One and Two Year Visual Outcomes from the Moorfields AMD Database - an Open Science Resource for the Study of Neovascular Age-related Macular Degeneration

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Abbreviations:

AMD – age related macular degeneration

VEGF - vascular endothelial growth factor

VA - visual acuity

ETDRS - Early Treatment Diabetic Retinopathy Study

RCT - randomized controlled trial

LTFU - lost to follow-up

EMR - electronic medical record

NHS - National Health Service

ICHOM - International Consortium for Health Outcomes Measurement

FRB - Fight Retinal Blindness

CATT - Comparison of Age-related macular degeneration Treatment Trials

VIEW - Vascular endothelial growth factor Trap-Eye: Investigation of Efficacy and Safety in Wet AMD study

ABSTRACT

Purpose: To analyse treatment outcomes and share clinical data from a large, single-center, well-curated database of patients with neovascular age related macular degeneration (AMD). We report visual acuity (VA) outcomes and predictive factors for VA gain of 8174 eyes / 6664 patients with 120,756 single entries in the electronic medical record (EMR) database over the first two years of treatment with anti-vascular endothelial growth factor (VEGF). By making our depersonalised raw data openly available, we aim to stimulate further research in AMD, as well as setting a precedent for future work in this area.

Methods: Retrospective, comparative, non-randomised EMR database cohort study of the UK Moorfields AMD database with data extracted between 2008 and 2018.

Main outcome measures: Change in VA at one and two years from baseline as measured in Early Treatment Diabetic Retinopathy Study (ETDRS) letters. Secondary outcomes were the number of injections and predictive factors for VA gain.

Results: Mean VA gain at one-year and two years were +5.5±14.7 and +4.9±16.1 letters respectively. Fifty-four percent of eyes gained ≥5 letters at two years, 63% had stable VA (±≤14 letters). Forty-four percent of eyes maintained good VA (≥70 letters) over two years. Patients received a mean of 7.7±1.9 injections during year one and 13.0±3.9 injections over two years. Younger age, lower baseline VA, and more injections were associated with higher VA gain at two years.

Conclusion: This study benchmarks high quality EMR study results of real life AMD treatment in a large single center and promotes open science in clinical AMD research by making the underlying data publicly available.

Strengths and limitations of this study

- Large sample size, retrospective, single centre, electronic medical record database study
- High quality real life data
- Open science approach with sharing of depersonalised raw data

INTRODUCTION

The treatment of neovascular age-related macular degeneration (AMD) has been revolutionised by the development of anti-vascular endothelial growth factor (VEGF) agents such as ranibizumab and aflibercept.(1–4) Unfortunately, real world results from retrospective studies are typically inferior to those from randomised controlled trials (RCTs), with fewer administered injections and significant inter-country and inter-center differences in therapy administration and outcomes.(5–9) Although retrospective studies and audits may be more likely than RCTs to reflect results in clinical practice, they still are not truly representative of outcomes in real world populations.(5–7,10,11) Major drawbacks of retrospective study designs are small sample sizes with selection bias and sub-optimal methods for handling of both missing data and losses to follow-up (LTFU).(11,12) Survival bias in particular can lead to skewed results: omission of cases LTFU from the analysis leads to selection of a non-random cohort with potential overestimation of visual acuity (VA) gains through exclusion of patients that stop treatment early due to irreversible visual loss such as foveal scarring or other adverse effects.

The advent of electronic medical records (EMR) has facilitated the collection of large amounts of data in routine clinical practice and thus has the potential to make retrospective study populations more representative of real life.(13–18) This is very much dependent, however, on the quality of data entry and the reliable follow-up of patients, and so these issues can remain problematic. The amount of data available from EMR systems also challenges the traditional methods of validation, analytics and reporting, and there is a struggle to implement the existing clinical research guidelines.(12,19–21) For example, in 2015, the RECORD statement highlighted the challenges of using routinely collected observational health data.(21) A further problem is the variation of data collection in the different EMR registers in different hospitals and countries. The International Consortium for Health Outcomes Measurement (ICHOM) AMD working group has also proposed a standard set of clinical characteristics, interventions, and outcomes including preferential methods of

VA recording (logarithm of the minimum angle of resolution or Early Treatment Diabetic Retinopathy Study (ETDRS) letters).(22)

At Moorfields Eye Hospital, 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 dataset from this which represents, to our knowledge, the largest single-center cohort of patients receiving treatment for neovascular AMD in the world. This Moorfields AMD dataset is increasing steadily, with 909 new patients in 2017 alone, a number typically only comparable in magnitude to multicenter studies.(14,16) Apart from its sheer size, key advantages of this dataset include the ability to clean and validate data directly, the completeness due to the mandatory input of relevant fields including VA, the consistency of VA measurements in 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 study visit.

