Ophthalmol Ther (2015) 4:43–49
DOI 10.1007/s40123-015-0031-5

BRIEF REPORT

Missed Hospital Appointments of Patients Receiving Ranibizumab Therapy for Neovascular Age-Related Macular Degeneration

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Received: February 9, 2015 / Published online: March 14, 2015

ABSTRACT

Introduction: The aim of this study was to investigate the frequency and duration of missed hospital appointments (MHAs) in a consecutive cohort of patients treated with ranibizumab for neovascular age-related macular degeneration (nAMD) and to assess their impact on outcomes of therapy in a real-world clinical setting.

Methods: Retrospective, cross-sectional study of consecutive patients attending medical retina clinics for nAMD treatment with ranibizumab.

Results: Seventy-eight eyes of 78 patients met the inclusion criteria for data analysis. Mean age was 78 years with mean follow-up of 27 months. Mean visual acuity (VA) was 52 ± 16 letters at baseline, 56 ± 17 letters at year 1 and 58 ± 16 letters at year 2. At the end of the second year, 90% of the patients had lost <15 letters, 26% had gained ≥15 letters and 10% had lost ≥15 letters. Nineteen patients had at least one MHA (24%) over 2 years. There were 26 MHA episodes in total leading to a median duration of 79 days (range 35–159) between attended hospital visits. None of these MHAs occurred during the first 3 months after treatment initiation. Mean VA and central retinal thickness difference between 2 years and baseline for the MHA group was not statistically different compared with the non-MHA group.

Conclusions: Our data suggest that MHA may be a relatively common occurrence in AMD treatment clinics, but good outcomes of treatment can be achieved over 2 years despite missed hospital visits if patients are reviewed on average six times in the first year after an initial loading phase of three injections and nine times in the second year of treatment.

Keywords: Age-related macular degeneration; Missed appointment; Ranibizumab

Electronic supplementary material The online version of this article (doi:10.1007/s40123-015-0031-5) contains supplementary material, which is available to authorized users.

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INTRODUCTION

Age-related macular degeneration (AMD) is the leading cause of blindness among elderly

patients in developed countries [1, 2]. While the neovascular form of AMD (nAMD) characterized by choroidal neovascularization (CNV) comprises approximately 10% of the disease, it is responsible for over 90% of cases of severe visual loss [3–5]. Over the last few years, introduction of anti-vascular endothelial growth factor (anti-VEGF) therapy, such as ranibizumab, has revolutionized the management of nAMD. The latter has been approved for use on the basis of phase III clinical trials with monthly follow-up and treatment over 24 months [6, 7]. Further research trialed anti-VEGF regimens of varying dosage and frequency of therapy administration, in an attempt to maximize visual acuity (VA) outcomes while minimizing treatment burden [8–14]. In studies reporting sustained improvements in vision, patients had very frequent follow-ups with monthly ophthalmic examinations. However in clinical practice, patients with nAMD often have significant coexisting medical conditions, which may impact on their ability to attend their regular AMD clinic appointments [6, 10]. It is also important to note that clinical trials often exclude patients who may not comply with mandated study visits and may only include patients who are able to attend monthly follow-up visits [12]. This may mean that in practice, the intensive follow-up and treatment paradigms used in clinical trials may be difficult to implement. If this is indeed a significant problem, then it has the potential to impact on the outcomes of therapy in clinical practice, as less intensive follow-up can result in poorer outcomes of treatment [15, 16].

The aim of this study was to report the proportion of patients with missed hospital appointments (MHAs) for nAMD assessment in a consecutive cohort of patients treated with ranibizumab and to report the duration of such MHAs. An additional aim was to report long-term functional and structural outcomes in this patient group and compare them with the subgroup of consecutively treated patients without MHAs, thus assessing the potential impact of MHAs on outcomes of therapy in a real-world clinical setting.

METHODS

This was a retrospective cross-sectional study. Consecutive patients with nAMD treated in AMD treatment clinics of Moorfields Eye Hospital were evaluated. The inclusion criteria consisted of treatment-naïve patients with all types of CNV secondary to nAMD managed with intravitreous ranibizumab therapy using a pro re nata (PRN) regimen and follow-up period of at least 24 months. The exclusion criteria included eyes with any prior treatment for nAMD (including laser photocoagulation, verteporfin photodynamic therapy and intravitreal pegaptanib sodium, ranibizumab or bevacizumab) and the presence of other retinal disease likely to compromise VA. Patient records were reviewed and the following data were collected: age, best-corrected VA assessed with the use of Early Treatment Diabetic Retinopathy Study (ETDRS) charts using the most up-to-date distance correction at each visit, follow-up period, analysis of baseline fluorescein angiogram (FFA) to establish CNV lesion type and lesion size, spectral-domain optical coherence tomography (OCT)-derived central retinal thickness (CRT) and the presence, number and duration of MHAs. MHA duration was defined as the interval between the appointment before the MHA and the next appointment at which the patient attended (giving the interval between attended hospital visits either side of

the missed visit). Data were analyzed with frequency and descriptive statistics. Mean values were compared using independent samples t test. A p value <0.05 was considered to be statistically significant. All statistics were calculated using SPSS software version 17.0 for Windows (SPSS, Inc, Chicago, Illinois, USA).

