Title:

Evolving treatment patterns and outcomes of neovascular age-related macular degeneration over a decade

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The effect of treatment paradigm change on nAMD

This article contains additional online-only material. The following should appear online-only: Figures 1S-10S and Table 1S.

Abstract

Purpose: Management of neovascular age-related macular degeneration (nAMD) has evolved over the last decade with several treatment regimens and different medications. This study describes the treatment patterns and, importantly, visual outcomes over ten years in a large cohort of patients.

Design: Retrospective analysis of electronic health records from 27 National Health Service (NHS) secondary care healthcare providers in the UK.

Participants: Treatment-naïve patients receiving at least three intravitreal anti-vascular endothelial growth factor (VEGF) injections for nAMD in their first six months of follow-up were included. Patients with missing data for age or gender and those aged less than 55 were excluded.

Methods: Eyes with at least three years of follow-up were grouped by years of treatment initiation, and three-year outcomes were compared between the groups. Data were generated during routine clinical care between 09/2008 and 12/2018.

Main outcome measures: Visual acuity, number of injections, number of visits.

Results: A total of 15,810 eyes of 13,705 patients receiving 194,904 injections were included. Visual acuity (VA) improved from baseline during the first year, but dropped thereafter, resulting in loss of visual gains. This trend remained consistent throughout the past decade. Although an increasing proportion of eyes remained in the driving standard, this was driven by better presenting visual acuities over the decade. The number of injections dropped substantially between the first and subsequent years, from a mean of 6.25 in year 1 to 3 in year 2 and 2.5 in year 3, without improvement over the decade. In a multivariable regression analysis, final VA improved by 0.24 letters for each year since 2008, and younger age and baseline VA were significantly associated with VA at three years.

Conclusion: Our findings show that despite improvement in functional VA over the years, primarily driven by improving baseline VA, patients continue to lose vision after the first year of treatment, with only marginal change over the past decade. The data suggest that these results may be related to suboptimal treatment patterns, which have not improved over the years. Rethinking treatment strategies may be warranted, possibly on a national level or through the introduction of longer-acting therapies.

Age-related macular degeneration (AMD) is a leading cause of severe and irreversible vision loss in older individuals worldwide. [1] The management of neovascular age-related macular degeneration (nAMD) has evolved over the last decade following the publication of the pivotal phase 3 trials MARINA and ANCHOR in 2006. [2,3] Their findings resulted in the adoption of ranibizumab, an anti-vascular endothelial growth factor (VEGF) inhibitor that inhibits all isoforms of VEGF-A. Global use of this treatment modality has become prevalent, resulting in a significant reduction in legal blindness and visual impairment due to AMD. [4]

Following the VIEW phase-3 trials' publication in 2012, [5] aflibercept was added to the treatment arsenal for nAMD, along with bevacizumab,[6,7] which is used off-label. Most recently, brolucizumab has been introduced as a future treatment modality. [8]

Along with the availability of additional medications, the past decade has seen an evolution of treatment paradigms, shifting from monthly treatment in the pivotal trials [2,3] to pro re nata (PRN),[6] extended interval fixed dosing and in recent years treat-and-extend (TAE), which may or may not follow an initial year of fixed dosing. [10] This shift may have resulted in a change to the mean number of annual injections.

Despite the short-term improvement in visual acuity (VA) seen in the major clinical trials, real-life studies have shown that over the long term VA tends to decline, [11–13] a trend which was also seen in extensions of major clinical trials. [14–17] Visual loss over time in patients with nAMD may be related to suboptimal dosing, [11,16] macular atrophy [14,16,18,19] or subretinal fibrosis. [16,20]
A previous publication by our group showed a decline in vision below baseline after two years of therapy. It demonstrated the importance of baseline VA in determining potential gains in VA and what metrics may be necessary for judging what is considered a “good outcome” of therapy. [21]

Although there are limited reports on long-term real-world treatment outcomes in patients with nAMD treated with anti-VEGF injections. [13,22–25], data on any change in outcomes over the years associated with the shift in treatment paradigms is lacking.

This study aims to describe treatment outcomes over a time period spanning ten years of treatment of patients with nAMD with anti-VEGF inhibitors in a large cohort of patients from 27 centers in the UK, to understand how treatment evolution may have affected patient outcomes. This information will help guide treatment strategies to optimize treatment delivery effectiveness and cost-effectiveness in clinical practice.

