Moorfields AMD database report 2: fellow eye involvement with neovascular age-related macular degeneration

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ABSTRACT

Background/Aims Neovascular age-related macular degeneration (nAMD) is frequently bilateral, and previous reports on 'fellow eyes' have assumed sequential treatment after a period of treatment of the first eye only. The aim of our study was to analyse baseline characteristics and visual acuity (VA) outcomes of fellow eye involvement with nAMD, specifically differentiating between sequential and non-sequential (due to macular scarring in the first eye) antivascular endothelial growth factor treatment and timelines for fellow eye involvement.

Methods Retrospective, electronic medical record database study of the Moorfields AMD database of 6265 patients/120 286 single entries with data extracted between 21 October 2008 and 9 August 2018. The data set for analysis consisted of 1180 sequential, 807 non-sequential and 3410 unilateral eyes.

Results Mean VA (ETDRS letters±SD) of sequentially treated fellow eyes at baseline was significantly higher (63±13), VA gain over 2 years lower (0.37±14) and proportion of eyes with good VA (≥70 letters) higher (46%) than the respective first eyes (baseline VA 54±16, VA gain at 2 years 5.6±15, percentage of eyes with good VA 39%). Non-sequential fellow eyes showed baseline characteristics and VA outcomes similar to first eyes. Fellow eye involvement rate was 32% at 2 years, and median time interval to fellow eye involvement was 71 (IQR: 27–147) weeks.

Conclusion This report shows that sequentially treated nAMD fellow eyes have better baseline and final VA than non-sequentially treated eyes after 2 years of treatment. Sequentially treated eyes also had a greater proportion with good VA after 2 years.

INTRODUCTION

Anti-vascular endothelial growth factor (VEGF) therapy has revolutionised the treatment of neovascular age-related macular degeneration (nAMD). Three anti-VEGF drugs, ranibizumab, aflibercept and bevacizumab (off-licence), form the mainstay of treatment and the former two received approval from the Food and Drug Administration in 2006 and 2011, respectively. The pivotal randomised controlled trials (RCTs) that led to the approval of these agents only included one eye per patient as a means of preventing bias due to correlation between eyes.[1 2] This is a necessary step in RCTs, as not accounting for this effect can lead to overestimation of precision and a falsely low p value.[3] However, this systematically excludes eyes of patients who subsequently develop nAMD in their fellow eye. Yet from a patient's perspective, vision-related quality of life is not wholly dependent on the course of visual acuity (VA) in the first treated eye.[4] Legal requirements largely focus on the VA of the better seeing eye. For example, in the UK, the VA standard for driving is 20/40 and the limit for obtaining a certificate of severe sight impairment is 20/400 (tested binocularly or in the better seeing eye).[5 6] Additionally, patients with bilateral nAMD have functional impairments that lead to a high socioeconomic burden.[7–9]

Data on treatment of fellow eyes, specifically sequentially treated fellow eyes, have been reported in small retrospective studies and in one large multicentre electronic medical record (EMR) report.[10–13] These studies concluded that fellow eyes commenced treatment with a higher baseline VA in comparison with the first treated eyes. In addition, they had a smaller gain in VA over time due to the relatively higher baseline VA, that is, a ceiling effect. However, these studies do not account for non-sequentially treated fellow eyes, that is, eyes starting treatment for nAMD in fellow eyes with an untreated first eye (eg, due to the development of nAMD in the first eye before anti-VEGF approval or late presentation at first eye involvement). Given that involvement of the fellow eye has a substantial impact on vision-related quality of life, accounting for patients who already have poor vision from macular scarring in their first eye clearly is important.[14]

The EMR database at Moorfields Eye Hospital National Health Service (NHS) Foundation Trust, London, UK, represents an ideal source to explore the unanswered questions on fellow eye nAMD outcomes.[15] An EMR was initiated in October 2008, and its successor, OpenEyes, was implemented in September 2012. Subsequently, data from both systems were merged into the current centralised repository, the data warehouse. We have created a data set from this which represents, to our knowledge, the largest single-centre cohort of patients receiving treatment for neovascular AMD in the world. This database consists of over 6000