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964, as revised in 2013. Informed consent was obtained from all patients for being included in the study.

RESULTS

During the interval chosen for the study, 78 eyes of 78 patients met the inclusion criteria for data analysis. The mean age was 78 years (range 52–93 years) and the mean follow-up was 27 months (range 24–38 months). There were 43 women (55%) and all 78 patients were Caucasian. Mean VA was 52 ± 16 letters at baseline, 56 ± 17 letters at year 1 and 58 ± 16 letters at year 2. At the end of the second year, 90% of the patients had lost <15 letters, 26% had gained ≥15 letters and 10% had lost ≥15 letters. Mean CRT was 311 ± 87 μm at baseline, 273 ± 72 μm at year 1 and 250 ± 68 μm at year 2. Mean number of injections was 6.7 (range 3–12) in the first year and 4.9 (range 0–12) in the second year. Mean number of hospital visits was 9.4 (range 5–12) in the first year and 8.9 (range 3–12) in the second year. Nineteen patients had at least one MHA (24%). Two patients had three MHAs, 3 patients had two MHAs and 14 patients had one MHA. There were 26 MHA episodes in total with a median duration of 79 days (range 35–159). None of these MHAs occurred during the first 3 months after treatment initiation. Table 1 summarizes baseline demographics, baseline lesion size and subtypes for the two groups. Table 2 displays the treatment-related metrics and Table 3 summarizes the outcomes of ranibizumab therapy. There was no statistically significant difference between the two groups regarding baseline age, baseline VA, baseline CRT and baseline lesion size. In addition, the two groups were similar in terms of baseline lesion type (Table 1). Mean VA and CRT difference between 2 years and baseline for the MHA group was not statistically different compared with the non-MHA group ($p = 0.981$, $p = 0.605$, respectively) (Figs. 1 and 2).

Table 1 Baseline demographics, lesion size and subtypes for the two groups

	Patients without MHAs	Patients with MHAs	Statistical significance
Number	59	19	
Baseline age (years, mean ± SD)	77 ± 8	79 ± 9	$p = 0.519$
Women	59%	42%	
Follow-up (months, mean ± SD)	27 ± 4	28 ± 3	
Baseline lesion size (mm^2, mean ± SD)	16 ± 8	13 ± 7	$p = 0.169$
Occult	69%	69%	
Predominantly classic/100% classic	24%	22%	
Minimally classic	7%	11%	

MHAs missed hospital appointments

Table 2 Treatment-related metrics

	Patients without MHAs	Patients with MHAs	Statistical significance
Number of injections during the 1st year (mean ± SD)	7 ± 2	6 ± 2	$p = 0.068$
Number of injections during the 2nd year (mean ± SD)	5 ± 3	4 ± 2	$p = 0.083$
Overall	12 ± 5	10 ± 4	$p = 0.066$
Hospital visits during the 1st year (mean ± SD)	9 ± 2	9 ± 2	$p = 0.849$
Hospital visits during the 2nd year (mean ± SD)	9 ± 2	9 ± 2	$p = 0.516$
Overall	18 ± 3	18 ± 4	$p = 0.649$

MHAs missed hospital appointments

DISCUSSION

The management of nAMD has been transformed by the introduction of anti-VEGF agents delivered by intravitreous injection. The licensed therapy, ranibizumab, has been brought to market on the basis of positive results of phase III randomized, controlled trials in which elderly patients with nAMD were seen at monthly intervals over 24 months [6, 7]. Other clinical trials with quarterly hospital visits did not lead to sustained improvements in vision [15, 16]. Concerns remain regarding long-term outcomes of therapy with ranibizumab and how well outcomes in clinical practice can replicate those seen in clinical trials [10, 17]. Furthermore, according to the 1-year results from the IVAN trial (ISRCTN.com # ISRCTN92166560), 35% of patients had at least one MHA [18]. These data indicate that despite the need for a strict follow-up, there are many co-existing factors that could compromise patient compliance and therefore also potentially impinge on treatment outcomes.