METHODS

Study Design and Inclusion Criteria

Twenty-seven sites making extensive use of the Medisoft Electronic Medical Record (EMR) system (Medisoft Ltd, Leeds UK) to record ophthalmology treatments agreed to contribute electronic health record (EHR) data to studies of retinal diseases, including AMD. Data were recorded between 14/08/2006 and 12/12/2018. Length of follow-up varied depending on when

the patient was first entered into the system and for how long the patient's treatment and VA assessments were recorded.

Population

All patients recorded as receiving treatment for "neovascular AMD", "wet age-related macular degeneration", "age-related macular degeneration", "suspected neovascular AMD" were included. Patients with missing data for age and gender were excluded. Patients who were not treatment-naïve at first entry into the EMR were excluded. Patients with a previous diagnosis of diabetic macular edema, proliferative diabetic retinopathy, or retinal vein occlusion at baseline were excluded from the analysis. The EMR used compulsory minimum data fields once anti-VEGF treatment entry is initiated on the EMR system, hence the data-rich environment. Patients aged less than 55 years were excluded to ensure that all patients were indeed being treated for AMD. To further ascertain that only patients with AMD were included, patients who did not have at least three injections in their first six months of follow-up were excluded, as non-AMD choroidal neovascularization (CNV) indications are often given as one injection followed by a PRN regimen. This was done to only include patients with loading injections, allowing for sufficient time to complete them in the case of unforeseen circumstances.

Outcomes

The key outcome measures extracted from the patient's EMR were: number of visits, treatment type, and ETDRS visual acuity. These cover the minimum recommended dataset outcome measures by the ICHOM group and are collected during routine clinical care, although no patient-reported outcomes are collected.[26]

Analyses

In order to assess the difference in outcomes over the years, eyes were grouped by years of treatment initiation, and three-year outcomes were compared between the groups. To that end, eyes were included if they had a follow-up of at least three years ± one month, and only this time period was compared between groups. Eyes and patients were sub-grouped according to the year when their treatment began, in groups of 2 years (i.e., 2008-2009 for eyes and patients whose treatment began during the years 2008-2009). To avoid a selection bias that may affect the results, a separate analysis was done, which included the same two-year grouping of patients without full three years of follow-up to explore if eyes lost to follow up early behave differently from those which were not. As the analysis was done to compare treatment trends over the years based on national guidelines, records prior to 1/9/2008 were excluded from that analysis, as the National Institute for Health and Care Excellence (NICE) approved the use of ranibizumab for AMD in the UK at the end of 8/2008.

The baseline date was defined as the date of the first injection, and the date of the last follow-up was defined as the date of the last visual acuity (VA) measurement. Data on age (years) and ethnicity were extracted from the local patient administration system.

To assess functional visual outcomes, "driving VA" and "blindness VA" were used. Driving VA was defined as visual acuity of 20/40 Snellen (70 ETDRS letters) or better, based on definitions of the Driver and Vehicle Licensing Agency (DVLA) in the UK. [27] Blindness VA was defined as 20/200 Snellen (35 ETDRS letters) or worse, based on the sight impairment definitions of the UK Department of Health. [28]

As a metric of assessing how well the fellow eye was treated in patients with bilateral involvement, we calculated the number of times an eye which was the worse eye at the beginning of a three-year follow-up became the better eye at the end of the three-year follow-up, suggesting that the eye that initially had nAMD ended up faring better than the fellow eye.

We calculated the probability of death for each individual to account for mortality during the study period using the Office of National Statistics National Life Tables UK. Gender, age at baseline, and follow-up period were considered individually.

Visual acuity measurement

Visual acuity was measured as a part of routine clinical practice and recorded as an Early Treatment Diabetic Retinopathy Study (ETDRS) score, Snellen, or LogMar acuity measurement. All numerical measurements were converted to an ETDRS letter score using a standard algorithm. [29] A number of eyes were recorded as having baseline vision or vision at any visit of "counting fingers" (CF), "hand movements" (HM), "light perception" (LP), or 'no light perception' (NLP). For the analysis, these values were changed to 0 when calculating mean ETDRS scores.

