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Ranibizumab treatment for neovascular age-related macular degeneration: from randomized trials to clinical practice

K Michalova, SS Wickremasinghe, TH Tan, A Chang, CA Harper, JA Downie, AP Hunyor and RH Guymer

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Learning objectives

Upon completion of this activity, participants will be able to:

1. Describe the efficacy of ranibizumab in patients with age-related macular degeneration (AMD) in the ANCHOR and MARINA trials
2. Describe the standard used for visual acuity assessment in this study
3. Describe the improvement in visual acuity seen over 12 months with ranibizumab in patients with AMD
4. Identify the dosing frequency of ranibizumab used for AMD to achieve efficacy in this study

Authors/Editors disclosure information

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CLINICAL STUDY

Ranibizumab treatment for neovascular age-related macular degeneration: from randomized trials to clinical practice

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Abstract

Background **Although randomized clinical trials (ANCHOR and MARINA) have shown excellent results of ranibizumab treatment in patients with neovascular age-related macular degeneration (AMD), it is unclear whether such an outcome is achievable in daily practice. We evaluated the results of ranibizumab treatment for neovascular AMD in clinical practice in Australia.**

Methods **A retrospective chart review of patients in four practices injected with ranibizumab in 2006 for AMD. Patients who had been diagnosed with subfoveal choroidal neovascular membrane in the preceding 6 months and had completed at least 6 months follow-up were enrolled. No standard treatment protocols were required. The main outcome measure was visual acuity (VA) at 6 and 12 months.**

Results **A total of 158 patients fulfilled the entry criteria. The mean baseline VA (decimal) was 0.35 ± 0.21 (Snellen equivalent 6/17). At 6 months, the mean VA improved to 0.46 ± 0.27 (6/13) and remained stable until month 12 (0.48 ± 0.30). The improvement in VA between baseline and months 6 and 12 was statistically significant ($P < 0.0001$). Both the mean and the median number of injections were four in the first 6 months and nine at 12 months. VA results were comparable with those of the ANCHOR and MARINA trials, and were achieved with a lower number of injections ($P < 0.0001$).**

Conclusion **VA results achieved in daily clinical practice using ranibizumab for neovascular AMD are similar to large prospective randomized trials.**

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Keywords: age-related macular degeneration; choroidal neovascular membrane; ranibizumab

Introduction

Randomized controlled trials (RCTs) offer the highest evidence in medicine. However, rigid treatment and follow-up protocols are usually mandated, and strict inclusion and exclusion criteria are necessary to assure homogeneity of population. Although this gives validity to the results of the trials, the use of the drug in the community is likely to differ, and therefore the results of trials may not be replicated in everyday life.

Recently, randomized, double-blind, placebo-controlled studies showed the treatment benefit of ranibizumab for neovascular age-related macular degeneration (AMD).[1–3] AMD is the leading cause of severe visual loss in the developed world,[4,5] and its neovascular complications are responsible for the majority of this visual loss.[6] Ranibizumab (Lucentis, Novartis, Novartis, Basel, Switzerland) is a recombinant, humanized monoclonal antibody fragment designed for intraocular use that binds to and inhibits the biological activity of all isoforms of vascular endothelial growth factor A.[7] The ANCHOR and MARINA trials proved the superiority of ranibizumab (0.3 and 0.5 mg, injected intra-vitreally each month for 12 months) over photodynamic therapy or placebo treatment.[1,2] The results of both of these trials were impressive beyond expectation, with 25–40% of patients gaining

significant improvements in vision (≥15 letters on ETDRS chart) at 12 months, and over 90% of treated patients maintaining stable vision (losing less than 15 letters on ETDRS chart) over this time period.[1,2]

In these trials, entry criteria meant that patients who had visual acuity (VA) outside 20/40–20/320 (6/12–6/96) range, whose lesions had significant fibrosis or blood (>50%), and patients with certain previous surgeries or treatments were excluded.[1,2] Since the trials were published, there has been a desire amongst treating clinicians to be more inclusive in the types of neovascular lesions treated. In addition, the large number of people with AMD who could now be offered treatment led to a practical need to try and reduce the frequency of injections and the follow-up regimen. The concept of treating based on clinical indications rather than rigid monthly timing was appealing, and offered the possibility of less frequent treatment and follow-up. Given these considerations, it cannot be presumed that the same efficacy of ranibizumab would be achieved when it was used in the wider community.