The aim of this study is to analyse one- and two-year VA outcomes, determine predictive factors of VA gain in treatment-naive eyes from the Moorfields AMD database, and to aid in scientific progress by making the de-personalised raw data from from our study openly available to the research community.(21,23)

METHODS

Data Collection:

Data for this retrospective, comparative, non-randomised cohort study were extracted from the data warehouse, the centralised storage for all EMR data, of Moorfields Eye Hospital. Data were extracted between October 21, 2008 and August 08, 2018. Extraction criteria were ≥ 1 ranibizumab or aflibercept injection, entry of “AMD” in the diagnosis field of the EMR, and a minimum of one year of follow-up. Exclusion criteria were unknown date of first injection, 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. The rationale for exclusion of bevacizumab is that in the National Health Service (NHS), neovascular AMD is generally treated with the licensed therapeutics ranibizumab or aflibercept, and not with the off-label bevacizumab.(24,25) The date of the first injection was defined as the baseline date. The dataset has been depersonalised for publication and approval for data collection and analysis was obtained from the Institutional Review Board at Moorfields (ROAD17/031). The study adhered to the tenets set forth in the Declaration of Helsinki.

Outcome Measures:

The primary outcomes were mean change in VA from baseline as measured in 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). Those endpoints have been used in the pivotal trials and/or have been included in the ICHOM reporting recommendations.(1–

4,22) Secondary outcomes included the number of injections, and effect of baseline characteristics and injection numbers on changes in VA. Definitions for one-year and two-year outcome dates were taken from previous real-world studies as visits closest to 52 weeks and 104 weeks post baseline date within ±8 weeks.(6,13) We used the STROBE cohort checklist when writing our report.(20)

Efforts to Minimize Bias:

Clinical information from patients with neovascular AMD is manually entered to the Moorfields Eye Hospital EMR (OpenEyes™) at each visit. The EMR requires mandatory completion for a number of fields at each patient visit, including VA, central retinal thickness, treatment decision, treatment drug, and injection number, thus minimizing the number of missing data entries. Of all 120,756 single entries, missing / zero visual acuity measurements were encountered in 4059 (4.1%) of all entries. After manual cleaning of all 4059 missing entries, missing data accounted for 808 (0.9%) entries. Patients aged <55 or >100 and eyes with injection numbers ≥50 were manually checked. Description of manual cleaning including a CONSORT diagram is shown in supplementary material (Supplementary 1, sFigure 1). Visual acuities below measurable ETDRS letters were converted to logMAR 2.0/-15 letters, logMAR 2.3/-30 letters and logMAR 2.7/-50 letters for count fingers, hand movements, and light perception respectively.(26) To avoid bias due to inter-eye correlation, statistical analysis was restricted to one eye per patient, i.e. the first eye of a patient if sequentially treated, and a randomly selected eye if simultaneously treated. Outcomes of second-treated fellow eyes are reported separately.(27)

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 +/- standard deviation (SD), and median, where appropriate. Differences between groups were evaluated using Mann Whitney U test and Pearson Chi-Square. Regression analysis was performed to assess relationship of predictive factors and VA gains. A p value of < 0.05 was interpreted as statistically significant.

Data Sharing Statement:

De-personalised data for this study will be openly available from the Dryad Digital Repository https://doi.org/10.5061/dryad.97r9289. Depersonalisation was carried out through hash function anonymisation of patient identification numbers, replacement of appointment dates with follow-up days to baseline, and categorising extreme age groups into age categories. Approval of adequate depersonalisation was obtained by Moorfields Information Governance.

RESULTS

Patient Demographics:

The full dataset consisted of 8174 treatment-naïve eyes/6664 patients with 120,756 single entries treated for neovascular AMD in the Moorfields database between October 21, 2008 and August 9, 2018.

The dataset for analysis consisted of 3357 eyes/patients (61% female). Mean age was 78±8 years at baseline. Mean VA was 56.4±15.0 letters. Of these, 1105 eyes (33%) were treated with ranibizumab, 1533 (46%) with aflibercept, and 719 eyes (21%) were treated with both ranibizumab and aflibercept. The starting year of treatment ranged between 2007-2018. Therapeutic choices at Moorfields Eye Hospital changed after 2013 and both ranibizumab and aflibercept were offered as alternative first line agents. After this change, a number of patients were switched from one agent to another resulting in over 50% of eyes receiving both drugs during the course of treatment. Baseline characteristics are shown in Table 1.

