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Original Article

Factors affecting visual acuity after one year of follow up after repeated intravitreal ranibizumab for macular degeneration

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Abstract

Aim: Providing intravitreal ranibizumab therapy for neovascular age related macular degeneration (nARMD) is a source of increasing strain for many UK eye departments. Whilst most units attempt to adhere to the product licence of following up patients at four weekly intervals; delays in follow up appointments can and do occur. We aim to see if mean follow up intervals during the maintenance phase are correlated with visual outcomes at one year and perform a multivariate analysis of patient factors in a bit to understand the factors affecting visual acuity outcomes.
Method: A continuously updated prospective audit of patients receiving ranibizumab therapy at the Royal Gwent Hospital was accessed and a coefficient of determination and Spearman's rank test undertaken to see whether mean follow up delays resulted in visual acuity penalties after nine months of maintenance. Multivariate analysis using ANOVA was then undertaken to examine in more detail the various factors affecting visual acuity outcomes.
Results: 805 eyes of 708 patients were included in the study. Mean follow up intervals varied between 28.0 and 96.3 days over the first six treatments of the maintenance phase (mean 49.2 – SD 10.7) with a mean change in visual acuity from baseline of +7.1 letters at 12 weeks and +4.6 letters at 52 weeks. There was a negative correlation seen between visual acuity gains after nine months of the maintenance phase and increasing clinic follow up times although Spearman's rank analysis demonstrated a correlation coefficient of only −0.078, which was not statistically significant. Variability in follow up appointments resulting in worse outcomes was however significant ($p < 0.01$), as was increasing age at presentation ($p = 0.04$). Smoking was found to decrease age of presentation by six years (74.2 years vs 80.0 years). The adjusted R^2 for the whole analysis was 0.44.
Conclusion: Wide variation in follow up intervals was associated with a worse visual acuity outcome although longer mean follow up interval was not. Smokers presented at a significantly younger age than non-smokers or ex-smokers. This was a large study with an adjusted R^2 of 0.44. The results are relevant to other macular degeneration service providers around the world.

Keywords: Age related macular degeneration, Ranibizumab, Smoking

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Introduction

It has been shown through multiple clinical trials that inhibition of vascular endothelial growth factor (VEGF) through intravitreal injection of 0.5 mg ranibizumab (Lucentis, Novartis Pharma AG, Basel, Switzerland; Genentech Inc, San Francisco, USA) is both safe and effective in treating neovascular age related macular degeneration (nARMD).[1–4] The burden of visual loss caused by nARMD is significant, as this condition alone is responsible for more than half of all United Kingdom blind and partial sight registrations in those over 50 years of age[5] and carries a marked adverse financial consequence for the economy itself.[6] Treating nARMD through the establishment of

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dedicated clinics and injection facilities is in itself a significant drain of resources for the National Health Service (NHS), necessitating the drafting of both Royal College of Ophthalmologists and National Institute for Health and Clinical Excellence (NICE) guidelines to operate anti-VEGF delivery services as efficiently as cost effectively as possible.[7,8]

The cornerstone of the United Kingdom NHS ranibizumab intravitreal injection programme is based on the variable dosing regimen outlined in the PrONTO Study, in which patients receive three consecutive monthly injections followed by retreatment dependent on certain criteria such as macular thickness and visual acuity changes being met.[9] This programme of monthly surveillance with injection as required following the initial three loading injections was shown to be non-inferior to continuous monthly injections as employed in the earlier trials, although later research showed that commencing the as-required programme from the very first injection did in fact result in poorer outcomes.[10] Whilst some studies have suggested that ranibizumab assessment and delivery systems based on the PrONTO model do in fact have poorer visual acuity and macular thickness outcomes at one year compared to studies in which patients receive regular monthly treatment regardless of disease activity[11] still others have published results outlining the safety and cost effectiveness of extending clinic follow up appointments for selected patients during the maintenance phase.[12]

