

Visual outcomes of age-related macular degeneration patients undergoing intravitreal ranibizumab monotherapy in an urban population

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Aim: To compare the visual outcomes of an urban population with age-related macular degeneration (AMD) undergoing ranibizumab monotherapy to the results from major clinical trials.

Procedures: Prospective data was collected from 164 wet AMD patients receiving intravitreal ranibizumab. Visual acuities were obtained with the Early Treatment Diabetic Retinopathy Study chart. All patients underwent a loading phase of three monthly treatments of ranibizumab. Patients were monitored monthly using a retreatment criterion. Treatment was further individualized by sequentially lengthening follow-up intervals when stable.

Results: At 12 and 24 months, respectively, the percentage of eyes that maintained vision was 91% and 88.6%. We found that 20.3% of eyes had improved vision at 12 months and 20% at 24 months. At 12 months, 8.3% of eyes' vision worsened and 12% worsened at 24 months.

Conclusion: Individualized ranibizumab monotherapy is effective in preserving vision in wet AMD and follows the same trends as the pivotal trials.

Keywords: visual acuity, comparison of age-related macular degeneration treatment trials, choroidal neovascular membrane

Introduction

Age-related macular degeneration (AMD) is the commonest cause of severe visual impairment in older people in the developed world.^{1,2} The two late phenotypes of AMD are geographic atrophy and wet AMD; together, these are responsible for two-thirds of registrations of visual impairment or blindness in the United Kingdom.² Vision loss in wet AMD is caused by formation of a choroidal neovascular membrane (CNVM) responding to vascular endothelial growth factor (VEGF). It is thought that wet AMD accounts for only 10%–15% of all AMD cases but is responsible for over 80% of AMD-related severe visual impairment or visual loss.³

The minimally classic/occult trial of the anti-VEGF antibody ranibizumab in the treatment of neovascular AMD (MARINA) and anti-VEGF antibody for the treatment of predominantly classic choroidal neovascularization in AMD (ANCHOR) trials were large multicenter double-blind studies which established that continuous treatment with intravitreal ranibizumab was an effective treatment for wet AMD.^{4,5} Following this, comparison of age-related macular degeneration treatment trials (CATT) proved that treatment with ranibizumab on an as-required basis following the initial three monthly loading dose was equally as effective as continuous monthly treatments.^{6,7}

The CATT trial retreatment criteria was based on signs of CNVM activity: fluid on optical coherence tomography (OCT), new or persistent hemorrhage, decreased visual acuity as compared with the previous examination, dye leakage, or increased lesion size on fundus fluorescein angiography.⁶

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Following these trials, ranibizumab intravitreal injections have been employed as first-line treatment for wet AMD. Since this change in the treatment of wet AMD, little has been published in the UK regarding real population visual outcomes. We wanted to analyze our inner-city AMD patient cohort and compare their visual outcomes following ranibizumab monotherapy to the major clinical trials.

Aims

To compare the results from an inner-city population to the results achieved in the major clinical trials described in the introduction.

Methods

From December 2007 to January 2012, prospective data were collected from 164 patients who underwent intravitreal ranibizumab treatment for wet AMD and entered into an in-house, password-protected spreadsheet. Baseline and follow-up visual acuity measurements were obtained with the Early Treatment Diabetic Retinopathy Study (ETDRS) chart. Patient consent to publish their demographics and visual outcome data was gained when the decision to proceed with treatment was made. The study was approved by the ethics committee at London North West Healthcare NHS Trust.

The patients who were included in the study were aged 50 years or older; had visual acuity between 0.00 and 2.30 logMAR; and had the presence in the study eye of previously untreated active CNVM as demonstrated by hemorrhage or leakage on FFA and OCT.

Patients who had received previous treatment, transferred to another trust, or who subsequently had another diagnosis were excluded from our analysis, as were patients who had no more than the three treatments in the loading phase. After applying these exclusions, 27 patients were removed from the study and the data for 123 eyes of 106 patients were analysed. None of the patients refused treatment. Data were collected for age, sex, baseline visual acuity, and monthly visual acuities over 2 years and for the mean number of treatments per year. This study did not analyze the disease progression of different AMD types; we solely wanted to report the visual outcome data of a real-life population undergoing ranibizumab monotherapy.

