United Kingdom Neovascular Age-Related Macular Degeneration Database.

Report 6: Time to Retreatment after a Pause in Therapy. Outcomes from 92,976 Intravitreal Ranibizumab Injections.

Authors

Krishnappa C Madhusudhana[1], MD, FRCS, FRCOphth, Aaron Y Lee[2,3,4]* MD, MSCI, Pearse A Keane[2,3], MD, Usha Chakravarthy[5], MD, PhD, Robert L Johnston[6], FRCOphth, Catherine A Egan[2,3], FRANZCO, Dawn Sim[2,3], FRCOphth, Javier Zarranz-Ventura[2,3,6], MD, PhD, Adnan Tufail[2,3], MD, FRCOphth, Martin McKibbin[7], FRCOphth on behalf of the UK AMD EMR Study Group

* Krishnappa C Madhusudhana and Aaron Y Lee are joint first authors.

Affiliations

1. Medical Retina Service, Hull and East Yorkshire Hospitals NHS Trust, Hull, United Kingdom.

2. NIHR Biomedical Research Centre at Moorfields Eye Hospital and the Institute of Ophthalmology, University College London, United Kingdom.

3. Medical Retina Service, Moorfields Eye Hospital NHS Foundation Trust, London, England, United Kingdom.

4. Department of Ophthalmology, University of Washington, USA.

5. Centre for Vascular & Vision Sciences, Queen's University, Belfast, United Kingdom.

6. Medical Retina Service, Gloucestershire Hospitals NHS Foundation Trust, Cheltenham General Hospital, Cheltenham, United Kingdom.

7. Eye Clinic, St. James's University Hospital, Leeds Teaching Hospitals NHS Trust, Leeds, United Kingdom.

Corresponding author

Martin McKibbin, FRCOphth, Eye Clinic, St. James's University Hospital, Beckett Street, Leeds, LS9 7TF, United Kingdom. Email: Martin.McKibbin@nhs.net

List of UK AMD EMR study group

Adnan Tufail, MD, FRCOphth; Robert Johnston, FRCOphth; Toks Akerele, MD, FRCOphth; Martin McKibbin, FRCOphth; Louise Downey, MBChB, FRCOphth; Salim Natha, MBChB, FRCOphth; Usha Chakravarthy, MD, PhD; Clare Bailey, MD, FRCOphth; Rehna Khan, MBChB; Richard Antcliff, FRCOphth; Stewart Armstrong, FRCOphth; Atul Varma, MSCOphth; Vineeth Kumar, FRCSEd(Ophth); Marie Tsaloumas,MBBS, FRCOphth; Kaveri Mandal, FRCSEd(Ophth); Wen Xing, MSc; and Catey Bunce, DSc.

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Abbreviations and Acronyms

AMD, age-related macular degeneration; CATT, Comparison of Age-Related Macular Degeneration Treatment Trials; EMR, electronic medical record; ETDRS,

Early Treatment Diabetic Retinopathy Study; IVAN, Inhibit VEGF in Age-Related Choroidal Neovascularisation; logMAR, logarithm of the minimum angle of resolution; nAMD, neovascular age-related macular degeneration; NHS, National Health Service; OCT, optical coherence tomography; PRN, pro re nata; TFI, treatment-free intervals; UK, United Kingdom; VA, visual acuity; VEGF, vascular endothelial growth factor

SUBTITLE

The likelihood of retreatment with ranibizumab for neovascular age-related macular degeneration reduces as the time without treatment increases. Nearly a third of eyes require retreatment within the next 12-months despite remaining injection-free for 12-months.

ABSTRACT

Background/aims: To study the time to retreatment in eyes with neovascular age-related macular degeneration (nAMD) that had been treatment-free for intervals of 3, 6, 9 and 12 months during the maintenance phase of ranibizumab therapy within the UK National Health Service.

Methods: In this multicentre national nAMD database study, structured data were collected from 14 centres (involving 12,951 eyes receiving 92,976 ranibizumab injections). Patients were treated with 3 fixed, monthly injections in a loading phase of treatment, followed by *pro-re-nata* retreatment regimen in a maintenance phase. Eyes with a treatment-free interval (TFI) of 3, 6, 9, or 12 months in the maintenance phase were identified and the time to retreatment after these TFIs was determined.

