·Clinical Research·

# 6-weekly bevacizumab versus 4-weekly ranibizumab for neovascular age-related macular degeneration: a 2-year outcome

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## Abstract

**• AIM: To compare visual acuity and central macular thickness (CMT) changes in neovascular age-related macular degeneration patients treated with either 6 weekly bevacizumab regimen or 4 weekly ranibizumab on an as required basis.**

**• METHODS: Patients made an informed choice between bevacizumab 1.25 mg or ranibizumab 0.5 mg. The selected treatment was administered in the first 3 visits. Bevacizumab patients were followed-up 6 weekly and ranibizumab 4 weekly. Retreatment criteria was based on the reduction of >5 letters in the best-corrected visual acuity (BCVA), the presence of retinal fluid on optical coherence tomography (OCT) or new retinal haemorrhage.**

**• RESULTS: Visual acuity at 2y bevacizumab patients gained 7.0 letters and ranibizumab 9.2 ($P$=0.31, 95% CI -6.4 to 2.0). At 2y 86% of bevacizumab and 94% ranibizumab patients had not lost 15 letters or more ($P$=0.13). Mean CMT decreased at 2y bevacizumab by 146 μm, ranibizumab 160 μm($P$=0.72). Mean number of injections was at 2y bevacizumzb 11.9, ranibizumab 10.3 ($P$=0.023).**

**• CONCLUSION: Bevacizumab 6 weekly on an as required basis was not demonstrably non-inferior to ranibizumab 4 weekly pro re nata (prn) in terms of BCVA and change in CMT. In the bevacizumab group, one more injection was required in the second year compared to the ranibizumab group.**

**• KEYWORDS:** bevacizumab; ranibizumab; neovascular age-related macular degeneration; treatment on as required basis

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## INTRODUCTION

Anti-vascular endothelial growth factor (VEGF) such as ranibizumab, aflibercept or the off label bevacizumab has become the mainstay of treatment for neovascular age-related macular degeneration (nARMD). The use of both intravitreal ranibizumab and bevacizumab has been studied extensively. In the CATT *et al*[1] and Chakravarthy *et al*[2] studies, both showed similar efficacy when given on a 4 weekly regimen or on as required basis. There were studies looking at either ranibizumab or bevacizumab starting with loading dose regime followed by 4-weekly as required retreatment with encouraging results[3-4].

As a larger molecule, bevacizumab has been shown to penetrate the primate retina poorly and therefore has a longer half-life in the eye [5]. The latter measured by aqueous sampling in non-vitrectomised human eyes was 9.8d [6]. The same group reported ranibizumab half-life of 7.2d using the exact technique [7]. These measurements were not taken from the posterior segment, however numerous animal models have shown that aqueous and vitreous samples to have very similar values[8-10].

Studies have showed bevacizumab effect can last up to 6 to 8wk [11-13] but not 12wk [14]. Tufail *et al*[15] had evaluated the efficacy of bevacizumab with 3 loading doses followed by further treatment if indicated on a 6 weekly interval and showed a mean gain of 7.0 letters at one year. In our institution, we employed bevacizumab in a similar fashion for a few years prior to changing it to 4-weekly after the publication of CATT *et al*[1] and Chakravarthy *et al*[2].

There has been no publication to date to compare the visual and central macular thickness change between 6-weekly bevacizumab and 4-weekly ranibizumab treatment on an as required basis for nARMD. Our aim is to report the first 2y outcome. We also looked at the number of injections required over this period.