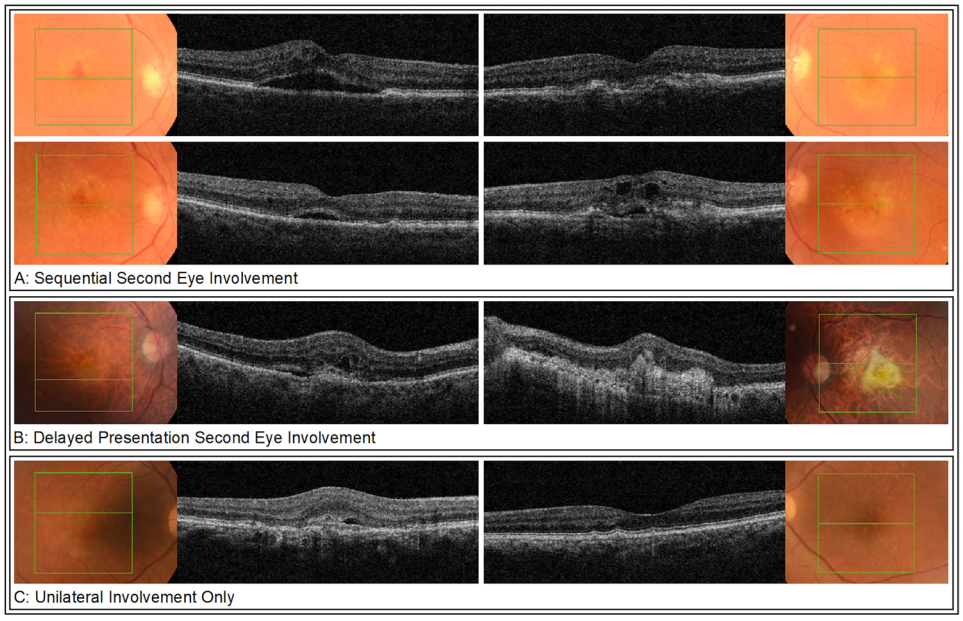

Figure 1 Representative fundus photographs and OCT images for each of the groups at involvement of the respective eye(s). Sequential treatment fellow eye involvement (A) of an 83-year-old man. Top row shows findings at first eye involvement: neovascular AMD with intraretinal haemorrhage, intraretinal fluid and subretinal fluid on OCT in the right eye, and early dry AMD in the left eye. One month later, new neovascular changes with intraretinal and subretinal fluid on OCT were found incidentally in the left eye, indicating second eye involvement (bottom row). Non-sequential treatment fellow eye involvement (B) of an 86-year-old man. Examination at first presentation revealed neovascular AMD in his right eye with intraretinal and subretinal fluid on OCT while in the left eye, a disciform scar with a visual acuity of hand movements was present. Unilateral involvement only (C) of an 86-year-old man. Examination at baseline showed neovascular AMD in the right eye with predominantly subretinal fluid on OCT and early AMD with drusen in the left eye. Until time of data extraction, there has been no progression to neovascular AMD in the left eye. AMD, age-related macular degeneration; OCT, optical coherence tomography.

patients with over 120 000 single entries and has undergone extensive manual data cleaning. Key elements that distinguish its quality compared with others include the completeness of data due to the mandatory input of relevant fields such as VA, the consistency of VA measurements using ETDRS letters, the lack of requirement to merge data from different sites and systems, the standardised treatment scheme following national guidelines and the ability to directly access the raw imaging data from each patient visit (online supplementary figure 1).[16 17]

The aim of this study was to analyse baseline characteristics and VA outcomes of fellow eyes (sequentially and non-sequentially treated) undergoing anti-VEGF therapy for nAMD, as well as the timelines for fellow eye involvement. We compared fellow eye outcomes with those of the respective first eyes of sequentially treated fellow eyes.

METHODS

Study population

Data for this retrospective, comparative, non-randomised cohort study was extracted from the Moorfields AMD Database, consisting of 6265 patients with 120 286 single entries acquired between 21 October 2008 and 9 August 2018. Extraction criteria were ≥1 ranibizumab or aflibercept injection, entry of 'AMD' in the diagnosis field of the EMR. Exclusion criteria were unknown date of first injection, missing VA at baseline, any treatment outside of routine clinical care at Moorfields before the first recorded injection in the database, including pegaptanib, previous laser or photodynamic therapy, and bevacizumab, details for which are shown in online supplementary figure 2 and have been reported in detail elsewhere.[15] The rationale for exclusion of other treatment modalities was the goal of analysing to-date treatment of care and specifically, exclusion of bevacizumab was done because in the NHS, neovascular AMD is generally treated with the licensed therapeutics ranibizumab or aflibercept and not with the off-label bevacizumab.[18 19]