In short, the very expensive monthly ranibizumab assessment and delivery services that have been setup around the United Kingdom to implement both NICE guidelines and those of the Royal College of Ophthalmologists are based upon the regime setup in some of the initial clinical trials but the true effect of varying follow up periods for patients in the first year of the maintenance phase is as yet unknown. It is a possibility that extending the follow up period during the maintenance phase has no effect on visual acuity and other parameters after a period of one year, in which case it might be argued that doing so would assist the planning of anti-VEGF nARMD services and the allocation of resources in an austere financial climate. On the other hand it might be the case that extending appointment times may result in poorer outcomes at one year and thus provide an evidence based reason for improving funding for these services as allowing follow up appointments to become delayed might result in patient harm. This very interesting question has not been previously addressed and we sought to do so using the continuously updated prospective audit of patients that has been ongoing at the Royal Gwent Hospital in Newport since ranibizumab services were first commenced in 2007. Since then, for various reasons, including resources, man power and patient factors, mean follow up appointments during the maintenance phase of ranibizumab therapy has varied over the first year of maintenance from 28.0 to 96.3 days. Whilst exploring this issue we also set out to see whether other factors such as the lesion type, age, and number of treatments given during the first year of treatment and baseline visual acuity parameters also had any bearing on visual acuity outcomes after nine months of maintenance. The other two main factors explored were those of smoking status and social deprivation.

Smoking is a known risk factor for nARMD[13] and a putative genetic link has been suggested for this[14] the exact nature of the risk posed by smoking to visual acuity outcomes in NHS macular clinics is not known and to date has not been explored. Likewise whilst social deprivation has been shown to be associated with poorer quality of life in the visually impaired, the exact relationship between social deprivation and visual acuity outcomes in the macular clinic has not been previously explored.[15]

We report here on whether the variation in follow up, smoking status, age, sex, baseline visual acuity, number of treatments in the first nine months of the maintenance phase and social deprivation has any bearing on visual acuity outcomes at one year.

Methods

Since the inception of the nARMD ranibizumab service at the Royal Gwent Hospital in 2007 a continuously updated prospective audit has been undertaken in order to assess outcomes. We accessed this database in order to select the patients who had been followed up for twelve or more months at the unit who had been receiving ranibizumab injections for nARMD of all types. Those with alternate diagnoses and those who had received prior photodynamic therapy (PDT) were excluded from our analysis.

The eligible patient data were analysed for change in visual acuity (in LogMAR letters) based on mean follow up interval during the first nine months of the maintenance phase and Spearman's rank regression analysis undertaken in order to determine the linear correlation between the two variables. The first nine months of maintenance were chosen specifically as the policy in our department is not to vary appointment times based on patient response until the second year of treatment, which would be a significant confounding factor. Classic and occult lesions were separated from these data and analysed individually to see whether they behaved differently from each other or from the group as a whole.

Patients were asked about their smoking status (smoker, ex-smoker or non-smoker) at initial presentation to the nARMD service. Social deprivation was defined by the postcode of their address, as the whole of Wales is divided into 1896 Lower Layer Super Output Areas (LLSOA) which are ranked by the Welsh Government by their levels of deprivation; the Welsh Index of Multiple Deprivation (WIMD), with 1 being the most deprived location and 1896 being the least.

Multivariate analysis in the form of ANOVA was undertaken, using the 'R' statistical program, on all of the measured variables.

Results

Analysis of the database revealed 805 eyes of 708 patients that had been followed up at the Royal Gwent Hospital ranibizumab service with a diagnosis of nARMD for twelve months or more, including nine months of maintenance therapy, that had also not received prior PDT. Follow up during the maintenance phase varied between 28.0 and 96.3 days with a mean of 49.2 days, a median of 48.1 days and a standard deviation of 10.7 days. The change in visual acuity (VA) for the group over nine months of maintenance therapy was −2.3 letters with a standard deviation of 11.1 letters.

Mean initial baseline LogMAR visual acuity in this group was 0.64, with 21% of patients being >0.30 LogMAR. The mean change in visual acuity from baseline was +7.1 LogMAR letters at 12 weeks (VA 0.50 and 38.0% >0.30) and +4.6 letters at 52 weeks (VA 0.55 and 35.2% >0.30). The mean number of ranibizumab treatments in the first year was 5.9.