All patients underwent a loading phase of three monthly treatments of 0.5 mg in 0.05 mL of intravitreal ranibizumab. Following this, patients were monitored monthly and the following retreatment criteria were used to establish whether further treatment was required:

- Loss of letters with fluid on OCT
- Any fluid on OCT – intraretinal fluid, subretinal fluid
- Increased size of pigment epithelial detachment

- New retinal hemorrhage
- New CNVM.

In addition, if FFA revealed active CNVM, treatment was repeated each month for three months. Treatment was further individualized by sequentially lengthening follow-up intervals when a period of stability had been established.

Each intravitreal ranibizumab injection was performed in theatre under aseptic conditions and chloramphenicol 0.5% eye drops were administered four times a day for 5 days following the treatment. During and post-procedure, the patients were monitored for topical and general adverse events.

Similar to both the ANCHOR and MARINA trials, efficacy analyses were performed on an intention-to-treat basis with the use of a last-observation-carried-forward method for missing data.^{4,5}

Results

Demographics

Similar to the ANCHOR trial but in contrast to the MARINA and CATT trials, our results had a majority of male patients (59%). Our population with a mean age of 83 years was much older than patients included in the other trials. Our largest age group was between 80 and 89 years compared to 75–84 years in the ANCHOR and MARINA trials and 70–79 years in the CATT trial. All the trials had a Caucasian majority of between 97% and 98%; we also demonstrate a Caucasian majority but of only 62% with 38% of patients from other ethnicities. Demographics are summarized in Table 1.

Visual outcomes

We compared our 1-year and 2-year visual outcomes to those found from the ANCHOR, MARINA, and CATT trials (Figures 1 and 2). We used their same criteria for defining the

Table 1 Comparison of present study demographics and mean baseline vision to pivotal trials

Demographics	Present study	CATT trial	ANCHOR trial	MARINA trial
Age				
Mean (years)	83	79	76	77
Largest group (years)	80–89	70–79	75–84	75–84
Sex				
Male (%)	51	40	54	37
Female (%)	49	59	46	63
Ethnicity				
Caucasian (%)	62	98	97	97
Other (%)	38	3	4	3
Mean baseline vision (ETDRS letters)	35			

Abbreviation: ETDRS, Early Treatment Diabetic Retinopathy Study.