The complete data set for analysis of the current study consisted of the 6577 eyes/5397 patients (online supplementary figure 2). Of these, 1180 patients had sequentially treated fellow eye involvement, while 807 eyes were non-sequentially treated fellow eyes (ie, untreated macular scarring in their respective first eyes). The 3410 unilateral/singular eyes (only treated in one eye over the observed period without advanced neovascular AMD in their fellow eye) together with the sequential first eyes were used for the survival analysis of fellow eye involvement. Definition of sequential involvement was a time interval of ≥28 days between the first injection of first and fellow eye over the course of the observed time period. The presence of a macular scar was manually graded in fundus photographs and optical coherence tomography (OCT) (Topcon 3D OCT, Topcon, Japan) scans. An exemplar case for each group is shown in figure 1.

Efforts to minimise bias

To minimise survival bias/loss to follow-up (LTFU), all first and fellow eyes that did not complete follow-up were manually validated for the correct date of first injection. All unilateral eyes (1520) underwent manual verification for the presence of a macular scar secondary to end-stage AMD in the fellow eye. We chose not to substitute missing values, but clearly show results for cohorts that complete a certain follow-up period. Visual acuities below measurable ETDRS letters were converted to logMAR 2.0/–15 letters, logMAR 2.3/–30 letters and logMAR

Table 1 Baseline visual acuity (VA) and VA outcomes of first and fellow eyes in sequential treatment fellow eye involvement and non-sequentially treated fellow eyes

	Sequential treatment fellow eye involvement				
Baseline characteristics n=number of eyes	**First eyes n=1180**	**P (paired) first/fellow eyes**	**Fellow eyes n=1180**	**P/adjusted p sequential/non-sequential fellow eyes**	**Non-sequential treatment fellow eye involvement, n=807**
Mean VA (letters)±SD	54±16	<0.001	63±13	<0.001	53±16
% of eyes with VA ≥20/40	21.5	<0.001	42.1	<0.001	21.4
% of eyes with VA ≤20/200	18.1	<0.001	6.2	<0.001	20.1
One-year outcomes n=number of eyes	**First eyes n=1094**	**P (paired) first/fellow eyes**	**Fellow eyes n=961**	**P/adjusted p sequential/non-sequential fellow eyes**	**Non-sequential treatment fellow eye involvement, n=668**
Mean VA change (letters)±SD	5.2±15	<0.001	2.4±12	<0.001	4.6±15
% of eyes with VA ≥20/40	37.9	<0.001	50.5	<0.001	36.1
% of eyes with VA ≤20/200	17.0	<0.001	8.3	<0.001	16.3
% of eyes with VA gain ≥5 letters	52.6	<0.001	42.6	0.938	47.3
% of eyes with change in VA <15 letters	69.4	<0.001	81.4	0.006	72.9
Mean injection number ±SD	7.7±2.1	0.503	7.7±1.9	0.740	8.0±1.7
Two-year outcomes n=number of eyes	**First eyes n=1005**	**P (paired) first/fellow eyes**	**Second eyes n=781**	**P/adjusted p sequential/non-sequential fellow eyes**	**Non-sequential treatment fellow eye involvement, n=534**
Mean VA change (letters)±SD	5.6±15	<0.001	0.37±14	<0.001	3.4±19
% of eyes with VA ≥20/40	38.9	<0.001	46.1	0.001	36.9
% of eyes with VA ≤20/200	19.8	<0.001	10.4	0.008	14.4
% of eyes with VA gain ≥5 letters	51.0	<0.001	39.2	0.094	46.3
% of eyes with change in VA <15 letters	69.4	<0.001	81.4	0.005	72.9
Mean injection number ±SD	13±4.2	0.921	13±3.9	0.953	13±4

2.7/–50 letters for count fingers, hand movements and light perception, respectively.[20]