Change in treatment trends over the years

Since patient data was anonymized, results are presented in the study without association with specific center outcomes. To assess treatment paradigm changes in each of the centers included in the study, the mean interval (in months, defined as the number of days divided by 30) between injections was calculated for each of the three treatment years for each eye. This was used to calculate the mean treatment interval for each year for each of the centers. Finally, an analysis was done for the mean monthly interval for each of the first three years of treatment, for each site, at each year from 2008.

Missing data points

No imputation was done for missing data.

Statistical analysis

To compare the different yearly cohorts' outcomes, measurements of daily mean VA were plotted for each group for all patients over three years from baseline on Loess regression curves using the Plotnine library for Python (version 0.7.0). For outcome analysis, time from baseline was calculated in days.

The effect of year of treatment initiation (modeled as a continuous variable, years from 01/09/2008) on visual acuity at three years was assessed using a multivariable linear regression model, adjusting for baseline visual acuity, age, and sex. Cox regression survival analyses were performed for time to the following visual outcomes: 5, 10, and 15 letter gain/loss sustained over at least two consecutive visits, from baseline visual acuity.

We estimated the loss to follow-up (LTFU) which could be attributed to deaths by calculating individual mortality rates adjusted for age at year of treatment initiation and gender, using period life expectancies from UK national life tables. [30] Data analyses were done in Python (version 3.7.3), using the Pandas library (version 1.0.5) [41] and in R (version 4.0.2). [31]

Ethical approval

Signed permission to analyze anonymized data was returned from the lead clinician and Caldicott guardian (the individual responsible for data protection in a National Health Service

(NHS) trust) at each participating center. The study adhered to the Declaration of Helsinki. Fully anonymized data was extracted on 13/12/2018.

RESULTS

A total of 52,552 eyes of 43,256 patients receiving 533,433 injections for nAMD were identified. After removing patients who received anti-VEGF treatment prior to September 2008, those that received fewer than three injections in the first six months of treatment, those with a previous retinal vein occlusion, diabetic macular edema or proliferative diabetic retinopathy, and those with fewer than three years of follow-up, 15,810 eyes of 13,705 patients, receiving 195,104 injections were included in the analysis (Figure 1). Of all patients, 2,105 (15.4%) had bilateral eye involvement. Drug information was missing for 22,700 (11.6%) injections.

Baseline demographic data are presented in Table 1.

Comparison of outcomes over time - Two-year stratification

Data on three-year outcomes of eyes for which treatment started at different year clusters is presented in Table 2. The total number of injections remained roughly the same, with a slight increase in eyes initiating treatment in 2014-2015. An analysis of the number of yearly injections revealed a significant drop in year two and an additional slight drop in year three (Figure 2).

The distribution of ranibizumab and aflibercept changed over the years, from 100% of ranibizumab injections in the 2008-2009 cohort, to twice as many aflibercept injections in the 2014-2015 cohort (33.7% of injections ranibizumab and 66.3% aflibercept).

The ratio between visits and injections remained approximately the same, with some decrease in eyes starting treatment in 2014-2015. Both baseline and last-visit VA increased over the years. The change in mean visual acuity throughout the three-years follow-up is presented in Figure 3.

The proportion of worse eyes becoming better eyes (calculated on a patient-level) was 4.1%, 4.4%, 4.9%, 3.5% for each yearly cohort, respectively.

To determine the effect of baseline visual acuity on the change in visual acuity over the years, baseline visual acuity was stratified and plotted for each of the cohorts (Figure 4). For baseline VA of 0-69 letters, there was a trend of vision gain followed by vision loss, with a longer period of gain for poorer baseline VA. For baseline VA of 70 letters or more, VA worsened over time. There was not much difference in the trend between the cohorts. However, eyes with baseline VA of 0-24 did significantly better if their treatment started in 2008-2009.

Alternative analysis of two-year stratification without dropping eyes with insufficient follow-up

A similar, separate analysis was done, which included eyes that did not have full three years of follow-up, i.e., eyes without a full three-year follow-up were not dropped ('No-drop analysis'). (Table 1S, Figure 1S, available at http://www.aaojournal.org). As could be expected, the number of injections and visits was smaller in this analysis. The other parameters were roughly similar -

baseline and last visit VA were worse by 1-4 letters in the no-drop analysis. The visual acuity trend over time remained the same.