To determine the efficacy of ranibizumab treatment in the community, in a non-selected population of patients with neovascular AMD, we have assessed the results over 6–12 months of treatment on patients within four high-volume retina practices in Australia.

Methods

Four retinal practices in metropolitan Australia (Sydney and Melbourne) took part in this project. No results of treatment in these practices were known before the start of the review and no standard treatment protocols were required. Retrospective review of patients' charts was undertaken after approval by the Ethics committee of the Royal Victorian Eye and Ear Hospital, Melbourne. Only charts of patients who signed an informed consent for this retrospective study and received their first injection of ranibizumab in 2006 were reviewed. Patients were included in the study if they were diagnosed with active, symptomatic new or recurrent choroidal neovascular membrane (CNV) secondary to AMD within 6 months preceding the first injection. This time period was chosen in an attempt to exclude patients with long-standing chronic CNV who were awaiting the arrival of ranibizumab. Previous treatments were permitted. Patients were required to have at least 6 months follow-up to be included, and data were collected up to 1 year after commencement.

Baseline characteristics were the data collected on the day of first injection or within the previous 7 days. Information recorded for the baseline visit included age, sex, relevant medical and ocular history, date of AMD and CNV diagnosis, and previous AMD treatment. The following information was extracted from the notes at every visit up to 1 year from first injection: VA, fundus biomicroscopic findings, and OCT findings. Fluorescein angiography photographs were reviewed, with the type and size of CNV assessed. For each visit, it was recorded whether or not an injection was administered. All patients received 0.3 mg per 0.05 ml of ranibizumab at the start of their treatment, as this dose was universally used in Australia until 1 April 2007. After this date, only the 0.5 mg/0.05 ml was dispensed in Australia. As all patients had their first treatment in 2006, at least the first injections were of the lower concentration of the drug.

Statistical analysis

Visual acuity scores for treated eyes were converted from Snellen measurements to fractions. If the VA was worse than 0.05 (Snellen 60/120) then the following standard was used for statistical evaluation: counting fingers was equal to 0.005, hand movement was 0.002, and light perception was 0.001.[8] For comparison with MARINA and ANCHOR studies, visual acuities were converted to logMAR and ETDRS letters. One month was defined as an interval of 30 ± 7 days. Monthly VA scores were determined as the last measure within each 30-day period from the first VA measurement. Last observation carried forward method was applied to replace missing values to the last measurement. Worsening of VA was defined as a drop in VA ≥50% of the previous decimal VA (doubling of visual angle or 3 lines worsening on a logMAR chart), an improvement as a doubling of decimal value of VA (halving of visual angle, or a gain of 3 lines or more on a logMAR chart), and VA was considered stable if a change in VA was between 50 and 200% of original decimal VA (±3 lines on a logMAR chart). Treatment periods for ranibizumab were calculated as the time between successive injections.

Comparisons of the current study with the results of the MARINA and ANCHOR studies were made using 95% confidence intervals. Generalized linear mixed model analysis was employed to determine the effect of baseline VA, time, and individual participant variability on changes to VA. This method of analysis was used as it allows all existing data to be used. All statistical programming was performed using SAS version 9.1 (SAS Institute Inc, Cary, NC, USA).

Results

A total of 158 patients (165 eyes) met the study criteria and were entered into the analysis. The baseline characteristics of the cohort are shown in Table 1.

Follow-up data were available for 9 months for 150 patients, and 1-year data were recorded for 78 patients.