## SUBJECTS AND METHODS

**Study Design and Patients** This is a retrospective study of patients who were treated with bevacizumab or ranibizumab

**Table 1 Demographics of patients**

| Characteristics | Bevacizumab ($n$=102) | Ranibizumab ($n$=101) | $P$ |
|---|---|---|---|
| Median age | 81 | 80 | 0.13[a] |
| <65 | 9 | 6 | |
| 65- <75 | 17 | 21 | |
| 75- <85 | 43 | 55 | |
| 85- <99 | 33 | 19 | |
| Gender (F: M) | 74:28 | 72:29 | 0.68[b] |
| Visual acuity (letters) and Snellen equivalent | | | 0.23[b] |
| 68-82 letters, 20/25-40 | 21 | 26 | |
| 53-67 letters, 20/50-80 | 38 | 27 | |
| 38-52 letters, 20/100-160 | 20 | 16 | |
| 23-37 letters, 20/200-320 | 23 | 32 | |
| Mean baseline visual acuity (letters) | 40.6 | 38.6 | 0.36[a] |
| Central macular thickness (μm) | 405 | 424 | 0.89[a] |

[a] Wilcoxon rank sum test; [b] Fisher's exact test.

on an as required basis at Leighton Hospital, UK. A sample of 100 eyes in each arm was required to provide a study power of 80% to detect non-inferiority limit of 5 letters (significance 2.5% , one-tailed) based on estimates from previous studies [15-17]. Consecutive treated patients clinical notes were reviewed.

Only one eye per patient was included in the study. The inclusion criteria were age 50y or older, defined subfoveal classical or occult nARMD by fluorescein angiography (FA), best corrected visual acuity (BCVA) of at least 25 letters on the 2 m Early Treatment Diabetic Retinopathy Study (ETDRS) chart (Snellen 20/320), absence of other sight threatening ocular comorbidities and good compliance with follow-up appointments.

**Treatment Regime** Each patient was given an informed choice in the first visit to choose between either bevacizumab or ranibizumab by the consultant (Kotamarthi V). The selected treatment was administered in the first 3 visits. The intravitreal dose for bevacizumab was 1.25 mg and ranibizumab 0.5 mg-both given in 0.05 mL solution. Patients on bevacizumab were follow-up strictly on a 6 weekly interval and ranibizumab 4 weekly. At each visit, the BCVA with ETDRS chart, a slit-lamp examination and macular optical coherence tomography (OCT) were performed. The FA was performed in the first visit and at the discretion of the ophthalmologists in sequent follow-ups if deemed necessary to aid retreatment. The criteria for retreatment were based on the reduction of more than 5 letters in the BCVA, the presence retinal fluid on OCT scans or new retinal haemorrhage and was uniformly followed by everyone.

**Outcome Measure** The primary outcome measure was the mean change in BCVA at 1 and 2-year from baseline. The secondary outcomes were the mean change in central macular thickness (CMT) on the OCT, the proportion of eyes gaining at least 15 letters, change of ±15 letters or losing 15 letters and number of injections required.

**Statistical Analysis** The demographic characteristics between the bevacizumab and ranicizumab patients were compared. The normality of continuous variables were analyzed using Shapiro-Wilk test. The Wilcoxon rank sum and Student's $t$-tests were performed on non-parametric and parametric data respectively. Categorical data were analyzed using Fisher's exact test. Significance was set at a $P$ value of less than 0.025 (one-tail).

The tenets of the Declaration of Helsinki were adhered to. Ethical committee board approval was not required for this clinical audit (reference number 1065).

## RESULTS

**Patients and Treatment** Consecutive patient notes were examined for those who had bevacizumab and ranibizumab since these treatments were made available in Leighton Hospital, UK. Those who met the study criteria were included. This was performed until the required number of at least 100 in each arm was achieved. All patients had treatment with either bevacizumab or ranibizumab from August 2008 to October 2010. The final follow-up was at least 2y. Figure 1 shows the flow chart detailing the patient selection process. The demographic data and pre-treatment parameters between the two groups were represented in Table 1.