Linear regression analysis

In a univariable analysis, VA at three years improved on average by 0.51 letters for each successive year from 1st September 2008. In a multivariable analysis, the improvement was only 0.24 per year. Younger age and baseline VA were also significantly associated with better VA at three years. In a multivariable analysis, these findings remained significant. Sex was not significantly associated with a difference in VA at three years (Table 3).

As better baseline visual acuity and a younger age were found to be associated with better VA at three years, a separate analysis was done to rule out a higher number of injections as the reason for these findings. While there was a small trend, there was no evidence for a substantially bigger number of injections for eyes with better baseline VA. The mean number of injections over 3 years was 8.9 ± 5.8, 10.9 ± 6, 12.1 ± 6, 12.9 ± 6, and 12.9 ± 6.2, for the 0-24, 25-39, 40-54, 55-69, and 70-84 baseline VA, respectively. There was also no evidence of a higher number of injections for younger age groups. The mean number of injections over three years was 11.4 ± 7, 12.7 ± 6.8, 12.9 ± 6.9, 13.1 ± 6.5, 12.6 ± 6.2, 12.1 ± 5.9, 11.7 ± 5.7, 11 ± 5.4, 11.2 ± 5.6 for consecutive age groups of five years starting at age 55 and ending at 100.

Survival analyses

Multivariate cox regression models showed older age and higher baseline visual acuity to be associated with a loss of 5, 10, and 15 letters ($p<0.001$). In contrast, younger age and poorer baseline visual acuity were associated with a gain of 5, 10, and 15 letters ($p<0.001$). Male sex was associated with 15-letter loss. Eyes treated more recently were slightly less likely to lose ten letters at three years ($p=0.038$) (Figure 5, figures 2S-9S available at http://www.aaojournal.org).

Functional visual acuity outcomes - two-year cohorts

Analysis of driving VA and blindness VA (as calculated on a patient-level) for each of the cohorts is presented in Table 4 and Figure 6.

The proportion of patients with driving VA at baseline and last visit increased over the years, with 57% of patients having driving VA at the end of three years for patients who started treatment in 2014-2015 compared with 46.5% in those with starting year 2008-2009. There was not much difference in that proportion between baseline and last visit over the years. The proportion of patients with blindness VA at baseline decreased over the years (from 7% in 2008-2009 to 4.2% in 2014-2015). Despite that, the proportion of patients with blindness VA at last follow-up decreased only marginally over the years and was always higher than that at baseline (roughly twice as much).

Treatment paradigm changes over the years

The average monthly interval for each treatment year, based on the year of treatment initiation, is presented in Table 5. The monthly interval between injections remained similar for the first year of treatment over the years. There was a mild decrease in the interval over the years in the second and third years of treatment (from 4 to 3.6 months, and from 4.8 to 4.1 months, respectively).

LTFU and mortality

We included 38,481 patients in the LTFU and mortality analysis (8 patients were excluded from the total due to the gender being unspecified). A total of 21,376 (55.6%) patients were LTFU during the study period and mortality could have accounted for 59% of these. The LTFU during the 2018 follow-up period could be explained by deaths. Figure 10S (available at available at http://www.aaojournal.org) shows the LTFU and expected deaths distribution by follow-up period among males and females.

Discussion

In this study, we analyzed ten years of data to assess whether treatment patterns have changed over the years and how they affected treatment outcomes. Our results show that over time patients gained vision initially but experienced vision loss in the second and third years of treatment, a trend which did not change over time. Although more eyes ended with driving VA at three years over time, and linear regression showed a slightly higher chance of improved visual outcomes year-on-year, analysis of treatment patterns reveals that there is room for improvement. The number of injections in the second and third year remained relatively low over the last decade, likely accounting for the decrease in visual acuity over time, at least in part.

Visual acuity in our overall cohort improved over most of the first year but decreased thereafter, resulting in loss of visual gains. This is also reflected in the functional VA outcomes, with the percentage of eyes with blindness VA at the end of three years decreasing only marginally. These results seem to be related to several factors.