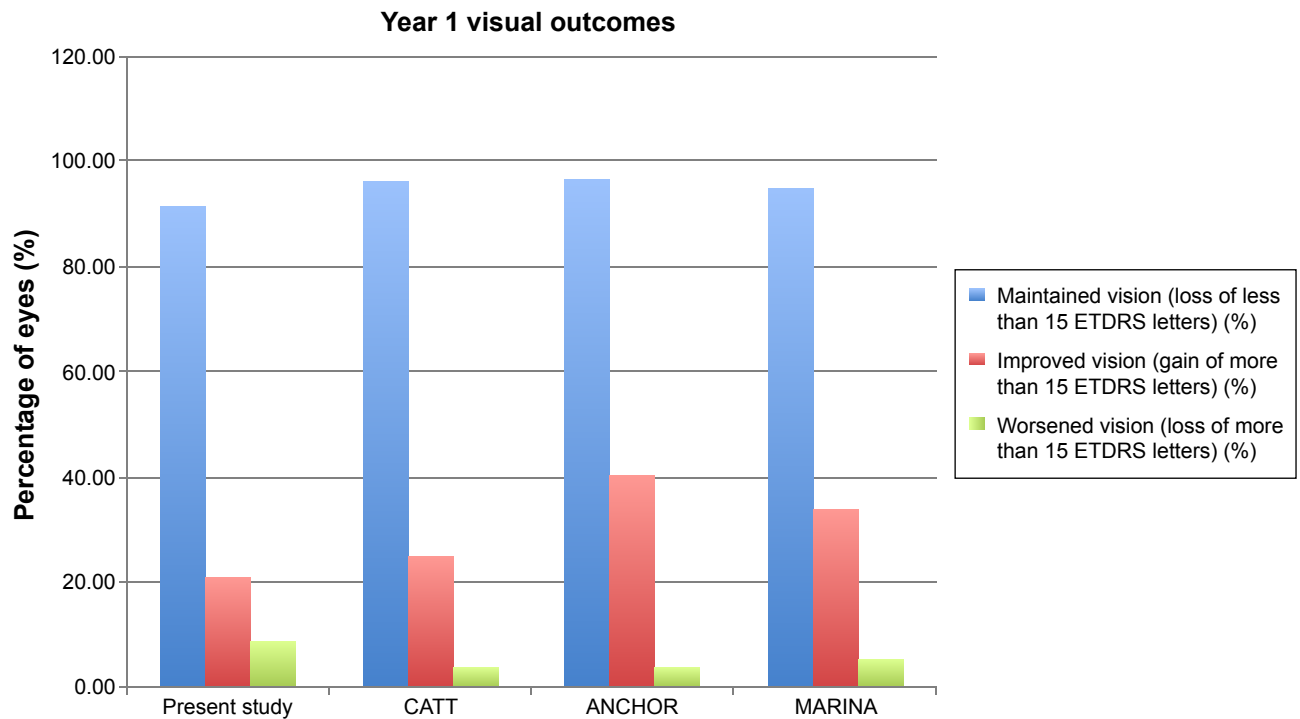


Figure 1 Graph comparing the visual outcomes after 1 year from this study to the CATT, ANCHOR, and MARINA trials.
Abbreviation: ETDRS, Early Treatment Diabetic Retinopathy Study.

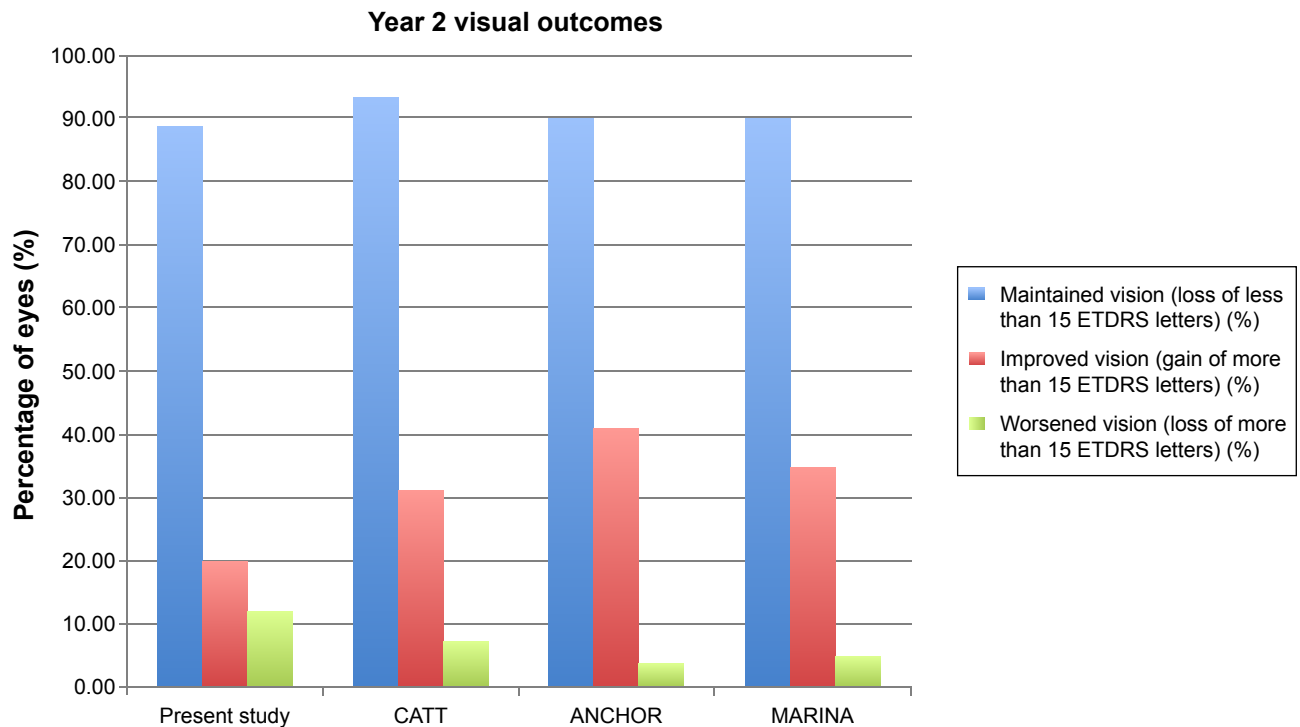


Figure 2 Graph comparing the visual outcomes after 2 years from this study to the CATT, ANCHOR, and MARINA trials.
Abbreviation: ETDRS, Early Treatment Diabetic Retinopathy Study.