**Visual Acuity** The visual acuity change distributions for bevacizumab and ranibizumab were normal (Shapiro-Wilk, $P$ >0.5). Both treatment groups had improvement in mean visual acuity at 1 and 2y from baseline. The number of letters gained with bevacizumab was 7.6 and ranibizumab 10.7 at 1y (Student's $t$-test, $P$ =0.10). The difference was 3.1 letters and the 95% confidence interval (CI) was -6.8 to 0.6 (Figure 2). As the CI straddles both the set margin of 5 letters and zero, non-inferiority was not demonstrated and the result was inconclusive.

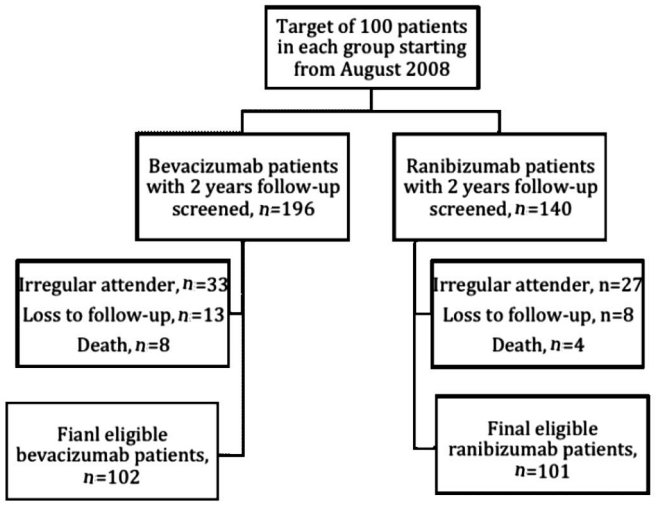


**Figure 1 Flow chart for patient selection.**

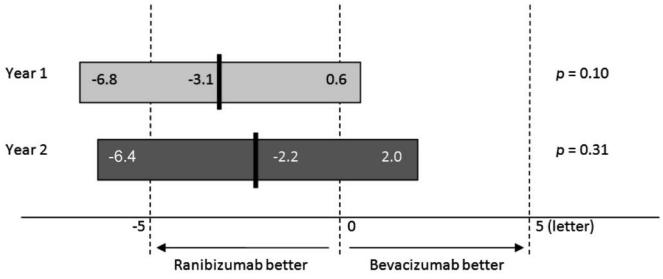


**Figure 2 Difference in letters gained between treatment group at 1 and 2y.**

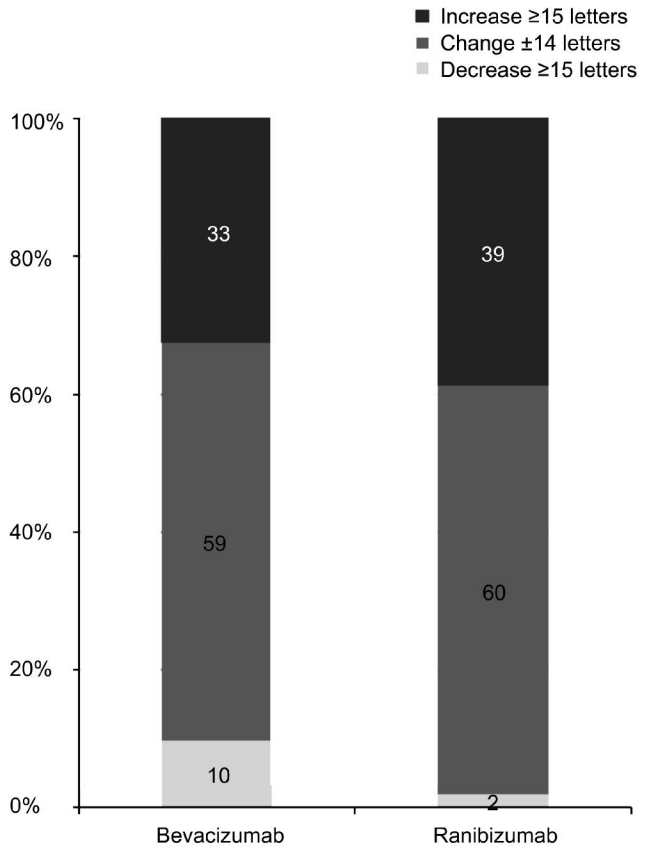


**Figure 3 Distribution of patient according to visual acuity change at 1y.**

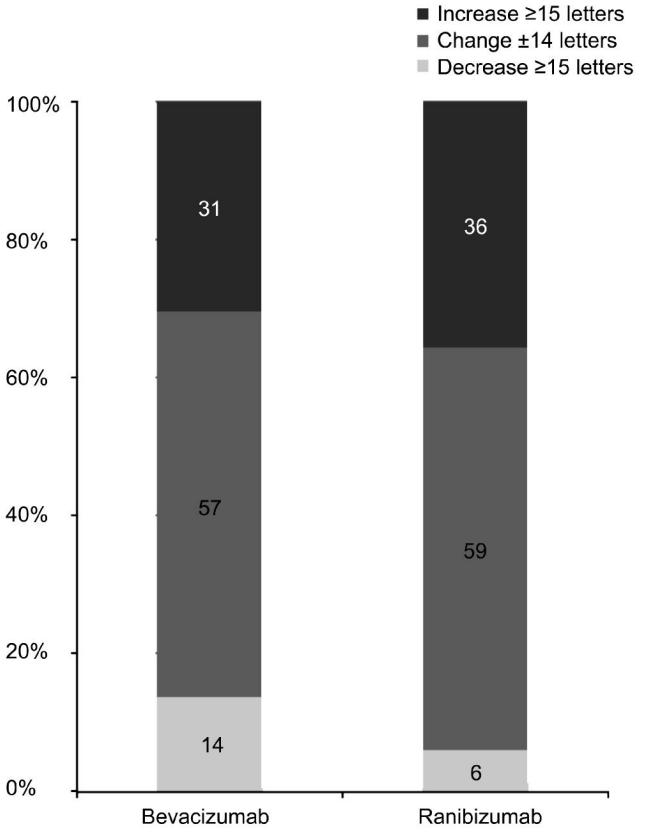


**Figure 4 Distribution of patient according to visual acuity change at 2y.**

At 2y, the improvements were 7.0 letters for bevacizumab and 9.2 for ranibizumab (Student's $t$-test, $P$=0.31). The 95% CI was -6.4 to 2.0 which once again straddles the 5 letter margin and zero mark rendering the result inconclusive.

At the 1y point, the number of patients who did not lose at least 15 letters in the bevacizumab group was 92 (90%) and the ranibizumab group 99 (98%) (Fisher's exact test, $P$= 0.054) (Figure 3). After 2y, these figures were 88 (86%) in the bevacizumab group and 95 (94%) in the ranibizumab group (Fisher's exact test, $P$=0.13) (Figure 4).

**Number of Injection** Despite patients on bevacizumab had longer interval appointments, the mean number of injections required at 1y was 6.6, which was more than ranibizumab at 5.9 (Wilcoxon rank sum test, $P$<0.001). At 2y, there were 11.9 for bevacizumab and 10.3 ranibizumab (Wilcoxon rank sum test, $P$=0.023).

**Central Macula Thickness** Both treatment groups had reduction of CMT compared to baseline at the measured time points. At 1y, the improvements were 139 μm for bevacizumab and 150 μm for ranibizumab (Wilcoxon rank sum test, $P$=0.85). At the end of the second year, these were 146 μm and 160 μm respectively (Wilcoxon rank sum test, $P$=0.72).

## DISCUSSION

Our study was the first one to compare a loading dose regimen followed by a 6 weekly bevacizumab with the conventional 4 weekly ranibizumab. The visual gain of intravitreal bevacizumab and ranibizumab treatment at 12-

and 24-month were inconclusive in our study. Changes in CMT showed no difference between the two treatment. At 2y, one more injection was required in the bevacizumab group compared with the ranibizumab group. Significant improvement in visual acuity and CMT were noted in both the ranibizumab and bevacizumab groups, and these improvements were maintained over the whole study period.

