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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.