Table 2 Comparison of present study visual outcomes and number of ranibizumab treatments to pivotal trials

Visual outcomes	Present study	CATT trial	ANCHOR trial	MARINA trial
12 months				
Maintained vision: loss of less than 15 ETDRS letters (% of eyes)	91.8	96.0	96.4	94.6
Improved vision: gain of 15 or more ETDRS letters (% of eyes)	20.3	25.0	40.3	33.8
Worsened vision: loss of more than 15 ETDRS letters (% of eyes)	8.1	4.0	3.60	5.4
Mean number of treatments	6	6.9	12	12
24 months				
Maintained vision: loss of less than 15 ETDRS letters (% of eyes)	88.6	93.0	90.0	90.0
Improved vision: gain of 15 or more ETDRS letters (% of eyes)	19.7	33.0	41.0	35.0
Worsened vision: loss of more than 15 ETDRS letters (% of eyes)	11.5	7.0	4.0	6.0
Mean number of treatments	4	5.7	12	12

Abbreviation: ETDRS, Early Treatment Diabetic Retinopathy Study.

three visual outcomes. The primary outcome measure was the percentage of eyes that maintained vision, meaning the percentage of eyes that lost less than 15 letters from baseline.⁴⁻⁶ Secondary outcome measures included the percentage of eyes that improved vision (meaning those that gained 15 letters or more from baseline) and the mean change in visual acuity.⁴⁻⁶ All 123 eyes underwent at least 12 months of monitoring and 61 eyes (50% of the initial study population) had visual outcome data for 24 months.

At 12 months, the percentage of eyes that maintained vision in our study was 91% compared to 96% in the CATT trial, 96.4% in the ANCHOR trial, and 94.6% in the MARINA trial.⁴⁻⁶ We found that 20.3% of eyes had improved vision compared to 25% in the CATT trial, 40.3% in the ANCHOR trial, and 33.8% in the MARINA trial.⁴⁻⁶ Finally, 8.1% of our study eyes' vision worsened compared to 4% in the CATT trial, 3.6% in the ANCHOR trial, and 5.4% in the MARINA trial (Table 2).⁴⁻⁶

At 24 months, the percentage of eyes that maintained vision in our study was 88.6% compared to 93% in the CATT trial and 90% in both the ANCHOR and MARINA trials.⁴⁻⁶ We found that 19.7% of eyes had improved vision compared to 33% in the CATT trial, 41% in the ANCHOR trial, and 35% in the MARINA trial.⁴⁻⁶ In our study, 11.5% of eyes worsened compared to 7% in the CATT trial, 4% in the ANCHOR trial, and 6% in the MARINA trial (Table 2).⁴⁻⁶

When comparing the mean visual progress over 2 years, our results did not show the initial steep gain of letters that was shown in the trials (Figure 3). Instead, the mean change in vision over 2 years was only between zero and three ETDRS letters. We also found that the change in mean visual acuity

was minimal ranging between 0.58 and 0.70 logMAR over 2 years (Figure 4). The mean number of injections given per eye was ten over 2 years; six in year 1 (range three to 12) and four in year 2 (range one to 12), compared to 12.6 in the CATT trial (Table 2).⁶

On investigating this further we found that from the group whose vision worsened by 15 letters or more, 73% of these eyes had severe vision loss (30 letters or more; range 16–97). Although this is a relatively small percentage of the total number of eyes (9%), this significant loss of letters may have been enough to skew the mean visual acuity and mean change in vision, thus hiding any initial dramatic increase in vision.

Discussion

The pivotal continuous and individualized clinical trials have changed how wet AMD is treated today. The trials were either continuous, where monthly injections of ranibizumab were given over 2 years, or individualized where, after the three monthly loading doses, the patient was evaluated monthly but ranibizumab therapy was only given according to set criteria relating to the activity of wet AMD in that individual. The ANCHOR and MARINA trials were the two continuous trials that recruited 423 and 716 patients, respectively.^{4,5} They both observed that 90% of patients maintained vision, and improvement in vision occurred in 41% of patients in the ANCHOR trial and 35% in the MARINA trial.^{4,5} The mean change in visual acuity from baseline was 10.7 letters in the ANCHOR trial and 6.6 letters in the MARINA trial.^{4,5}

The recently published CATT trial was significantly larger with 1,208 patients.⁶ They compared visual outcomes of eyes that underwent treatment with ranibizumab to those that had