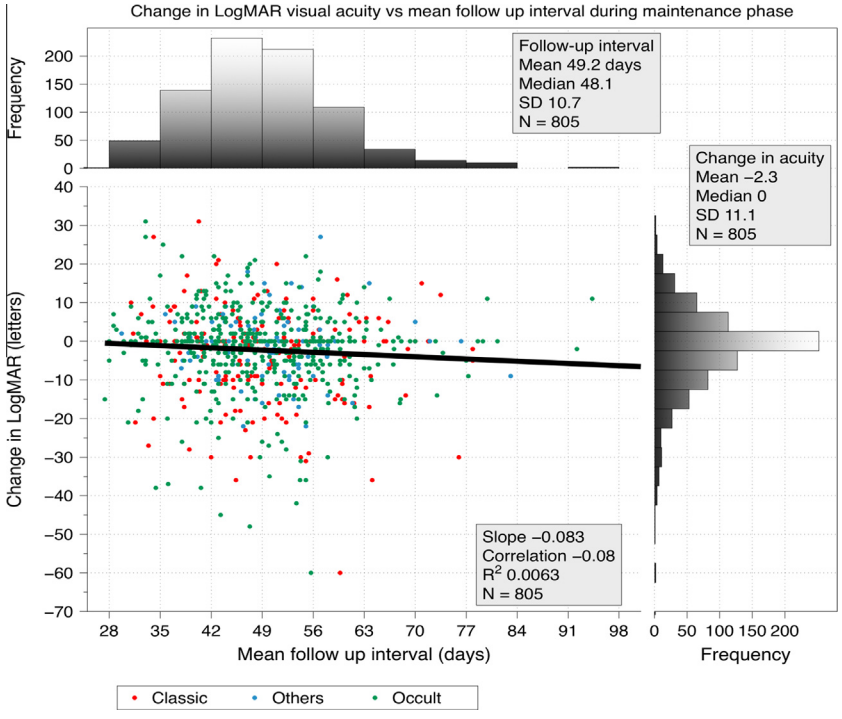
When change in visual acuity was plotted against follow up interval during the maintenance period regression analysis demonstrated a slope of -0.083 and a coefficient of determination (R^2) of 0.0063 (See Graph 1). Spearman's rank analysis of these data demonstrated a correlation coefficient of −0.078 with a *P* value of >0.05.

Multivariate analysis of all the recorded variables was performed using the Analysis of Variants (ANOVA) test with the '*R*' statistical package. This demonstrated that increased age at presentation, measured in years, was correlated with a poorer outcome at -0.108 letters after nine months of maintenance ($p = 0.04$). If smokers ($n = 171$) and ex-smokers ($n = 206$) were grouped together and compared with non-smokers ($n = 428$) then although there was no statistically significant difference in outcome at one year of follow up what was striking was that the mean age of the smokers at 74.2 years old was significantly younger than those who had never smoked, at 80.0 years. Better visual acuity at baseline (−0.082 letters at one year per extra letter seen initially, $p < 0.01$) and greater improvement during the loading phase (−0.181 letters, $p < 0.01$) were both strongly associated with poorer outcomes at one year, although this would be expected as part of a ceiling effect.

Most interestingly, the mean follow up interval during maintenance, the prime variable under investigation in this study, was not associated with a statistically significant worse outcome after nine months of maintenance (−0.131 letters per extra day delay in follow up, $p = 0.08$) although an increased variability in follow up independent of mean delay (−0.389 letters, $p < 0.01$) was significant. Greater number of ranibizumab treatments administered was associated with a worse outcome (−0.384 letters per extra treatment, $p = 0.05$). Sex of the patient, membrane morphology and social deprivation were not associated with any statistically significant variation in visual acuity outcome. Altogether the coefficient of determination (R^2) for the whole study was 0.44.

Discussion

The financial and structural implications of introducing ranibizumab services for nARMD have been debated since it was first introduced[12,16]. Since the first trials, most notably MARINA[3] and ANCHOR,[2] first demonstrated considerable visual acuity benefits to treating nARMD on a fixed monthly regimen efforts have been made to see whether less intense regimes can maintain the benefits whilst being overall more cost-effective. As both of these studies demonstrated a ceiling effect of ranibizumab efficacy after the first three injections the PIER study[4] assessed whether reducing the injection frequency to quarterly following the initial monthly three loading dose injections was a non-inferior alternative. Whilst the PIER study did indeed demonstrate poorer outcomes compared with regular monthly injection subsequent studies employing varying criteria to determine whether retreatment was necessary; SAILOR[17] and PrONTO[9] especially, have now formed the basis of most ranibizumab



Graph 1. The above graph demonstrates the large spread in visual acuity outcomes after treatment with ranibizumab and that these are largely independent of the mean follow up intervals. Classic membranes, represented with red dots, are just as evenly distributed as occult membranes, represented in green. The correlation between follow up interval and acuity outcomes, represented by the slope, are surprisingly not significant for any form of neovascular membrane.

services offered in the United Kingdom National Health Service for nARMD.