	Baseline characteristics	One year outcomes				Two year outcomes
		Full cohort	One year only completers	One year vs. two year completers	Two year completers	
Number of eyes / patients	3357	3357	1601		1756	2177
Baseline age (years)±SD	78±8	78±8	79±8	p<0.001	77±8	77±8
Gender female / male	61 / 39	61 / 39	61 / 39		61 / 39	61 / 39
Baseline VA (letters) ±SD	56.2±14.7	56.2±14.7	54.4±15.1	p<0.001	57.9±14.2	57.8±14.3
Mean VA (letters)±SD	56.2±14.8	61.8±16.9	58.5±18.4	p<0.001	64.8±14.8	62.7±16.6
Change in VA (letters±SD		5.5±14.7	4.1±15.8	p<0.001	6.8±13.6	4.9±16.1
% of eyes gaining ≥ 5 letters		54%	51%	p<0.001	58%	54%
% of eyes with stable vision (±<15 letters)		66%	65%	p=0.378	66%	63%
% of eyes with good VA (≥20/40)	24%	42%	35%	p<0.001	49%	44%
% of eyes with poor VA (≤20/200)	17%	11%	16%	p<0.001	6%	10%
Mean injection number ±SD over time		7.8±1.9	7.6±1.8	p<0.001	8.0±1.9	13.0±3.9

Table 1: Baseline characteristics, one and two year outcomes, VA - visual acuity, SD - standard deviation

Of the 1162 patients not completing the two year follow-up date, 254 patients had died. LTFU occurred in 27% of eyes for two year follow-up. To address the potentially resulting survival bias of, one-year outcomes for the cohort not completing 2-year follow-up and the cohort completing the 2-year follow-up are shown.

Visual outcomes at one and two years

Mean VA gain at one and two years were +5.5±14.7 and +4.9±16.1 letters respectively. The mean number of injections over the first year and first two years were 7.8±1.9 and 13.0±4.0 respectively (Figure 1). 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 2.

Comparison of subgroups that did not complete the two-year follow-up and the cohort that did complete the two-year follow-up showed a significantly lower mean baseline VA for those with a follow-up of less than two years (54.4 vs. 57.9 letters, $p<0.05$) a lower mean gain of letters (4.1 vs. 6.8 letters, $p<0.05$) as well as a lower injection frequency (7.6 vs. 8.0, $p<0.05$) at one year.

Determinants of change in VA at one and two years

Regression to predict change in VA at one and two years from gender, baseline age, baseline VA, and injection number, showed only baseline VA, baseline age and injection number as significantly adding to the prediction (one year: $F(8, 3384)=67.2$, $p<0.001$, $R^2=0.1383$); two years: $F(8, 2168)=64.26$, $p<0.001$, $R^2=0.1917$). Lower baseline VA, lower baseline age, and higher number of injections are associated with a higher VA change at two years (Figure 3).

DISCUSSION

In this study, we show that patients treated with ranibizumab and/or aflibercept for neovascular AMD at Moorfields Eye Hospital achieve good visual outcomes, particularly those patients who present at an earlier age with better visual acuity, and who subsequently receive frequent intravitreal injections.

The Moorfields AMD Database is a large, consistent, and clean dataset of neovascular AMD treatment and visual outcomes, perhaps the largest single-center dataset of its kind worldwide. We have made this freely available to download with this manuscript in an effort to benefit the AMD research community. At a minimum this will allow for use of alternative statistical approaches and facilitate research reproducibility. (21) We also hope it will allow for the testing of new hypotheses and thus provide new insights into the treatment of this condition.(28) We have also developed systems so that the Moorfields AMD Database is automatically updated over time, with minimal need for manual cleaning of data. Just under 1000 new cases of neovascular AMD present to Moorfields Eye Hospital on a yearly basis - this may be particularly useful as new therapeutics for AMD continue to be introduced. Additionally, we plan on releasing data for long-term follow-up of these (five years and beyond), as well as their associated raw imaging data (colour fundus photography and optical coherence tomography (OCT) imaging in every eye at every visit).

