of disease activity after very few injections. All
these patients had been treated with ranibizumab for
relatively prolonged periods of time prior to being switched to
aflibercept, and one theory is that permanent structural damage
to the photoreceptors may have resulted in limited potential
for visual gain. However Miki et al\textsuperscript{[17]} reported that prolonged
blockade of VEGF receptors for up to 12wk did not result in
damage to retinal photoreceptors. Julien et al\textsuperscript{[18]} in 2013,
on the contrary, reported that intravitreal aflibercept, and not
ranibizumab, led to individual retinal pigment epithelium cell
death in monkey models.
The group selected for treatment with aflibercept were by
definition “poor responders” to anti-VEGF treatment using
ranibizumab and therefore may be also less likely to respond to
other anti-VEGF agents including aflibercept.

Therefore, patients with nAMD refractory to treatment with
intravitreal ranibizumab respond anatomically to aflibercept.
This improvement is greatest at month 1 but some gain is
sustained at month 12. No statistically or clinically significant
change in VA was recorded.
Our results are similar to other studies in the literature from
outside the UK\textsuperscript{[19-23]} All studies demonstrated that patients
switched from ranibizumab to aflibercept had favourable
anatomical response but this did not translate into visual
benefits or decrease in injection frequency. A study by Chang
et al\textsuperscript{[20]} in 2014 did however show significant visual and
anatomical benefits at 6mo when aflibercept was injected every
8wk following a loading dose of 3 monthly injections. Kumar
et al\textsuperscript{[21]} in 2013 also showed a significant improvement in VA
of logMAR 0.1 in addition to anatomic improvements in their
retrospective analysis of 33 patients, however this was likewise
after only a 6-month follow up.
Limitations of this study include a small sample size, retro-
spective design, lack of a control arm, and aflibercept treatment
decision at the discretion of the individual retinal specialists.
Further research is necessary to determine the usefulness of
aflibercept injections in patients with nAMD and a previous
sub-optimal response to ranibizumab injections.

**ACKNOWLEDGEMENTS**

Conflicts of Interest: Lim RHF, None; Gupta B, None; Simecock P, None.

REFERENCES

1 Rofagha S, Bhistikul RB, Boyer DS, Sadaa SR, Zhang K; SEVEN-UP
Study Group. Seven-year outcomes in ranibizumab-treated patients in
ANCHOR, MARINA, and HORIZON: a multicenter cohort study (SEV-

2 Tadayoni R. Choroidal neovascularisation induces retinal edema and its

3 National Institute for Health and Care Excellence. Ranibizumab and
pegaptanib for the treatment of age-related macular degeneration, NICE
www.nice.org.uk/Guidance/ta155

4 National Institute for Health and Care Excellence. Aflibercept solution
for injection for treating wet age-related macular degeneration, NICE
www.nice.org.uk/Guidance/ta294

5 Stewart MW, Rosenfeld PJ, Penha FM, Wang F, Yehoshua Z, Bueno-Lope-
ez E, Lopez PF. Pharmacokinetic rationale for dosing every 2 weeks ver-
sus 4 weeks with intravitreal ranibizumab, bevacizumab, and aflibercept

6 Martin DF, Maguire MG, Fine SL, Ying GS, Jaffe GJ, Grunwald JE,
Toth C, Redford M, Ferris FL 3rd. Ranibizumab and bevacizumab for
treatment of neovascular age-related macular degeneration: two-year re-

7 Cho H, Shah CP, Weber M, Heier JS. Aflibercept for exudative AMD
with persistent fluid on ranibizumab and/or bevacizumab. Br J Ophthal-
Aflibercept in nAMD refractory to ranibizumab


10 Wykoff CC, Brown DM, Maldonado ME, Croft DE. Aflibercept treatment for patients with exudative age-related macular degeneration who were incomplete responders to multiple ranibizumab injections (TURF trial). *Br J Ophthalmol* 2014;98(7):951-955.