Results: The time to retreatment for the 20th and 50th centile was 0.58/2.54 months after a 3-month TFI, 2.07/9.62 months after a 6-month TFI, 3.69/15.84 months after a 9-month TFI and 5.90/22.49 months after 12-month TFI. Following a TFI of 3, 6, 9 and 12 months, 68%, 44%, 31% and 21% of eyes required retreatments after an additional 6 months of follow-up respectively. Similarly, after 12-months of follow-up, 77%, 56%, 43% and 34% of these eyes required retreatment.

Conclusions: This study provides times to retreatment in eyes with nAMD that have been treatment-free for intervals of 3-12 months and demonstrates the likelihood of repeat therapy within the next year, even after a treatment-free interval of 12 months. These outcomes can help plan appropriate follow-up intervals for patients who have been treatment-free for intervals of up to 12 months.

INTRODUCTION

With the approval of ranibizumab for neovascular AMD (nAMD) in 2008 by the UK National Institute of Health and Clinical Excellence (NICE), ranibizumab has been used exclusively in the National Health Service (NHS), until the recent emergence of aflibercept. In accordance with the original European product licence, ranibizumab was administered in routine clinical practice as a loading phase of 3 injections, given at monthly intervals, followed by as needed or *pro re nata* (PRN) regimen if active disease was detected at regular assessment visits, based on visual acuity, slit lamp examination and retinal imaging with optical coherence tomography (OCT), a regimen largely based on the Prospective Optical Coherence Tomography imaging of patients with Neovascular AMD Treated with Intra-ocular Ranibizumab (PrONTO) study.[1,2] Although the Avastin (bevacizumab) for choroidal neovascular age-related macular degeneration trial (ABC Trial), Comparison of Age-Related Macular Degeneration Treatments Trials (CATT) and Inhibit VEGF in Age-Related Choroidal Neovascularization (IVAN) trials have subsequently shown that this approach gives comparable outcomes, no real-world studies have achieved the outcomes demonstrated by clinical trials.[3-11]

There is a paucity of high-quality data regarding the likelihood of retreatment with ranibizumab in eyes that have remained treatment-free for variable period of time. It is essential to evaluate this to plan the frequency of follow-up in such patients and help reduce the demand on healthcare services, which are already overburdened, without compromising the quality of care.

Appropriately designed and used electronic medical record (EMR) systems offer the ability to capture and pool a large proportion or even all treated patient outcomes to assess the real-life clinical outcomes. They have the benefit that all data are collected as a by-product of routine clinical practice, often in the context of paperless clinics and, in the UK, have been designed to mandate capture of a predefined minimum dataset. Therefore, they approximate a clinical trial electronic case report form. The UK Neovascular AMD database project was developed to collate data from multiple centres using EMRs in routine clinical practice to understand real-world outcomes of ranibizumab therapy for nAMD. The aims of this specific report were to look at the time to retreatment in eyes with nAMD that have remained treatment-free during the maintenance phase of ranibizumab therapy (after three fixed monthly injections)and to assess their visual outcome.

MATERIALS AND METHODS

Study Design

Two EMR systems from different companies in the UK are known to collect nAMD treatment and assessment data. Sites known to make comprehensive use of these systems were contacted; however, only sites using 1 EMR system met the deadline given with regard to permissions to extract data. All data therefore were derived from 1 supplier (Medisoft Ophthalmology, Medisoft Limited, Leeds, UK). The lead clinician and Caldicott Guardian (who oversees data protection) at each centre gave written approval for the data extraction. Patient identifiers were stripped out completely and site and clinician data were pseudo-anonymised; on this basis, an ethics committee determined that formal ethics approval was not required. Further details on data entry into EMR have been published in our previous papers.[12-14]

This study was conducted in accordance with the declaration of Helsinki and the UK's Data Protection Act.