Table 1 Baseline characteristics of the cohort

Number of patients	158
Male	42 (26.6%)
Female	116 (73.4%)
Age (years)	
Mean ± SD	80 ± 7.3
Range	59–95
Previous systemic history	
Hypertension	73 (46%)
Stroke	10 (6%)
Myocardial infarction	8 (5%)
Cancer	13 (8%)
Eyes treated	165
Right	76 (48%)
Left	75 (48%)
Both	7 (4%)
Ocular history	
Cataract surgery	69 (42%)
Visually significant cataract	4 (2.4%)
Glaucoma	11 (7%)
Previous CME	1 (0.6%)
Macular hole surgery	1 (0.6%)
Previous treatment for CNV	
PDT	17 (10%)
Laser photocoagulation for extrafoveal/ juxtafoveal CNV	8 (5%)
Bevacizumab	5 (3%)
Pneumatic displacement of macular haemorrhage	1 (0.6%)
Baseline fluorescein angiogram available	154 eyes (93%)
Predominantly classic CNV	35 (23%)
Minimally classic	27 (17%)
Occult	92 (60%)

CME: cystoid macular oedema, CNV: choroidal neovascular membrane, PDT: photodynamic therapy.

The mean follow-up time was 368 ± 83 days (range 172–574 days, median 370 days).

Systemic medical and ocular history was gathered only from the notes and, therefore, it is not possible to be assured that all details of the history were captured. The total of 138 (84%) eyes had no previous treatment for CNV, whereas 17 (10%) eyes had earlier treatment, most commonly with photodynamic therapy (PDT) (Table 1). Concomitant treatment with PDT was used in 11 (7%) patients.

All eyes

When considering the whole cohort, the decimal baseline VA (mean ± SD) was 0.35 ± 0.21 (Snellen equivalent 6/17), with the range of 0.005–1.0 (Snellen equivalent count fingers (CF)—6/6). At 6 months, the mean VA improved to 0.46 ± 0.27 (6/13), range 0.005–1.0 (Snellen CF—6/6) and this remained stable at the month 12 review when the VA was 0.48 ± 0.30 (6/13), range 0.08–1.0 (Snellen 6/75–6/6), for those eyes wherein follow-up data was available (Figure 1). The difference in VA between baseline and either months 6 or 12 was statistically significant ($P<0.0001$). VA was stable in 67% of eyes at 6 months and in 68% at month 12. Improvement in VA compared with baseline was noted in 27% of eyes at 6 months and in 23% of patients at 12 months. Worsening of VA occurred in 6% of eyes by month 6 and in 7% by month 12. At baseline, 20 eyes (12%) had VA worse or equal to 0.1 (6/60 Snellen equivalent) and this decreased to 13 (8%) at 6 months and to 4 (5%) at month 12. VA better or equal to 0.5 (6/12) was found in 30% of eyes at baseline and this increased to 46% at month 12.

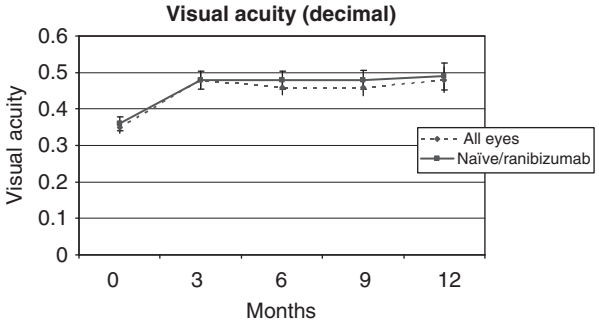

Figure 1 Decimal acuity (mean, error bars show standard error of mean) of all eyes and of eyes with no previous treatment treated only with ranibizumab.