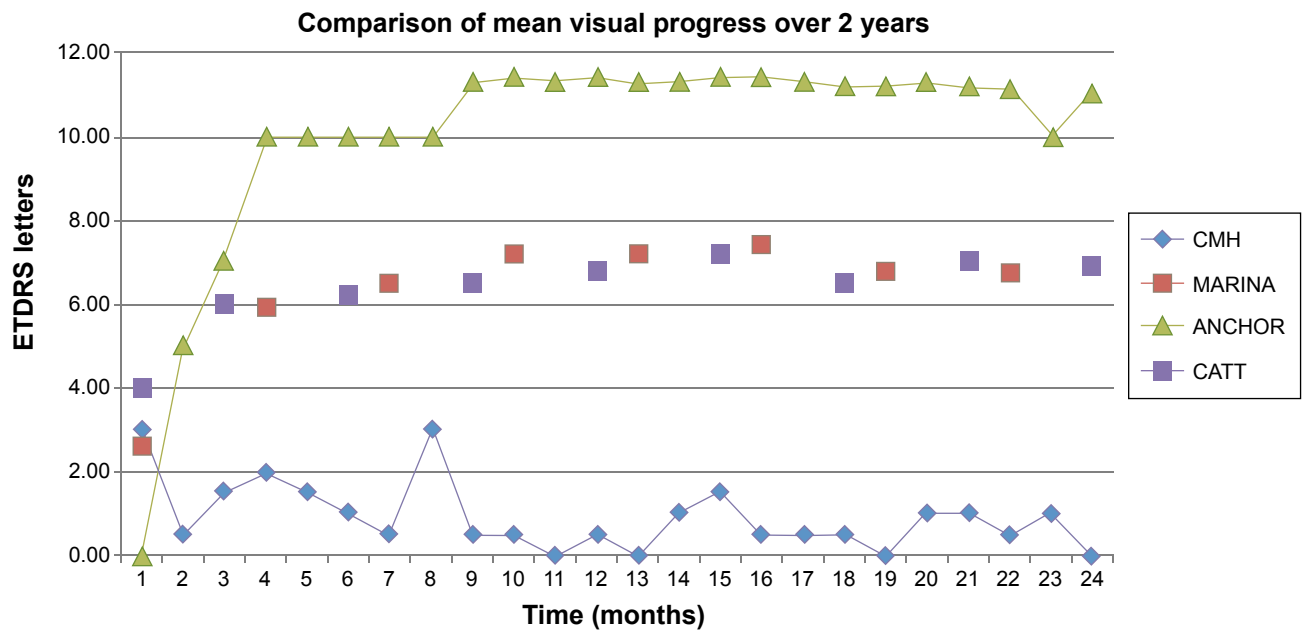


Figure 3 A graph comparing the mean visual progression of this study to the CATT, ANCHOR, and MARINA trials.
Abbreviations: CMH, Central Middlesex Hospital; ETDRS, Early Treatment Diabetic Retinopathy Study.

bevacizumab and also the visual outcomes of patients who underwent continuous treatment versus individualized, as-needed treatment.⁶ The arm of the trial that observed individualized treatment with ranibizumab showed maintenance of vision in 93% of patients, improvement of vision in 33% of patients, and a mean change in visual acuity of 6.7 letters over 2 years.⁶

The results from our study follow a similar pattern to the pivotal trials, where the initial findings from year 1 were largely maintained throughout year 2. At 2 years, the

percentage of eyes that maintained vision was 88.6%, compared to 93% in the CATT trial and 90% in the ANCHOR and MARINA trials.⁴⁻⁶ However, the number of eyes that improved vision was approximately a third less than the pivotal trials; 19.5% compared to 33% in the CATT trial, 41% in the ANCHOR trial, and 35% in the MARINA trial.⁴⁻⁶ The number of eyes whose vision worsened by losing more than 15 letters was greater than in all the trials; 11.5% compared to 7% in the CATT trial, and 4% and 6% in the ANCHOR