Whilst the evidence for the superiority of regular monthly dosing was questioned by the CATT study[18] efforts are continuing to try to find a more cost-effective way of managing the huge workload that maintaining nARMD services has become through treat and extend regimes.[12] These have been planned studies and to date no study has looked into the implications of variable follow up appointments in nARMD clinics during the maintenance phase in a real world setting. Our study is the first to look at whether variations to mean follow up appointment times during the maintenance period of the first year of ranibizumab therapy, caused by fluctuations in system capacity and delivery capabilities as well as patient non-attendances, has a significant bearing on visual acuity outcome.

The mean change in visual acuity from baseline in our patients was +7.1 LogMAR letters at 12 weeks and +4.6 letters at 52 weeks, significantly worse than similar published figures in the main trials quoted above. It must be noted however that 21% of our patients had visual acuities of >0.30 at baseline, which is outside of the inclusion criteria for most of the major studies, in line with evidence that ranibizumab therapy stabilizes good vision in these patients,[19] which would obviously have a bearing on these results. Our study also demonstrates the importance of this ceiling effect. Patients entering the programme with good visual acuity or performing very well during the induction phase had a statistically significant greater chance of reduced LogMAR visual acuity during the maintenance phase.

The biggest surprise out of all the data was that variations in mean follow up interval did not statistically significantly affect visual acuity in the study. Whilst our data do suggest a negative correlation between final visual acuity outcome after nine months of maintenance therapy and an increasing follow up interval, the regression analysis demonstrated a slope of -0.083 and an R^2 of 0.0063 with Spearman's rank analysis demonstrating a correlation coefficient of -0.078; which indicates little linear correlation which was not statistically significant.

This set of results carries weight principally because it includes results of patient episodes from routine NHS practice and reflects the reality of providing a government health programme with service constraints and a significant delayed attendance rate outside the controlled environment of a clinical trial. It is possible that were certain groups isolated from the cohort such as those not missing a single appointment or others excluded such as those with catastrophic drops in visual acuity for various reasons the result would fit a more linear pattern. It might be argued that a further analysis of the figures over a two or three year period of maintenance rather than only nine months might form the basis of a more robust relationship between mean follow up intervals and visual acuity outcomes. Although there was a significant spread the suggestion from our figures does suggest that if this relationship continued or even increased over an extended time period the results might become more significant. It seems unlikely that this is possible using our data set though as beyond nine months of maintenance clinical decision making comes into play and appointments are extended purposefully; thus introducing a major confounding factor beyond this point. What was highly significant however was the finding that increased variability in follow up appointments, as opposed to an increase in the mean, resulted in worse outcomes ($p < 0.01$) and this might be important in advising patients and those planning nARMD services of the importance of reducing variation, perhaps at the cost of an increase in the mean follow up interval. This is however the first set of published figures to demonstrate this though and further work here would be desirable before concrete recommendations can be made.

The suggestion that smokers, whilst faring no worse after a year of treatment compared to their ex-smoking or non-smoking counterparts, present almost six years earlier is striking. We believe that this has not been demonstrated thus far in a real-world health setting and might be important in advising future smoking cessation campaigns.

The observation that patients undergoing increased numbers of treatments had statistically significantly worse results ($p = 0.05$) may be because those with the most aggressive disease would tend to require more injections of ranibizumab, although interestingly there was no correlation between membrane morphology and acuity outcomes. It is also surprising perhaps that social deprivation did not have any affect on visual acuity outcomes, although we are planning to examine this area in more detail in future studies.

Perhaps the most striking statistical finding is that of all the data analysed in this large study the R^2 was only 0.44, indicating that the parameters analysed only accounted for 44% of the observed variation in acuity outcomes. It is notable that this study did not include such ocular co-morbidities as the presence of cataract, glaucoma or any systemic medical condition that could affect sight and that the reason for appointment delay, being booking system or patient centred, was not a part of the dataset. Patients who serially did not attend were also included, provided they attended at least once more at nine months from the completion of the loading phase.

Perhaps the best way of ascertaining whether an increase in mean follow up interval truly did affect visual acuity outcomes might be to set up a prospective study randomly allocating patients to different fixed follow up schedules, keeping note of all other ocular and systemic co-morbidities from the beginning, following patients up for more than nine months. The causes of variation in visual acuity outcomes between different patients attending nARMD clinics though does seem to be demonstrably more complex than perhaps previously thought and ascertaining as many of these variables as possible to provide a tailored follow up service for each patient might one day be the most effective solution to the current stresses affecting macular services.

Conflict of interest

The authors declared that there is no conflict of interest.