Outcome measures

The primary outcomes were analogous to the pivotal RCTs and as recommended by The International Consortium for Health Outcomes Measurement (ICHOM) AMD study group for 1 and 2 years: mean change in VA from baseline as measured using ETDRS letters, proportion of eyes gaining ≥5 letters, proportion of eyes with stable vision (change in VA <15 letters to baseline), proportion of eyes with good vision (≥20/40 or 70 letters) and proportion of eyes with poor vision (≤20/200 or 35 letters).[1 2 19 20] Secondary outcomes included the number of injections and time to involvement of fellow eyes (for survival analysis of timeline in fellow eye involvement, all baseline unilateral and first fellow eyes were included). Definitions for 1-year and 2-year outcome dates were taken from previous real-world studies as visits closest to 52 weeks and 104 weeks postbaseline date within ±8 weeks.[21 22]

Statistical analysis

The data were analysed using the statistics software R (https://www.r-project.org/; provided in the public domain by R Core team, 2017, R Foundation for Statistical Computing, Vienna, Austria). The ggplot2 package was used for plots. The eye was defined as unit of analysis. Descriptive statistics included mean±95% CI, and median, where appropriate. Differences between groups were evaluated using Mann-Whitney U test and Pearson χ^2 test. A p value of <0.05 was interpreted as statistically significant.

Data sharing statement

Depersonalised data as well as the code used for analysis for this study are openly available from the Dryad Digital Repository https://doi.org/10.5061/dryad.4mw6m906b. This should allow for both independent replication of our results and additional novel analyses. Depersonalisation was carried out through hash function anonymisation of patient identification numbers and replacement of appointment dates with follow-up days to baseline. Approval of adequate depersonalisation was obtained by Moorfields Information Governance.

RESULTS

Baseline characteristics

Of the 5397 patients starting treatment in one eye, 1180 (22%) developed fellow eye involvement, 807 (15%) were identified as non-sequentially treated fellow eye involvement, whereas 3410 (63%) were singular/unilateral eyes. Online supplementary figure 2 shows the flow chart for eyes through the analysis. Mean baseline VA was 54±16 letters for first eyes and 63±13 letters for fellow eyes in sequentially treated patients, and 53±16 letters for non-sequentially treated fellow eyes (table 1). In sequentially treated patients, fellow eyes had a significantly higher baseline VA than first eyes (p<0.001); more than 40% of fellow eyes had a VA of ≥20/40 compared with 21% of respective first eyes at baseline. Compared with non-sequentially treated fellow eyes, sequentially treated fellow eyes had higher baseline VA (p<0.001).

VA outcomes

At 1 year, mean gain in VA was 5.2±15 letters for first eyes, 2.4±12 letters for sequentially treated fellow eyes and 4.6±15

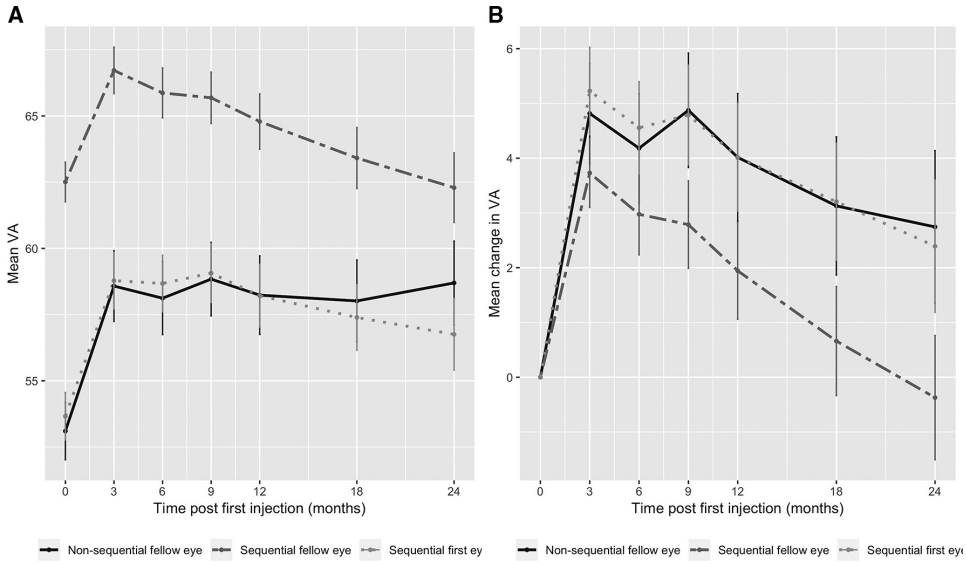

Figure 2 Mean VA from baseline (A) and change in VA (B) over time and 95% CI stratified by the different groups: first and second eyes in sequentially treated fellow eye involvement and delayed presentation fellow eyes. VA, visual acuity.