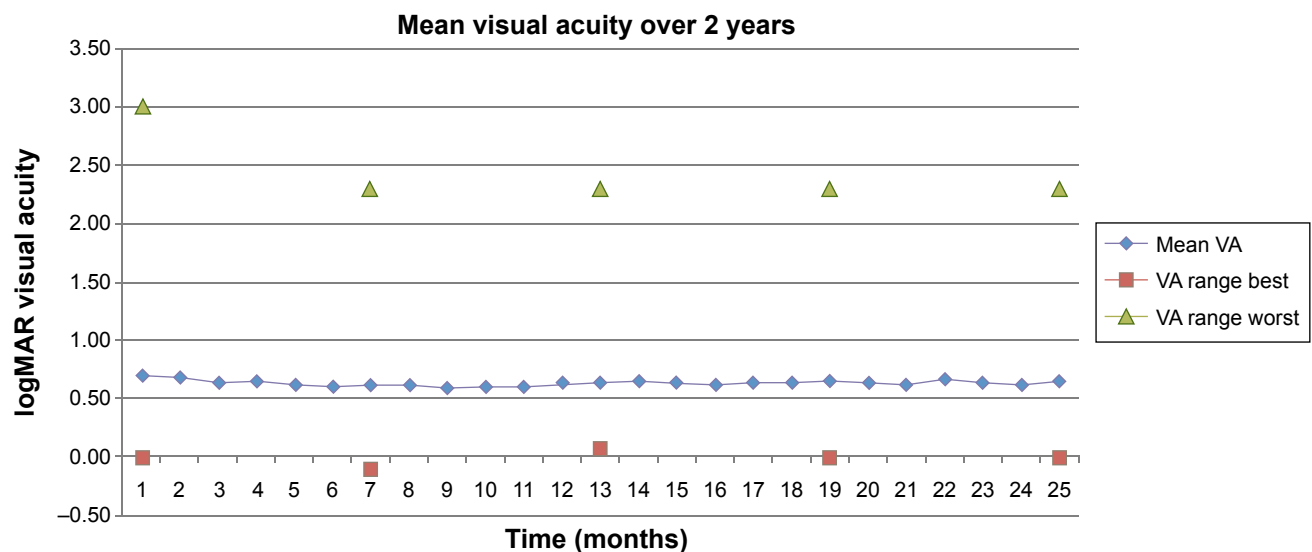


Figure 4 A graph comparing the mean visual acuity of this study to the CATT, ANCHOR, and MARINA trials.
Abbreviation: VA, visual acuity.

Table 3 Comparison of present study results to ten other studies of real life AMD populations treated with ranibizumab monotherapy around the world

	Present study UK	Bandukwala et al ¹³ Canada	Cohen et al ¹⁰ France	Dadgostar et al ¹¹ USA	Feng et al ¹⁷ Poland	Małgorzata and Stanekiewicz ⁸ Poland	Hjelmqvist et al ¹⁶ Sweden	Kang et al ¹⁴ Korea	Querques et al ¹² France	Shienbaum et al ¹⁹ USA	Subramanian et al ¹⁵ USA
Number of eyes	123 (year 1) 61 (year 2)	95	124	131	93	25	370	64	96	7	7
Mean age (years)	83	81	78	81	80	73	78	70	77	81	80
Sex											
Male (%)	59	37	30	35.5	41.5	44	30	72	29	N/A	86
Female (%)	41	63	70	64.5	58.5	56	60	28	71		14
Maintained vision: loss of less than 15 ETDRS letters (%)	91.8 (year 1)	82	90	83.8	84.9	100	89.1	85.9	94.8 (year 1)	100	85
Improved vision: gain of more than 15 ETDRS letters (%)	20.3 (year 1)	11	8	30	25.8	32	14.7	N/A	87.5 (year 2)	60	N/A
Worsened vision: loss of more than 15 ETDRS letters (%)	19.7 (year 2)	18	2	15	15	0	10.9	14.1	25 (year 2)	0	15
Mean number of ranibizumab injections	11.5 (year 2)	5.1	3.79	5.2	4.3	6	4.7	4.2	12.5 (years 1 and 2)	4.7	4
Mean visual acuity change (ETDRS letters)	3.5 (year 1)	2.5	3.5	5	N/A	10.6	1	1	5.5 (year 1)	17	6.3
Follow-up period (months)	3 (year 2)	12	12	12	11	12	12	12	5.1 (year 2)	12	12
Retrospective or prospective	P	R	R	R	R	R	R	R+P	R	R	P

Abbreviations: AMD, age-related macular degeneration; ETDRS, Early Treatment Diabetic Retinopathy Study; N/A, not applicable; P, prospective; R, retrospective.

and MARINA trials, respectively.^{4,6} The lack of dramatic visual improvement was also observed in the mean visual progress over 2 years, which was quite variable and failed to demonstrate the initial steep rise following the 3-month loading phase. This is further supported by the mean visual acuity over 2 years, which remained fairly static at 0.6 log-MAR (range -0.1 to 2.30). As mentioned previously, this may be due to the fact that 9% of eyes did particularly poorly, losing between 30 and 97 letters, which may have skewed the average visual outcomes.