Settings

Fourteen NHS hospitals that deliver ranibizumab AMD treatment services in England and Northern Ireland submitted data to this study. Following NICE approval for the use of ranibizumab for nAMD in the NHS in August 2008, all sites used this drug exclusively, although before this date, some sites offered treatment with bevacizumab. The study was initiated on February 1, 2012 and data extraction was performed by April 2, 2012.

Variables

Analysis was restricted to eyes that had remained treatment-free for variable durations (3, 6, 9 and 12 months) during the maintenance phase of ranibizumab treatment following three fixed monthly injections (loading phase). The treatment-free interval could start anytime during this maintenance phase. Patients undergoing combined therapies or having prior bevacizumab in either eye were excluded, as were patients who had received prior laser based therapies.

Although this study itself is retrospective, the structured dataset used for the management of nAMD in the EMR system was defined and set up before the date of first data collection in this study. This contrasts with a conventional retrospective chart review with unstructured data and is more akin to the electronic case report form used in clinical trials, but with the data captured as a by-product of routine clinical care.

Data Sources and Measurements

In this report, the best-measured visual acuity (VA) was the best VA with refraction or habitual correction, pinhole, or both as measured on an Early Treatment Diabetic Retinopathy Study (ETDRS) chart. The vast majority of sites measured VA with habitual correction rather than best-corrected refracted VA at all time points. Analysis for eyes with very low VA was undertaken by substituting counting fingers, hand movements, and light perception with 2.0, 2.3, and 2.7, respectively.[15]

Follow-up

All patients received a loading phase of 3 intravitreal injections of 0.5 mg ranibizumab (Lucentis, Novartis Pharma AG, Basel, Switzerland) given at monthly intervals, followed by PRN treatment if active disease was detected at scheduled assessment visits.

During the maintenance phase, some centres ran a 2-stop service (assessment and treatment on different days). For ease of analysis and to allow standardised comparison of follow-ups between centres, follow-ups within a ± 2-week block were regarded as single visit.

All eyes had OCT examinations at practically every visit. Many sites did not perform OCTs at the time of the second and third injection visits (of the loading phase) because the patients were definitely receiving injections, but thereafter, OCT assessments were performed at every intended monthly follow-up.

'Retreatment' with ranibizumab after a certain treatment-free period was left to the discretion of individual clinicians as per The Royal College of Ophthalmologists' guidance which recommends retreatment if patients showed any sign of disease activity. Activity was denoted by new or persistent retinal, subretinal, or sub-RPE fluid or haemorrhage as determined clinically and/or on OCT, lesion growth on FFA (morphological), and/or deterioration of vision (functional).[16]

Statistical Methods

Data were extracted from the EMR for patients who had received at least 1 intravitreal injection of ranibizumab for nAMD. STATA software version 11 (Stata Corp, College Station, TX), SPSS software version 19 (SPSS, Inc, Chicago IL) were used to generate basic demographics and outcomes (AT, WX). To check for errors in combining and reshaping large datasets, primary outcomes were verified in statistical software databases separately by the two of the authors (AT, AL) and statisticians (CB, WX). R software (version 3.0.2) and Perl (version v5.16.2) were used to combine, clean, reshape, merge, recode, and analyse data (AL) used in the primary analysis in this manuscript.

RESULTS

Participants

Data were extracted for 12,951 eyes of 11,135 patients receiving a total of 92,976 ranibizumab injections (Fig 1). The mean age of patients in the database at the time of first ranibizumab injection was 78.9 years (range, 55–108 years) for those who received unilateral treatment only and 79.5 years (range, 55–98 years) for patients who received bilateral treatment at any time during follow-up. The percentage of

females was significantly higher in bilateral than in unilateral disease (68.7% vs. 62.5%; $P < 0.001$).

There were 8,184 eyes that were treatment-free for at least 3 months. Similarly there were 5,134 eyes, 3,522 eyes and 2,452 eyes that were treatment-free for at least 6 months, 9 months and 12 months respectively.

The OCT data was not analysed as it was out of scope of this study.

Time to retreatment after a pause in therapy

The Kaplan Meier survival analysis shows the time to retreatment after a pause in treatment (Fig 2). The time to retreatment for the 20th centile was 0.58 months in eyes with 3-month treatment free interval (TFI), 2.07 months in eyes with 6-month TFI, 3.69 months in those with 9-month TFI and 5.90 months in eyes with 12-month TFI.