Naïve eyes treated only with ranibizumab

A total of 128 eyes (78% of entire cohort) had no previous treatment for AMD and received ranibizumab as the only treatment. For this group, the baseline VA was 0.36 ± 0.21 (mean ± SD, Snellen equivalent 6/17), range 0.005–1.0 (CF—6/6). At 6 months, the VA improved to 0.48 ± 0.28 (6/13), range 0.005–1.0 (CF—6/6) and at 12 months, it was 0.49 ± 0.27 (6/12), range 0.08–1.0 (6/75–6/6) for the 58 eyes completing 12-month follow-up. The difference between baseline VA and 6- and 12-month results was statistically significant ($P=0.0003$ and $P=0.0020$, respectively) (Figure 1). Stable VA (that is, ± 3 lines on logMAR chart) was observed in 66% of eyes at 6 months and in 67% at month 12. Improvement in VA was found in 27% of eyes by month 6 and in 26% by month 12. Worsening VA compared with baseline occurred in 6% of eyes by month 6 and in 7% by month 12 (Figure 2). The visual outcome of this subgroup was not statistically different to the visual outcome of all other eyes ($P=0.37$).

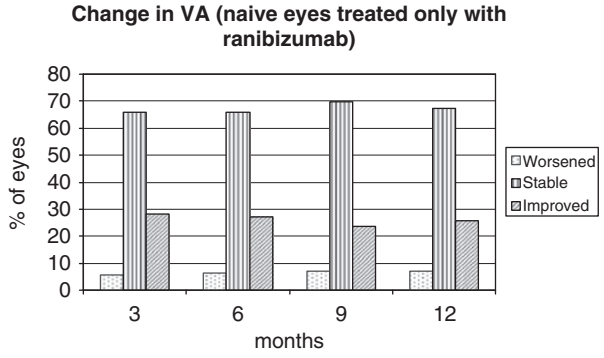

Figure 2 Visual acuity change (compared with baseline) in all previously untreated eyes receiving only ranibizumab. Worsening was defined as halving of the decimal value (doubling of visual angle, loss of more than 3 lines on logMAR chart), improvement as doubling of decimal value (halving of visual angle, gain of at least 3 lines on logMAR chart). All other eyes were considered stable.

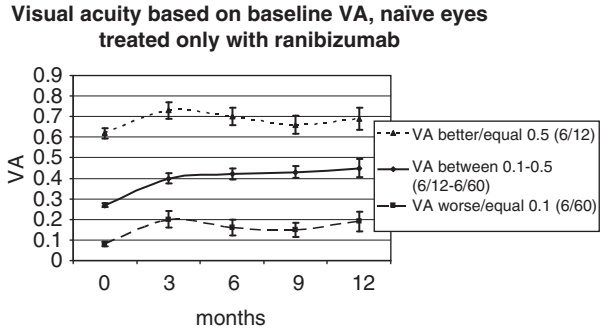

Figure 3 Decimal visual acuity (VA) change, categorized by baseline visual acuity. Error bars indicate standard error of mean.

Within this group of naïve patients treated only with ranibizumab, the group that most closely resembled the participants recruited into the randomized clinical trials was the subgroup ($n = 74$) whose baseline VA was between 6/12 and 6/60. This subgroup experienced the greatest improvement in VA, from its baseline VA of (mean ± SD) 0.27 ± 0.08 (Snellen equivalent 6/22) to 6 months mean VA of 0.42 ± 0.23 (6/14), and 12 months mean VA of 0.45 ± 0.29 (6/13). The difference between baseline and months 6 and 12 was significant ($P < 0.0001$) (Figure 3).

Number of injections

The mean number of injections in the first 6 months was 3.9 ± 1.3 per patient. In those patients who finished the 12-month follow-up, the number of injections given was 9.2 ± 2.7 (including the month 12 injection).