letters for non-sequentially treated fellow eyes (table 1). At 2 years, mean gain in VA was 5.6±15 letters for first eyes, 0.37±14 letters for fellow eyes in sequentially treated patients and 3.4±19 letters for non-sequentially treated fellow eyes. Fellow eyes showed a significantly lower gain in VA than first eyes and non-sequentially treated fellow eyes at 1 and 2 years ($p<0.001$). However, percentage of eyes with good vision (VA ≥70 letters/>20/40) at presentation was 42%, double that of first or non-sequential fellow eyes ($p<0.001$) and stayed at 46% at 2 years, significantly higher than both other groups ($p\leq0.001$). VA and change in VA over time are shown in figure 2. Percentages of eyes gaining vision (change in VA ≥5 letters), stable vision (change in VA <15 letters), good vision (VA ≥70 letters/>20/40) and poor vision (VA ≤35 letters/≤20/200) are shown in table 1 and figure 3.

Time to involvement of second eye

Median time interval between involvement of first and fellow eye in sequential involvement was 71 weeks (IQR: 27–147 weeks). After time point of fellow eye involvement, 1160 (98%) of first eyes continued to have anti-VEGF treatment. Chance of fellow eye involvement for eyes starting treatment in one eye was 21% (486 eyes) at 1 year and 32% (742 eyes) at 2 years, and it was dependent on age at presentation of the first eye. At 2 years, the risk of fellow eye involvement was 20% for patients younger than 60 years and 40% for patients in their eighties. Survival analysis of fellow eye involvement is shown in figure 4.

Injection frequency

Mean number of injections was 8 in all groups at 1 year and 13 at 2 years, with no significant differences between the groups (table 1).

DISCUSSION

Our study shows that fellow eye involvement of nAMD affects 20% to 40% over a 2-year period, depending on age at presentation of the first eye and that there is a significant difference in both baseline VA and VA outcomes depending on whether the respective first eye has received treatment.

Fellow eye involvement in nAMD is very common, reaching 20%–40% depending on age at presentation after 2 years in our cohort. This rate falls within the range reported in the comparison of AMD treatment trials (20.6% at 2 years) and other studies.[12 13 23–25] With demographic ageing, sight loss and blindness are predicted to increase by 2.4% from 2013 until 2050, reaching approximately 4 million people in the UK and the share of AMD is estimated to rise from 23% to 30%, representing 1.23 million people.[8] AMD is thus a major and growing contributor to healthcare burden. Considering the annual societal cost per bilaterally treated AMD patient estimated at 5300€ in 2005, the frequency of bilateral involvement makes this patient cohort an important target for vision loss prevention and healthcare cost reduction.[7]

In sequential treatment, fellow eyes have a higher baseline VA and maintain good vision over 2 years of treatment despite the absence of an initial gain in VA comparable with first eyes. This ceiling effect has been well-described and implies a rationale for earliest possible detection and treatment of neovascular changes in AMD.[13 16] Example A (figure 1) reflects this fellow eye advantage, in which neovascular AMD in the fellow eye was detected presymptomatically and treatment was started immediately. Patients might profit from the routinely performed bilateral OCT imaging at every visit, be more vigilant of VA changes in their fellow eye while undergoing treatment for the first eye and profit from the already in-place pathway to access treatment for the fellow eye quickly. This effect has led to a discussion about strategies for early detection of nAMD and optimal interval of monitoring of AMD patients.[12 13 26] Specifically, analysis of imaging biomarkers, possibly aided by artificial intelligence, might prove to be key in risk stratification of fellow eye involvement.[27 28]

Our study demonstrates that non-sequentially treated fellow eyes do not share the typical fellow eye characteristics. They start treatment with a relatively low baseline VA and their gain in VA is higher, very similar to first eyes of sequentially treated patients. Explanations for this could be that patients with non-treatable advanced neovascular disease in the first eye are not regularly monitored or that there is systematic delay in access to treatment. This is supported by the existing lack of awareness