Similarly, the time to retreatment for the 50th centile was 2.54 months in the 3 month TFI eyes, 9.62 months in the 6 month TFI eyes, 15.84 months in the 9 month TFI eyes and 22.49 months in the 12 month TFI eyes.

Retreatment was noted to occur earlier in eyes that had shown improvement or stabilisation of vision with ranibizumab treatment (‘better eyes’ and ‘same vision eyes’), when compared to baseline visual acuity prior to loading phase (Fig 3).

Table 1.

	Proportion of eyes requiring retreatment by given time point			
	At 3 months follow-up	**At 6 months follow-up**	**At 9 months follow-up**	**At 12 months follow-up**
TFI 3 months	54%	68%	74%	77%
TFI 6 months	30%	44%	51%	56%
TFI 9 months	20%	31%	37%	43%
TFI 12 months	14%	21%	28%	34%

Table 1 depicts the percentages of eyes that required retreatment with ranibizumab after remaining treatment-free for variable periods. Following a TFI of 3, 6, 9 and 12 months, 68%, 44%, 31% and 21% of eyes required retreatments after further 6-months of follow-up respectively. Similarly, after 12-months of follow-up, 77%, 56%, 43% and 34% of eyes from the same groups required retreatment.

Visual Outcome

The mean visual acuities at the start of the TFIs and before and after retreatment are shown in Table 2. At the time that retreatment was initiated there was a decrease in mean VA of 2.93 to 4.25 letters. Although the visual acuity improved with retreatment, it did not recover to that recorded at the beginning of TFI, with a mean loss of 1.83 to 3.23 ETDRS letters.

Table 2.

	Mean visual acuity (ETDRS letters)		
	At the beginning of treatment-free period	**At the time of retreatment**	**At first visit after retreatment**

TFI 3 months	57.26	54.33	55.43
TFI 6 months	56.90	53.24	54.32
TFI 9 months	56.47	52.29	53.44
TFI 12 months	57.50	53.25	54.27

DISCUSSION

This is the largest study thus far reported in the literature to focus on the likelihood of retreatment in eyes with nAMD that have remained treatment-free during the maintenance phase of treatment with intravitreal ranibizumab therapy when using a PRN posology. The study provides real-world data that highlight some important findings: (1) Differences in time to retreatment in eyes with variable treatment-free intervals, with eyes remaining treatment-free for prolonged periods having longer intervals before requiring retreatments; (2) Risk of reactivation/retreatment irrespective of whether the eye has been injection-free for 3, 6, 9 or 12 months.

In our study, we found that the likelihood of retreatment reduces as the time without treatment increases. Following a treatment-free interval of 3, 6, 9 and 12 months, 68%, 44%, 31% and 21% of eyes required retreatments after further 6-months of follow-up respectively. Similarly, after 12-months of follow-up, 77%, 56%, 43% and 34% of eyes from the same groups required retreatment. It is interesting to note that despite remaining treatment-free for 12-months, nearly a third of eyes required retreatment within the next year.

Our results showed that the time to retreatment for the 20th centile (i.e. 1 in 5 eyes requiring retreatment at that time point) was 0.58 months in the 3-month, 2.07 months in the 6-month, 3.69 months in the 9-month and 5.90 months in the 12-month treatment free groups. This information is useful in guiding clinicians in how to plan less frequent follow-ups of patients who have remained treatment-free for longer duration or in their choice of retreatment posology. Once eyes remain treatment-free for six months, 2-monthly follow-ups appear reasonable. Similarly, 3-monthly follow-ups may be reasonable once eyes remain treatment-free for 9 months.

In the overburdened NHS setting, where there are acute capacity issues in medical retina clinics, patients whose treated eye (s) remain injection-free for 12 months or more may not need regular review in dedicated one-stop nAMD clinic (where assessment and injections, if required, are given at the same visit) but less frequent review in a 2-stop monitoring retina clinics appears reasonable. This could potentially allow the clinicians to reduce the burden on eye clinics and plan the nAMD workload more efficiently and help guide future PRN and treat and extend treatment intervals and strategies.