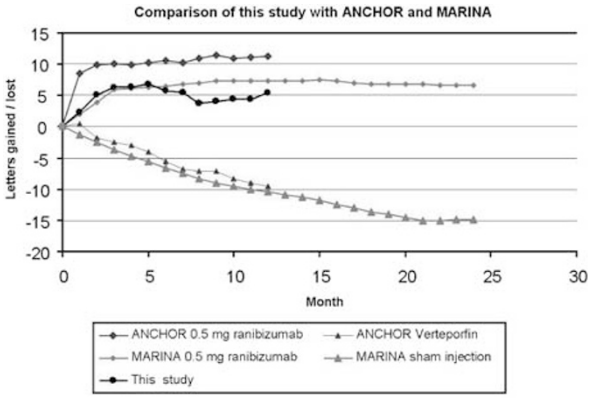

Figure 4 Comparison of this study with results from ANCHOR and MARINA studies.

Comparison with ANCHOR and MARINA

As our cohort received 0.3 mg early in their treatment and then subsequently 0.5 mg dose, we compared it with the ANCHOR and MARINA 0.5 mg ranibizumab groups.[1,2] Using the confidence intervals method, the age of our cohort (80 ± 7.3 years) was significantly greater than that in ANCHOR (76.0 ± 8.6 years) and MARINA (77 ± 8 years) ($P < 0.05$). At baseline, mean VA of our cohort was significantly better (logMAR letters = 57.6 ± 15.5) than MARINA (logMAR letters = 53.4 ± 12.8), and both studies had VA better than ANCHOR (logMAR letters = 47 ± 13.1). At 3, 6, and 12 months, improvement in VA for our entire cohort was very similar to that achieved in both of these studies, with 6-month results showing a 5.79 ± 14.1 letter improvement in our cohort compared with 9.2 ± 13.6 in ANCHOR and with 6.0 ± 12.3 in MARINA (confidence intervals method, each comparison at alpha = 0.05, no significant difference); and similarly at 12 months, a 5.47 ± 13.75 letter improvement in our cohort compared with 9.9 ± 14.6 in ANCHOR and with 6.9 ± 13.6 in MARINA (confidence intervals method, each comparison at alpha = 0.05, no significant difference) (Figure 4) was seen. There were, however, a significantly lower number of injections given in our cohort over the 12-month period, with an average of 0.86 (SD = 0.16) injections per month compared with the value of 1 (the planned mean number of injections per month for ANCHOR and MARINA) ($P < 0.0001$, one-sample *t*-test).

Adverse ocular and thromboembolic events

The patients' notes revealed one case of mild anterior uveitis lasting 1 week and one patient developed a corneal epithelial defect that healed within days. One patient was noted to have a branch retinal vein occlusion

in the fellow eye. Two patients were diagnosed with acute myocardial infarction while on treatment; one of these patients also had a cerebral vascular accident (CVA). Two more patients had CVAs and one patient had a transient ischaemic attack. One patient underwent percutaneous transluminal coronary angioplasty and arterial leg-bypass in the same month. One additional patient was diagnosed with coronary artery disease.

Discussion

Ranibizumab was shown to be an effective treatment for neovascular AMD in phase III, randomized, prospective, double-blind trials, using a monthly dosing regimen of the drug.[1,2] In these studies, the mean VA improved in the ranibizumab treatment arms rapidly and was sustained throughout the first year. Our study shows that similar gains in VA can be achieved in everyday clinical practice. This improvement was seen when all patients treated for subfoveal CNV secondary to AMD were included in the analysis, some of whom would not have been eligible for inclusion in the original trials. These results were achieved with a smaller number of injections administered over 12 months compared with the original (ANCHOR and MARINA) studies. When a RCT was designed to try and reduce the number of injections, in the PIER study,[3] in which patients received three injections over the first 2 months and then quarterly on a strict regimen, the visual results of the ANCHOR and MARINA study[1,2] were not achieved. The average number of injections over 12 months in our cohort (9) fell between that of PIER (scheduled 6 injections) and ANCHOR and MARINA (scheduled 12 injections), yet the improvement of mean VA was similar to that for ANCHOR and MARINA. The decision to re-inject in our cohort was not based upon a defined protocol, but was left to the individual clinician's judgment.