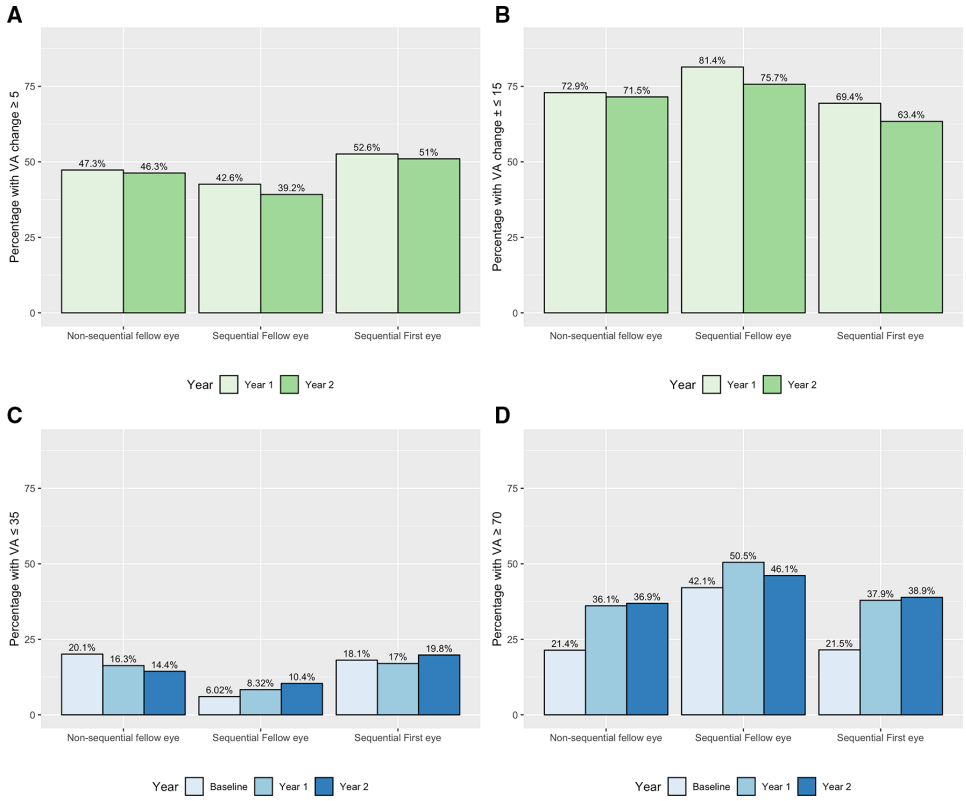

Figure 3 (A) Percentages of eyes with gain in VA (≥5 letters) at 1 and 2 years for fellow eyes in sequential/non-sequential treatment and first eyes in sequential treatment. (B) Percentages of eyes with stable vision (change in VA ≤±14 letters) for fellow eyes in sequential/non-sequential treatment and first eyes in sequential treatment. (C) Percentages of eyes with poor vision (VA ≤35 letters or 20/200) for fellow eyes in sequential/non-sequential treatment and first eyes in sequential treatment. (D) Percentages of eyes with good vision (VA ≥70 letters or 20/40) for fellow eyes in sequential/non-sequential treatment and first eyes in sequential treatment. VA, visual acuity.

of AMD and evidence of substantial delay from symptoms to treatment in the UK AMD care pathways.[29] Interestingly, in this cohort of patients, vision loss secondary to macular scarring in the first eye does not appear to result in increased vigilance that could lead to early detection of fellow eye involvement. One might argue that scarring in the first eye implies more aggressive disease causing worse VA at presentation of fellow eyes, but the similar VA gain over time to first eyes in our cohort does not support this theory. Potentially, a treatment deferral in those eyes could be caused by socioeconomic factors that were already preventing timely treatment in the first eye. Treatment start of non-sequential eyes was not skewed towards the earlier years of anti-VEGF treatment, so we believe that there was no substantial bias introduced into the data which one could hypothesise to be caused by longer referral times or awareness in the beginning of anti-VEGF era (online supplementary figure 3). To our