First, baseline visual acuity. As seen in Figure 4, eyes with worse baseline VA gained more vision, which was sustained over a longer period of time. This was confirmed in a Cox regression. This phenomenon was previously reported by our group. [21,32] Of interest, although Cox regression showed a higher chance of vision loss over three years of treatment, linear regression analysis indicated that eyes with better VA at baseline tended to have better final visual outcomes at three years. In contrast, eyes with worse VA at baseline, although having a higher chance of visual gain over the years, ended up with worse absolute VA at three years. This is in line with a recent publication by Ho et al., [33] which included 162,902 eyes from the American Academy of Ophthalmology's Intelligent Research in Sight (IRIS) Registry. Eyes with better baseline VA tended to lose some vision during the two-year study follow-up time, while those with poorer baseline VA were more likely to gain vision. However, overall those with baseline VA >= 6/12 were more likely to maintain 6/12 or better VA at two years, supporting previously reported benefits of early initiation of treatment. [32,34]

Anatomical changes may also explain the trend of vision loss seen in our cohort over time. Although we did not examine the effect of such changes on outcomes in this study, they were reported in several studies. In the SEVEN-UP study, poor visual outcome was mostly correlated with an increased area of macular atrophy. [16] In the IVAN trial, less than a third of eyes developed marked macular atrophy by the end of the second year, with worse VA outcomes compared to eyes without intralesional macular atrophy. [19] In the long-term follow-up extension to the CATT study, the proportion of patients with an abnormally thin retina was 22% at the end of year 2, rising to 36% at year five and the prevalence of geographic atrophy grew from 20% to 41%, respectively. [14]

Most importantly, the reason for the decline in VA after the first year in our study might be related to the number of injections, which was lower in the second and third year consistently over the years (Table 2 Figure 2). That is despite a minor decrease in the interval between injections over the years in years 2 and 3 (Table 5). The pivotal clinical trials suggested that a much higher number of annual injections (12 in ANCHOR and MARINA trials, [2,3] 7.5 in VIEW 1 and VIEW 2, [5] 6.3-7 in CATT (estimation based on 12.6 for ranibizumab and 14.1 for bevacizumab treatment arms at two years) may be protective against medium-term visual acuity decline on average. [35] Our results show that, consistently, the number of injections in year 1 was almost optimal, partially resulting from mandatory loading injections at the beginning of that year. Indeed, the data shows that, across all centers, the mean interval between injections in that year was 1.5 months, across all time points. The number of injections halved or more in the second and third year, as reflected by the substantially longer monthly interval.

While we do not believe the visual outcomes in this study are the result of a shift in the prominent anti-VEGF drug as reflected in Table 2, as ranibizumab and aflibercept have been shown to have similar efficacy,[5] that shift may have resulted in a change to the treatment patterns which might have affected the number of injections. In preparing this manuscript, we first attempted to gain information on treatment patterns in the different centers by conducting a survey. Although only partial data was gained (due to difficulty in the exact recalling of treatment patterns), some patterns emerged. For ranibizumab, treatment consisted of loading injections followed by PRN, and in some centers, TAE in later years. For aflibercept (treatment with which started in 2013 following NICE approval in most centers), treatment was based on the year of treatment. In the first year, most centers would administer bimonthly injections following loading injections. In subsequent years there was a more mixed pattern, including PRN, bimonthly, and TAE. Our numbers suggest that the majority were probably treated as PRN after year 1, as bimonthly injections would have resulted in 6 monthly injections and TAE between 4-12 (based on activity). Based on the PrONTO study, we would expect about 4.5 annual injections for a PRN regimen. [9] Our analysis of the visits/injections ratio supports this assumption (Table 2). In a purely TAE treatment regimen, it would be ideally 1, as it would be in a purely monthly or bi-monthly treatment regimen, while PRN would drive the number up. In reality, patients may come back for non-scheduled visits or other non-nAMD disorders, resulting in a higher ratio for TAE regimens, which is poorly reported in TAE publications. For example, a previous study reported a ratio of 1.2. [36] Although the ratio decreased over the years in our study, it is far from 1 (reaching 2 for the latest cohort). The data on treatment interval over the years (Table 5) also supports this conclusion. Although some improvement was observed over the years, the mean interval is too high for optimal outcomes.