References

1. Boyer DS, Antoszyk AN, Awh CC, Bhisitkul BB, Shapiro H, Acharya NR. Subgroup analysis of the MARINA Study of ranibizumab in neovascular age-related macular degeneration. *Ophthalmology* 2007;**114**:246–52.
2. Brown DM, Michels M, Kaiser PK, Heier JS, Sy JP, Ianchulev T. Ranibizumab versus verteporfin photodynamic therapy for neovascular age-related macular degeneration: two year results of the ANCHOR Study. *Ophthalmology* 2009;**116**:57–65.

3. Rosenfeld PJ, Brown DM, Heier JS, Boyer DS, Kaiser PK, Chung CY, et al. Ranibizumab for neovascular age related macular degeneration. *N Engl J Med* 2006;**355**:1419–31.
4. Regillo CD, Brown DM, Abraham P, Yue H, Ianchulev T, Schneider S, et al. Randomised, double-masked, sham-controlled trial of ranibizumab for neovascular age-related macular degeneration: PIER Study. *Am J Ophthalmol* 2008;**145**:239–48.
5. Owen CG, Fletcher AE, Donoghye M, Rudnicka AR. How big is the burden of visual loss caused by age related macular degeneration in the United Kingdom? *Br J Ophthalmol* 2003;**87**:312–7.
6. Brown MM, Brown GC, Stein JD, Roth Z, Campanella J, Beauchamp GR. Age-related macular degeneration: economic burden and value-based medicine analysis. *Can J Ophthalmol* 2005;**40**:277–87.
7. Royal College of Ophthalmologists. *Age-related macular degeneration guidelines for management*. London: Royal College of Ophthalmologists; 2009.
8. National institute for health and clinical excellence. *Ranibizumab and pegaptanib for the treatment of age related macular degeneration*. London (UK): National Institute for Health and Clinical Excellence; 2008.
9. Lalwani GA, Rosenfeld PJ, Fung AE, Dubovy SR, Michels S, Feuer W, et al. A variable-dosing regimen with intravitreal ranibizumab for neovascular age-related macular degeneration: year 2 of the PrONTO Study. *Am J Ophthalmol* 2009;**148**:43–58.
10. Gupta B, Adewoyin T, Patel SK, Sivaprasad S. Comparison of two intravitreal ranibizumab treatment schedules for neovascular age-related macular degeneration. *Br J Ophthalmol* 2011;**95**:386–90.
11. Biarnes M, Mones J, Villalbi JR, Arias L. As-needed treatment with ranibizumab 0.5 mg in patients with neovascular age-related macular degeneration. *Eur J Ophthalmol* 2011;**21**:282–9.
12. Gupta OP, Shienbaum G, Patel AH, Fecarotta C, Kaiser RS, Regillo CD. A treat and extend regimen using ranibizumab for neovascular afe-related macular degeneration clinical and economic impact. *Ophthalmology* 2010;**117**:2134–40.
13. Chan D. Cigarette smoking and age-related macular degeneration. *Optom Vis Sci* 1998;**75**:476–84.
14. Chakravarthy U, McKay GJ, de Jong PT, Rahu M, Seland J, Soubrane G, et al. ARMS2 increases the risk of early and late age-related macular degeneration in the European Eye Study. *Ophthalmology* 2013;**120**:342–8.
15. Williams GP, Pathak-Ray V, Austin MW, Lloyd AP, Millington IM, Bennett A. Quality of life and visual rehabilitation: an observational study of low vision in three general practices in West Glamorgan. *Eye* 2007;**21**:522–7.
16. Brown GC, Brown MM, Brown HC, Kinermann S, Sharma S. The goal of value-based medicine analysis: comparability. The case for neovascular macular degeneration. *Trans Am Ophthalmol Soc* 2007;**105**:160–9.
17. Boyer DS, Heier JS, Brown DM, Francom SF, Ianchulev T, Rubio RG. A phase IIIb study to evaluate the safety of ranibizumab in subjects with neovascular age-related macular degeneration. *Ophthalmology* 2009;**116**:1739–41.
18. Martin DF, Maguire MG, Fine SL, Ying GS, Jaffe GJ, Grunwald JE, et al. Ranibizumab and bevacizumab for treatment of neovascular age-related macular degeneration: two-year results. *Ophthalmology* 2012;**119**:1388–98.
19. Williams TA, Blyth CP. Outcome of ranibizumab treatment in neovascular age related macular degeneration in eyes with baseline visual acuity better than 6/12. *Eye* 2011;**25**:1617–21.