At one and two years, our results of mean VA gains confirm the existing evidence in real-life studies, e.g., the Fight Retinal Blindness (FRB) group in Australia/New Zealand for ranibizumab/aflibercept with nearly identical baseline characteristics and visual acuity outcomes for mixed ranibizumab/aflibercept treatment (Table 2).(10,29)

Two year results	Retrospective, real-life studies				Prospective randomised trials	
	Moorfields R / A 1737 eyes	EMR Users R 4990 eyes	FRB B / R / A 1189 eyes	FRB A 136 eyes	CATT R / B 1107 eyes	VIEW A 2063 eyes
Baseline age (years)	77	80	79	77	79	75.6-76.5
Baseline VA (letters)	57.8	55	56.5	61.4	59.9-61.6	53.6-54.0
Change in VA (letters)	4.9	+1	+5.3	+6	8.0-8.5	7.6-7.9
% of eyes with good VA (≥20/40)	44%	30%	45%	58%	67-68%	30.7-34.9
% of eyes with poor VA (≤20/200)	10%	-	11%	10%	4.7-8.4%	-
Mean injection number	13.0	9.4	13	13.6	11.8	16.5

Table 2: Comparison of two year outcomes with other real-life studies and randomised controlled trials. VA - visual acuity, A - aflibercept, R - ranibizumab, B - bevacizumab, EMR - electronic medical record, FRB - fight retinal blindness, CATT - comparison of Age-related Macular Degeneration Treatments Trials, VIEW - VEGF Trap-Eye: Investigation of Efficacy and Safety in Wet AMD

However, VA gains reported by the Writing Committee for the UK Age-Related Macular Degeneration EMR Users Group are considerably poorer which likely is explained by the reported capacity constraints resulting in reduced treatment frequency of with a mean of 9.4 injections over 2 years versus over 13 in our cohort and the FRB.(16) VA results from randomised prospective studies (e.g., the Comparison of Age-related macular degeneration Treatment Trials (CATT) and Vascular endothelial growth factor Trap-Eye: Investigation of Efficacy and Safety in Wet AMD study (VIEW)) have been shown to be superior to retrospective real-life data.(1,4)

This is also reflected in our data and is explained by the broader inclusion criteria, and the less strict treatment regimens with fewer administered injections. Comparison of cohorts that completed only one year of follow-up versus two or more years showed that eyes with shorter follow-up were older, had lower baseline VA, gained fewer letters at the one year follow-up, and received fewer injections over the first year. The loss to follow-up reflects the real-life setting of the study where patients transfer to stable AMD clinics, their vision has deteriorated and rendered further treatment unreasonable, or they are not able to further attend clinics. We deliberately did not perform any imputational replacement of missing data, but clearly describe the baseline characteristics and compare the one year results of the cohort LTFU before two years.(12)

VA gain over time is dependent on baseline characteristics and injection frequency.(12,14,30) Increasing age diminishes the VA gain expected as does a higher baseline acuity due to ceiling effect.(31) Baseline VA could even emerge as a surrogate measure for accessibility to treatment and quality of care, since simply looking at VA gains would underestimate centers that achieve short time from diagnosis to first treatment resulting in above average baseline VA but ceiling effect on VA gains.(8,12,16) Injection frequency has been recognised as another significant factor influencing VA gain and has been hypothesised to be the major factor in studies comparing ranibizumab and aflibercept due to the change in posology from treatment as needed to treat-and-extend concomitant with the change from ranibizumab to aflibercept in clinical practice.(14,30,32,33).

The retrospective nature and EMR-based data collection of our study introduce several limiting factors. Smoking status of our patients was not consistently available and thus, could not be included in the prediction model. Smoking has been identified as a risk factor for the development of neovascular AMD, but might also impact treatment response.(34) There is invariably survival bias within the data, as LTFU cannot be assumed to occur at random. However, baseline characteristics of LTFU as well as differences in outcomes for one and two year follow-up cohorts have been clearly described to address this. To date, there is no systematic collection of patient-reported outcome measures

(mobility and independence, emotional well-being, as well as reading and accessing information questionnaires) as suggested by ICHOM.(22) The main advantages of this study are the quality and amount of data coming from one single center and one database. Moorfields Eye Hospital has a standardised treatment protocol for neovascular AMD, formerly treatment as needed, and fixed-first year/treat-and extend regimen with the introduction of aflibercept in 2014 (flow chart for aflibercept use is shown in Supplementary 2). The extensive manual cleaning and the homogeneous standards of data input (VA in ETDRS letters, mandatory fields) have formed a highly reliable resource which will be enhanced in the future with an automated update and validation to allow for continued growth and quality improvement of clinical AMD data.