Several factors might explain the decline in the number of injections over the years. First, compliance, both by the patient and by the treating clinician. It is possible that after the first year of treatment, clinicians feel less pressured to inject frequently (given the optimal results),

patients may tire of the frequent injections, or both. Due to the suggested relationship between the number of injections over the years and the change in vision over that period, our results suggest that adherence to more frequent injections should be encouraged. A more uniform policy may help to achieve this goal.

The low number of annual injections revealed in our study is not unique. A study by Gillies et al. reported 10-year outcomes in two cohorts with nAMD - Australia and New Zealand (ANZ) and Switzerland. [22] The median number of injections in the first three years of treatment in the ANZ cohort was 7, 4, 4, respectively, and in the Swiss cohort, it was 6, 3, and 2. Accordingly, VA remained at least five letters above the baseline level for five years in the ANZ cohort, whereas the mean VA in the Swiss cohort dropped from the baseline level during the second year and thereafter. This suggests that four injections per year may lead to better outcomes than three if all other factors were identical. However, the two populations were also treated differently (TAE in ANZ vs. PRN in Switzerland, according to the data), which, apart from other inherent differences between the populations, might explain the results. Another study, by Haddad et al., [23] included 132 eyes treated for nAMD in a general ophthalmology clinic in rural France and followed up for at least five years. Of note, 97/132 eyes were previously treated. Treatment was given according to a PRN regimen following an initial loading dose. The mean number of injections for the first three years of treatment was 4.61, 2.98, and 3.14, respectively. Although exact numbers are not given, interpretation of the plot reveals that, among treatment-snaïve eyes, most improvement in visual acuity occurred during the first three months (loading phase), followed by a plateau for another three months, and then a decline in vision. Although direct comparisons are impossible, the difference between this and our study suggests that more injections are needed in the first year to achieve optimal benefit from treatment. Finally, pre-published data by MacCumber et al.,[37] which included 33,601 eyes from the IRIS registry, showed that, during a follow-up period of two years, the mean number of injections per eye was 5.6 in year 1 and 5 in year 2. The figures are even lower than those in our study for the first year, and overall represent fewer annual injections than would be expected with adherence to TAE injection protocols.

In a linear regression analysis, we found that better baseline VA was related to better VA at three years, as previously mentioned. A separate analysis showed that the number of injections could not explain this finding, as it was not substantially different between baseline VA groups. Year of treatment initiation was associated with better final VA, although to a minimal degree (0.24 letters per year). In addition, younger age was associated with better vision (in a multivariate analysis, 3.5 letters were found to be lost over three years of follow-up for every ten years of age). This was also found in the Cox regression, which showed that older age was associated with vision loss, whereas younger age was associated with vision gain. A separate analysis ruled out a higher number of injections as a reason for this finding. Explanations might include frailty or comorbidities, which could lead to missed appointments. It could also lead to clinicians' decision to choose a longer treatment interval for older patients who find it difficult to travel. However, our findings suggest the older population is more at risk of vision loss, and it seems that more injections, rather than fewer, should be encouraged in this subgroup. Finally, it is possible that some of the anatomical processes seen in nAMD, such as atrophy or scarring, are age-related, possibly related to the aging RPE choriocapillaris response, but further studies are needed on that.

Our study has several limitations. Although only patients with AMD at the time of treatment commencement were included, we did not assess for evolution of other conditions (including diabetic macular edema, proliferative diabetic retinopathy, or retinal vein occlusion) during the follow-up period. Our analysis showed that 55.5% of patients were LTFU during the study