Our results do follow the same trend as the pivotal trials but not to the same degree of success. This may be due to the smaller sample size of 123 eyes, of which only 61 had follow-up for the entire 24 months. The main reason for this reduction of 50% of the study population was that those patients had only undergone 12 months of treatment at the time of analysis, as despite the study including patients whose treatment began in 2007, the initial recruitment was slow with low patient numbers. Other reasons included: patients who failed to attend further appointments (n=4), patients whose treatment was stopped due to poor visual prognosis (n=3), and patients who died from other illness (n=3).

We also wanted to see how our visual outcome data compared to other single centers. Currently, there is no data published from the United Kingdom; however, ten other papers have been published by other centers (see Table 3 and Figure 5). Our study results compared to these ten studies were very similar. The mean number of eyes that maintained vision from the other studies was 88.8%, compared to 88.6% in our study. The mean number of eyes that improved vision from the other studies was 20.7%, compared to 19.7% in our study. Finally, the mean number of eyes that worsened from the other studies was 10.3%, compared to 11.5% in our study.

Conclusion

This prospective study of individualized ranibizumab monotherapy over 24 months shows that individualized therapy in an inner-city population is effective in preserving vision in wet AMD and follows the same trends as the pivotal trials. Although our results, and those from other clinical settings, do not quite match the degree of vision preservation and gain as the large clinical trials, they are not dramatically dissimilar. We also hope this study encourages more AMD clinical settings to publish their data for comparison, particularly centers in the United Kingdom.

Disclosure

The authors report no conflicts of interest in this work.

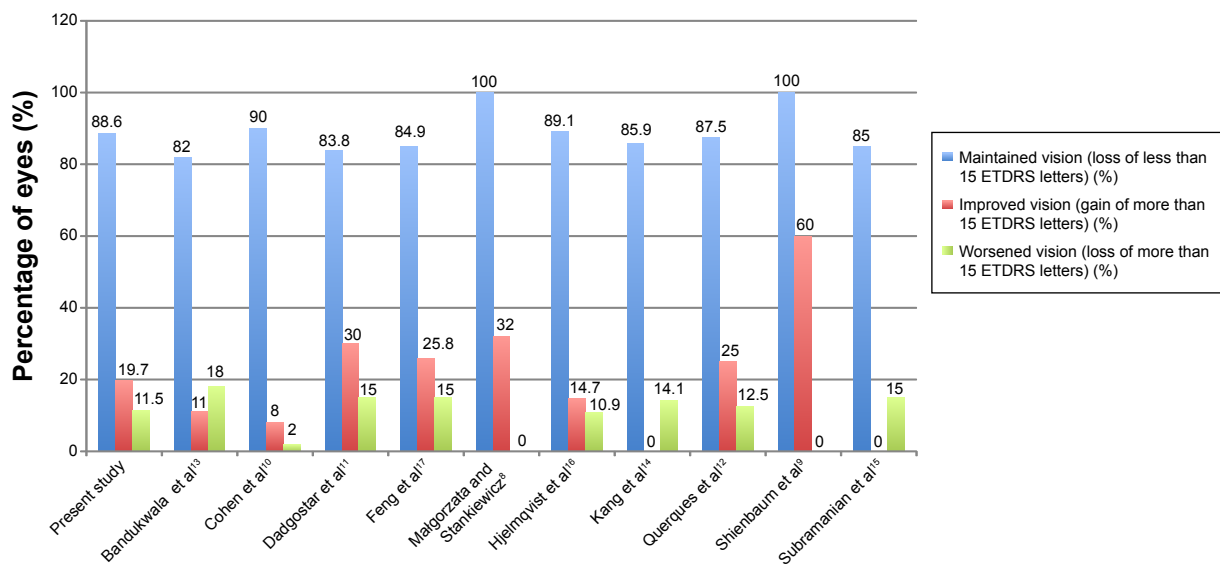


Figure 5 A graph comparing the visual outcomes of this study to ten other single-center studies of real-life populations.

Abbreviation: ETDRS, Early Treatment Diabetic Retinopathy Study.

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