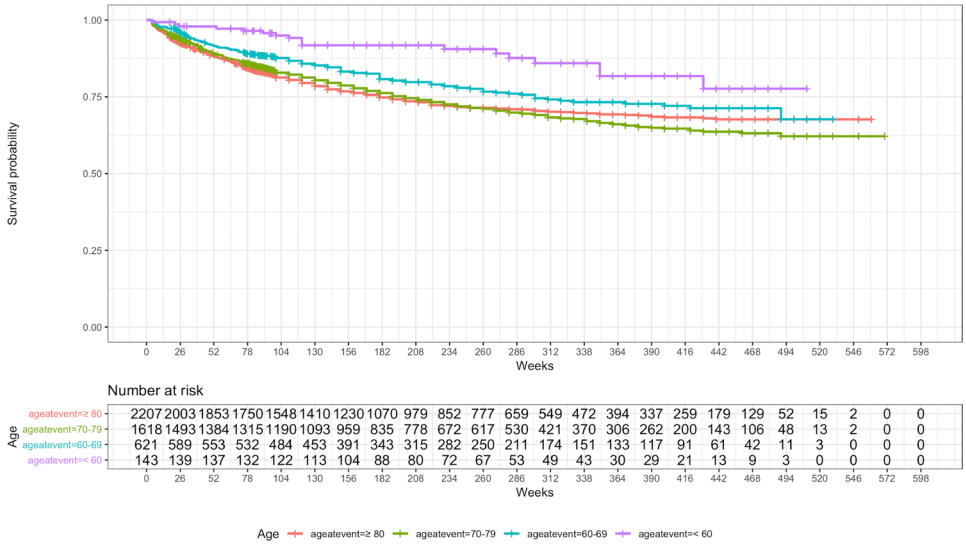

Figure 4 Survival probability for fellow eye involvement over time (weeks).

knowledge, the findings on non-sequential fellow eye involvement have not been reported before and highlight the arguably most vulnerable cohort of patients in which vision loss in their fellow and better or functionally only seeing eye will lead to significant visual impairment and socioeconomic burden.[7 8]

The limitations of this study lie within its retrospective nature based on EMR and the LTFU. Of particular significance is that LTFU can introduce survival bias. Retrospective cohort studies can be sensitive to this when subcohorts are compared in terms of averaged outcomes at given time-points, for example, VA at 1 year. Especially as these averaged metrics do not account for missing values. However, this is not the case for event-history analyses (eg, time to fellow eye involvement) as LTFU data are accounted for here. Exclusion of other treatment modalities, specifically photodynamic therapy, might lead to bias excluding polypoidal choroidal vasculopathy, but since the exact connection of this morphologic type of neovascularisation to AMD remains somewhat controversial we believe this exclusion leading to a valid pure AMD cohort treated only with to date standard of care anti-VEGF therapy.[30] We cannot exclude that previous other treatment modalities in first eyes might have an influence on fellow eye outcomes and thus, their exclusion leads to selection bias; however, the number of excluded patients is small (44 patients) and we intended to limit possible confounders to pure ranibizumab/aflibercept treatment. Another limitation of the study is that even though anti-VEGF treatment is carried out according to guidelines as shown in online supplementary figure 1, it is real-life data and we cannot speculate over exact treatment regimen. The identical mean injection number over 2 years in all groups indicates no major bias due to greatly differing treatment intensity between the groups. Strengths of this study include the large sample size for fellow eye cohorts and the quality of data coming from one single centre and a curated database with additional substantial manual cleaning. Additionally, and maybe most importantly, we encourage an open science approach to replicate our results with freely available depersonalised raw data and code.

In conclusion, this study highlights the superior visual outcomes of fellow eyes compared with first eyes in the common scenario of sequential fellow eye involvement in nAMD as well as the inferior outcomes of fellow eyes in case of untreated late stage neovascular disease in the first eye. Future research should account for those idiosyncratic subgroups of fellow eyes undergoing treatment for nAMD, as these could prove to represent the span of quality of care in AMD treatment.

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Contributors KF has drafted the manuscript and contributed to data acquisition, analysis and interpretation of data. She is accountable for all aspects of the work and has approved the final version to be published. SW and KK have contributed to design of the study, interpretation of data as well as critical revision of the manuscript. They share accountability for all aspects of the work and have approved for the final version to be published. LF, DJF and AYL have contributed to analysis and interpretation of the data and critical revision of the manuscript. They share accountability for all aspects of the work and have approved for the final version to be published. GM, GP, RC, EG and NP have contributed to acquisition of data and critical revision of the manuscript. They share accountability for all aspects of the work and have approved for the final version to be published. KB, PJP, AT and PAK have contributed to conception of the work, interpretation of data and critical revision of the manuscript. They share accountability for all aspects of the work and have approved for the final version to be published.

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Ethics approval Approval for data collection and analysis from Moorfields (ROAD17/031).

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