Our results showed that of the 102 patients receiving bevacizumab, 33% patients gained 15 or more letters from the baseline visual acuity, mean visual acuity increased by 7.6 letters with a median of 6.6 injections in the first year. These results are comparable to that in the ABC trial[15] where of the 65 patients in the bevacizumab group, 32% gained 15 or more letters, mean visual acuity increased by 7.0 letters with a median of 7 injections.

In the ranibizumab group, our mean visual acuity gained was 9.2 letters, central foveal thickness was reduced by 160 μm, 36% gained more than 15 letters with 10.3 injections over 24mo. PrONTO study [3] showed a slightly better outcome where their mean gain of letters was 11.1, had 212 μm reduction of CMT, 43% gained more than 15 letters with 9.9 injections over same period of time. This could be due to a higher baseline acuity in PrONTO compared to ours.

In our study, we adopted the treatment regimen employed in PrONTO[3] for the ranibizumab group and ABC trial[15] for the bevacizumab group where patients received three loading dose followed by pro re nats (prn) 4 or 6 weekly treatment. The use of loading dose has shown better outcome than no loading dose [18-19]. The rationale that bevacizumab resides longer in the vitreous cavity since it is a larger molecule than ranibizumab; and phase I study on bevacizumab has demonstrated that a single injection could achieve a therapeutic effect lasting six up to 8wk [11-12] but not sustained if given longer than 12wk [14]. This approach would make the use of bevacizumab less resource intensive and reduce burden of frequent follow up visits.

Following the recent approval of aflibercept from the National Institute for Health and Care Excellence (NICE) in the United Kingdom, we have funding provided for the use of both aflibercept and ranibizumab as the treatment of choice for neovascular AMD and hence, the use of bevacizumab has been reduced significantly in our institution. Nonetheless, bevacizumab has a place in a healthcare system that have a limited resources especially it has been shown to be non-inferior to ranibizumab [1-2]. The 6 weekly regimen for bevacizumab can be considered for those patients who cannot attend 4 weekly appointments or afford other licenced alternatives.

There have been different treatment protocols developed as individualised therapy. Treat-and-extend protocol has become increasingly popular with the goal of keeping the macular dry by controlling the treatment interval which can be gradually extended to a maximum interval of 12wk. In the LUCAS trial [20] ($n$=432), the improvement in visual acuity were 8.2 and 8.0, and the mean number of injection was 8.0 and 8.8 for both ranibizumab and bevacizumab respectively at year 1. It is interesting to note that these results are comparable to that of ours in visual acuity gain in both treatment groups but at the expenses of 2 more injections needed compared to our study. Nonetheless, it showed equivalent effects on visual acuity gain in both ranibizumab and bevacizumab.

Our study did not look at the rate of adverse effects, as it was not powered to examine the safety profile for the two drugs. There was however no documented ocular or systemic adverse effect over the use of either agents.

This study had a few limitations. It was a retrospective and non-randomised trial. A prospective study, with an additional arm of bevacizumab at 4 weekly may provide more useful information into whether 6 weekly regimen is non-inferior to the current recommended treatment. However, we do not have adequate number of patients for this.

In conclusion, we could not demonstrate that bevacizumab 6-weekly prn was non-inferior to ranibizumab 4-weekly prn in terms of BCVA gained. Despite the 6-weekly interval, bevacizumab required one more injection compared to ranibizumab at the end of year 2.

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Chiam PJ conceived the study idea; Hickley NM, Chiam PJ analyzed and collected the data; Ho VW, Chiam PJ wrote the manuscript; Kotamarthi V provided critical review.

**Conflicts of Interest: Chiam PJ,** None; **Ho VW,** None; **Hickley NM,** None; **Kotamarthi V,** None.

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