However, reduction in the frequency of follow-up visits will also reduce the opportunities to detect disease early in the fellow, usually better-seeing, eye.[13] Since there is frequent involvement of fellow eyes the potential for synchronizing both eye treatments may limit the ability to extend visits.[13] One must cautiously consider the trade-off between the implications of continued follow-ups on eye clinics and the risk of reactivation.

Our real-world data suggest that eyes that have remained injection-free for intervals of 3-12 months suffer a decline in visual acuity with disease reactivation. Although further treatment leads to some visual recovery, the average decrease in acuity was 1.83 to 3.23 ETDRS letters, as compared to visual acuity at the beginning of injection-free period. This may reflect the chronic and inexorable nature of nAMD, as also reported in the SEVEN-UP study, in addition to a degree of under or sub-optimal treatment in the real-world outside clinical trial conditions.[17]

Previous studies have reported visual and socioeconomic benefits with a 'treat-and-extend' regimen (TER) in the management of nAMD.[7, 18] In TER, patients are treated at each visit regardless of disease activity, with the time between visits extended gradually if there is no evidence of active nAMD. Rayess et al, have recently demonstrated that patients treated with TER showed visual outcomes comparable to ANCHOR and PrONTO studies at 24 months of follow-up with 50% fewer examinations of patients.[18] In our study, nearly all of the maintenance phase treatments were reactive and driven by disease activity as opposed to proactive treatment in TER. This was standard practice up to the time of data extraction in 2012. Considering the higher retreatment rates in eyes that have remained injection-free for shorter intervals, it appears that TER may have a role in patients who have remained injection-free for six months or less on PRN regimen. However, as the number of retreatments is less when the patients remain injection-free for longer intervals, it appears that TER may lead to excess treatments in such patients compared to PRN. Hence, a switch to TER may not be appropriate for eyes that have been stable for more than six months.

The strengths of this study include the large sample size, the collection of a standardised minimum dataset as mandated by the use of an EMR, the reflection of routine clinical practice, and the large number of centres involved. Our study reflects the real-world practice in the UK and is of relevance to many sites worldwide. A weakness of this study is the loss to follow-up of significant numbers of patients over time, as is inevitable in a real-world clinical setting, but this is taken into account using Kaplan-Meier analysis. Some of the patients may also have been discharged from regular follow-up. The treatment-free groups were not exclusive and also we cannot exclude treatment with a TER approach during the follow-up, although this was not a common practice before the data for this paper was collected in 2012.

In conclusion, this study has shown that, with a longer treatment-free interval, eyes with nAMD are less likely to be retreated with ranibizumab when a PRN approach is adopted. This information can help clinicians to plan the appropriate follow-up interval for eyes with nAMD and help to reduce the load on overburdened eye clinics. One should also bear in mind that nearly a third of eyes that have remained injection-free for 12 months require retreatment within the next 12 months, suggesting that ongoing follow-up is still required.

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Contributorship Statement

All authors have given final approval of this version to be published. AT, MM, RLJ and UC participated in study codesigning, data collection and screening, data-analysis and evidence synthesis, and revising the manuscript. KCM and AYL participated in literature search, data-analysis and evidence synthesis and drafting the manuscript. PK, CE, DS, JZ participated in study codesigning, data collection and revising the manuscript.

Figure legends

Figure 1. Consolidated Standards of Reporting Trials-style diagram showing the patients and eyes treated in the study. EMR = electronic medical record; nAMD = neovascular age-related macular degeneration; VEGF = vascular endothelial growth factor.

Figure 2. A, B, C and D. Kaplan Meier survival analysis in eyes that have remained treatment-free for 3 months, 6 months, 9 months and 12 months.

Figure 3: Kaplan Meier survival analysis showing time to retreatment in eyes presenting with same, better or worse vision as compared to baseline visual acuity.

Table legends

Table 1: Proportion of eyes requiring retreatment after a certain treatment-free interval (TFI).

Table 2: Change in mean visual acuity (ETDRS letters).