period, with mortality accounting for only about 60% of these cases, leaving roughly 22% of the study population LTFU for other reasons, which may have led to some bias in our results. This attrition rate is expected in this elderly cohort and is similar to that found in longitudinal studies in other disease areas. [38] When comparing cohorts, missing data may influence the comparisons. Ascertaining whether the data are missing at random or not is problematic. We, therefore, explored the data in multiple ways: a) Loess regression curves on eyes that had complete follow up. Loess regression curves allow for easier comparison to historical clinical trial and real-world outcomes data, [21,39] but would be prone to bias if the pattern of loss to follow up was different in each of the year cohorts compared. b) A comparison was made for eyes that did not have full three years of follow-up ("no-drop analysis"), i.e., eyes without a full three-year follow-up were not dropped (Online supplementary Table 1, Figure 1) to see if this affected the conclusions. c) Kaplan-Meier curves handle missing data by censoring events, allowing less biased comparisons for dichotomous outcomes (i.e., tightly censored events such as time to 15-letter-loss or sight impairment or blindness). [4,40] However, this does not allow for comparison to historical data and is not the convention. Although our group has previously advocated the importance of binocular functional outcomes related to blindness as an impactful way of reporting real-world data that is robust to missingness, it is not as easy to relate to by clinicians. Hence we have reported both approaches. d) Given the age of the patients, we explored what proportion of the loss to follow up could be explained by mortality using Life Tables.

In conclusion, our findings suggest that, while some parameters, such as driving VA and the linear regression results, show that patients' visual outcomes have improved year-on-year over the last decade, that is in part driven by initiating treatment at better starting acuities, the majority of the data shows otherwise. Despite an initial gain of vision, patients lose vision after the first year at a similar rate. Our study shows that real-life treatment patterns are far from ideal after the first year of treatment, a trend which has improved only marginally over the years, as reflected in treatment intervals. Previous studies have shown this to be a global rather than an isolated problem. These results suggest that a change in treatment strategy is needed, possibly on a national level or through the introduction of longer-acting therapies, if these outcomes are to be improved.

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Figure legends

Figure 1 - Consolidated Standards of Reporting Trials-style diagram showing the patients included in the study. VEGF = vascular endothelial growth factor. nAMD = neovascular age-related macular degeneration. EMR = Electronic medical records.

Figure 2 - Change in the number of injections over the years. The horizontal axis represents the cohorts based on the year of treatment initiation, and the vertical axis the number of injections in each of the years (represented by the different bar colors).

Figure 3 - Loess regression curves of visual acuity over three years of follow-up, for eyes with full three years of follow-up, stratified by year of first treatment. ETDRS - Early Treatment Diabetic Retinopathy Study.

Figure 4 - Loess regression curves of visual acuity over three years of follow-up, for eyes with full three years of follow-up, stratified by baseline visual acuity (VA).

Figure 5 - a and b) Forest plots portraying the effect of age, gender, years from 2008, and baseline visual acuity on loss or gain of 15 letters, respectively. c and d) Kaplan-Meier curves for loss or gain of 15 letters, respectively, stratified by year of treatment initiation and baseline visual acuity.

Figure 6 - Functional visual acuity outcome measures over three years for eyes with three years of follow-up stratified by years of treatment initiation. VA = visual acuity. SI = sight-impaired.

Figure 1 supplementary - Daily mean visual acuity over three years of follow-up, for eyes with and without full three years of follow-up (No-drop analysis), stratified by year of first treatment.

Figures 2 supplementary - Forest plots portraying the effect of age, gender, years from 2008, and baseline visual acuity on gain of 5 letters

Figures 3 supplementary - Forest plots portraying the effect of age, gender, years from 2008, and baseline visual acuity on loss of 5 letters

Figures 4 supplementary - Forest plots portraying the effect of age, gender, years from 2008, and baseline visual acuity on gain of 10 letters

Figures 5 supplementary - Forest plots portraying the effect of age, gender, years from 2008, and baseline visual acuity on loss of 10 letters

Figure 6 supplementary - Kaplan-Meier curves for gain of 5 letters, stratified by year of treatment initiation and baseline visual acuity.

Figure 7 supplementary - Kaplan-Meier curves for loss of 5 letters, stratified by year of treatment initiation and baseline visual acuity.

Figure 8 supplementary - Kaplan-Meier curves for gain of 10 letters, stratified by year of treatment initiation and baseline visual acuity.

Figure 9 supplementary - Kaplan-Meier curves for loss of 10 letters, stratified by year of treatment initiation and baseline visual acuity.

Figure 10 supplementary - Losses to follow-up (LTFU) and expected deaths by follow-up period and gender. A comparison of the size of the cohort according to the follow-up period, the LTFU and expected deaths are shown in the left histograms. The right stacked bar plots show the proportion of expected deaths among the LTFU. **A**, male cohort. **B**, female cohort.