The need for intensive monthly follow-up over 24 months should be balanced against the pragmatism of offering this therapy to an elderly cohort of patients who may not be able to comply with such strict follow-up in view of other co-morbidities and other factors. Despite the importance of MHAs in this context and the potential of MHAs to impact on long-term outcomes of therapy for nAMD, to our knowledge there have been no reports of both the incidence of MHAs and the impact of such MHAs on the long-term outcomes of

Table 3 Outcomes of ranibizumab therapy

	Patients without MHA	Patients with MHA	Statistical significance
Baseline VA (ETDRS letters, mean ± SD)	53.6 ± 15.2	45.5 ± 15.8	$p = 0.053$
1-year VA (ETDRS letters, mean ± SD)	57 ± 16.5	53 ± 19.4	$p = 0.381$
2-year VA (ETDRS letters, mean ± SD)	59.3 ± 14.1	52.2 ± 20.7	$p = 0.188$
Baseline CRT (μm, mean ± SD)	321.1 ± 87.3	272.5 ± 77.8	$p = 0.055$
1-year CRT (μm, mean ± SD)	281.1 ± 74.6	245.4 ± 54.6	$p = 0.080$
2-year CRT (μm, mean ± SD)	257 ± 72	219.7 ± 41.6	$p = 0.092$

MHAs missed hospital appointments, *VA* visual acuity, *ETDRS* Early Treatment Diabetic Retinopathy Study, *CRT* central retinal thickness

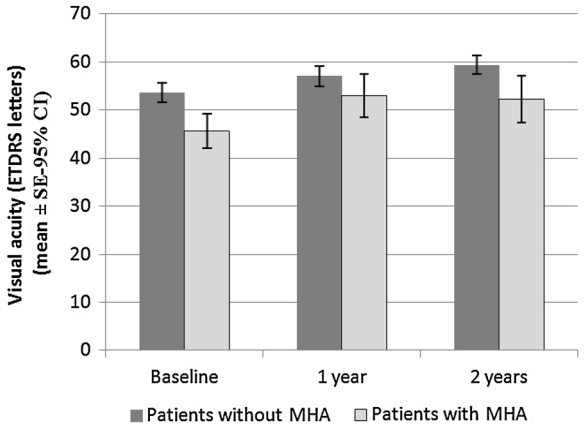

Fig. 1 Graph showing the mean visual acuity for the two groups at baseline, year 1 and year 2. *MHAs* missed hospital appointments, *ETDRS* Early Treatment Diabetic Retinopathy Study

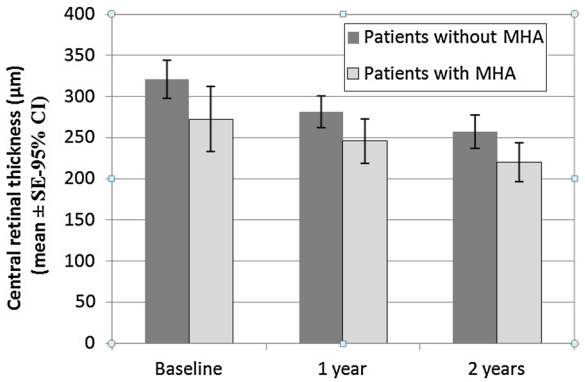

Fig. 2 Graph showing the mean central retinal thickness for the two groups at baseline, year 1 and year 2. *MHAs* missed hospital appointments

ranibizumab therapy. In this study we found that although MHAs were not uncommon in patients who had been undergoing ranibizumab therapy over a minimum of 24 months occurring in 24% of patients, there was no significant impact on the outcomes of treatment when compared with a group of consecutively treated patients without MHAs over the same period. We found that median duration of MHAs was less than 3 months (78.5 days). This may explain why no differences were seen in the outcomes of treatment in the groups with or without MHAs. Furthermore, over 2 years, there were a similar number of hospital visits and ranibizumab injections in both groups suggesting that when an MHA occurred, a new clinic appointment was made relatively rapidly, reducing the review-free interval and potentially preventing vision loss. This work suggests that good treatment outcomes with ranibizumab can be achieved with nine hospital visits in the first year and nine hospital visits in the second year. In the first year this would mean a hospital visit on average every 7 weeks after the initial loading phase of treatment (when an injection is given every 4 weeks for 3 injections) and every 5.8 weeks in the second year of treatment.

There are many weaknesses in this work including its retrospective nature and non-standardized approach to treatment and limited sample size; however there are also several strengths including the report of "real-life" outcomes from patients treated at a large tertiary referral center.

CONCLUSION

These data suggest that missed hospital visits may be a relatively common occurrence in AMD treatment clinics, but good outcomes of treatment can be achieved over 2 years if patients are reviewed on average six times in the first year after an initial loading phase of three injections (one injection a month for 3 months) and nine times in the second year of treatment.

ACKNOWLEDGMENTS

No funding or sponsorship was received for this study or publication of this article. All named authors meet the International Committee of

Medical Journal Editors (ICMJE) criteria for authorship for this manuscript, take responsibility for the integrity of the work as a whole and have given final approval for the version to be published.

Conflict of interest. Praveen Patel has received travel support to educational meetings from Novartis UK and has received honoraria through Advisory Board participation. Robin Hamilton has received travel support to educational meetings from Novartis UK. Michael Karampelas, Maria Pefkianaki, Angela Rees, Navdeep Gill, Aachal Kotecha and Eleni Nikita declare that they have no conflict of interest.

Compliance with ethics guidelines. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964, as revised in 2013. Informed consent was obtained from all patients for being included in the study.

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