Good visual results with lower number of injections were achieved previously in a formal study by Fung *et al*.[9] The study (PrONTO), was a small, open-label, prospective study, in which a loading dose of three injections was used and the decision to re-treat was based on clinical and OCT findings, and achieved similar visual results as RCTs with lower number of injections (average of 5.6 injections over 12 months). However, as all RCTs did, the PrONTO study excluded patients with VA outside of 20/40 and 20/400 range as well as patients with some previous CNV treatments or earlier vitrectomy.[9]

Although our results are not statistically significantly different from the ANCHOR and MARINA results, there is a reduced number of letters gained in our cohort. However it must be remembered that our cohort was older than that participating in the ANCHOR and MARINA, and age was associated with a poorer outcome in the subgroup analysis of these trials.[10,11] In addition, the baseline VA in our cohort was better, which could produce a ceiling effect, as was seen in the ANCHOR and MARINA subgroup analysis.[10,11] Finally, our cohort started with 0.3 mg dose before the dose was increased to 0.5 mg, yet we compared our cohort with the 0.5 mg ANCHOR and MARINA groups. This could contribute to a worse result in our study, but if this were the case, we might expect better results to be achieved from now on, as the 0.5 mg dose is uniformly used.

Of interest is the decline in the acuity results at 8 months. This '8-month dip' has also been noted by others (personal communication–discussion at RANZCO Scientific Congress Melbourne, Australia, 24 November 2008). We speculate that if this is happening more commonly, it perhaps relates to either patient or doctor fatigue in keeping up with regular reviews and injections. Further study into the results of community treatment of neovascular AMD is necessary to elucidate this, as this decrease was not observed in ANCHOR and MARINA studies,[1,2] in which mandatory monthly treatment was required.

With respect to the safety of treatment, it is not possible to know whether all adverse events were detected and recorded. However, those recorded were at a level expected for patients with AMD in this age group.[12]

The study has obvious limitations. It is a retrospective study, evaluating only patients who have returned for follow-up. Thus, it is possible that patients who did poorly did not return. However, the study's strength lies in the fact that it reflects what happens in the community, in the non-standardized patient population treated by different doctors using their best judgment rather than following a strict protocol. The results are similar to those achieved in rigorous clinical trials. This finding is very important, as the benefits shown in the definitive RCTs were a major advance in our ability to treat neovascular AMD. To be able to confidently tell our patients that they will be able to expect a similar outcome is reassuring and a valuable information for the treating doctor, the patient, and for governments currently evaluating the economic impacts of this treatment.

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1. Which of the following best describes the percentage of patients with significant gains in visual acuity with ranibizumab treatment in the ANCHOR and MARINA trials at 12 months?

A 10% to 20%
B 25% to 40%
C 45% to 60%
D Over 70%

2. A 75-year-old patient is being considered for ranibizumab treatment for age-related macular degeneration (AMD) and is just able to count fingers. Which of the following best describes his visual acuity score using the standard for this study?

A 0.002
B 0.05
C 0.001
D 0.005

3. Which of the following best describes the relative increase in percentage of patients with visual acuity of 0.5 or better in patients with AMD treated with ranibizumab for 12 months?

A 50%
B 30%
C 20%
D 40%

4. Which of the following best describes the mean number of monthly injections with ranibizumab for the first 6 and 12 months of treatment, respectively, in patients with AMD in this study?

A 3 and 8
B 4 and 7
C 4 and 9
D 5 and 10

Activity evaluation

1. The activity supported the learning objectives.

Strongly disagree				Strongly agree
1	2	3	4	5

2. The material was organized clearly for learning to occur.

Strongly disagree				Strongly agree
1	2	3	4	5

3. The content learned from this activity will impact my practice

Strongly disagree				Strongly agree
1	2	3	4	5

4. The activity was presented objectively and free of commercial bias.

Strongly disagree				Strongly agree
1	2	3	4	5