In conclusion, this study shows that with a diligent approach, analysis of well maintained EMR data can lead to high quality real-life results and electronic availability of data facilitates maximisation of its potential in sharing research resources with the community, ultimately with the goal of improving patient care in real-life. In the near future, we plan to report on long-term visual outcomes (e.g., after 5-years), anatomic outcomes, and fellow-eye involvement, as well as the differential therapeutic effects of ranibizumab and aflibercept. In each case, we plan to release the raw data that underpins these reports - we hope that this will help promote an open-science approach to the study of neovascular AMD, and thus to direct patient benefit in the longer term.

Author statement

All authors have substantially contributed to the conception of the study, analysis and interpretation of results, the drafting and final approval of the manuscript for publishing, and are accountable for all aspects of the work.

REFERENCES

1. Martin DF, Maguire MG, Fine SL, et al. Ranibizumab and Bevacizumab for Treatment of Neovascular Age-related Macular Degeneration. *Ophthalmology* [Internet]. 2012 Jul;119(7):1388–98. Available from: http://linkinghub.elsevier.com/retrieve/pii/S0161642012003211

2. Brown DM, Michels M, Kaiser PK, et al. Ranibizumab versus verteporfin photodynamic therapy for neovascular age-related macular degeneration: Two-year results of the ANCHOR study. *Ophthalmology* [Internet]. 2009 Jan;116(1):57–65.e5. Available from: http://dx.doi.org/10.1016/j.ophtha.2008.10.018

3. Rosenfeld PJ, Brown DM, Heier JS, et al. Ranibizumab for neovascular age-related macular degeneration. *N Engl J Med* [Internet]. 2006 Oct 5;355(14):1419–31. Available from: http://dx.doi.org/10.1056/NEJMoa054481

4. Heier JS, Brown DM, Chong V, et al. Intravitreal aflibercept (VEGF trap-eye) in wet age-related macular degeneration. *Ophthalmology* [Internet]. 2012 Dec;119(12):2537–48. Available from: http://dx.doi.org/10.1016/j.ophtha.2012.09.006

5. Holz FG, Tadayoni R, Beatty S, et al. Multi-country real-life experience of anti-vascular endothelial growth factor therapy for wet age-related macular degeneration. *Br J Ophthalmol* [Internet]. 2015 Feb;99(2):220–6. Available from: http://dx.doi.org/10.1136/bjophthalmol-2014-305327

6. Cohen SY, Mimoun G, Oubraham H, et al. Changes in visual acuity in patients with wet age-related macular degeneration treated with intravitreal ranibizumab in daily clinical practice: the LUMIERE study. *Retina* [Internet]. 2013 Mar;33(3):474–81. Available from: http://dx.doi.org/10.1097/IAE.0b013e31827b6324

7. Finger RP, Wiedemann P, Blumhagen F. Treatment patterns, visual acuity and quality of life outcomes of the WAVE study–A noninterventional study of ranibizumab treatment for neovascular age related macular degeneration in Germany. *Acta* [Internet]. 2013; Available from: http://onlinelibrary.wiley.com/doi/10.1111/j.1755-3768.2012.02493.x/full

8. Liew G, Lee AY, Zarranz-Ventura J, et al. The UK Neovascular AMD Database Report 3: inter-centre variation in visual acuity outcomes and establishing real-world measures of care. *Eye* [Internet]. 2016 Nov;30(11):1462–8. Available from: http://dx.doi.org/10.1038/eye.2016.149

9. Eleftheriadou M, Gemenetzi M, Lukic M, et al. Three-Year Outcomes of Aflibercept Treatment for Neovascular Age-Related Macular Degeneration: Evidence from a Clinical Setting. *Ophthalmol Ther* [Internet]. 2018 Jul 7; Available from: http://dx.doi.org/10.1007/s40123-018-0139-5

10. Barthelmes D, Nguyen V, Daien V, et al. Two year outcomes of “treat and extend” intravitreal therapy using aflibercept preferentially for neovascular age-related macular degeneration. *Retina* [Internet]. 2018 Jan;38(1):20–8. Available from: http://dx.doi.org/10.1097/IAE.0000000000001496

11. Chong V. Ranibizumab for the treatment of wet AMD: a summary of real-world studies. *Eye* [Internet]. 2016 Feb;30(2):270–86. Available from: http://dx.doi.org/10.1038/eye.2015.217

12. Mehta H, Tufail A, Daien V, et al. Real-world outcomes in patients with neovascular age-related macular degeneration treated with intravitreal vascular endothelial growth factor inhibitors. *Prog Retin Eye Res* [Internet]. 2018 Jan 2; Available from: http://dx.doi.org/10.1016/j.preteyeres.2017.12.002

13. Lotery A, Griner R, Ferreira A, et al. Real-world visual acuity outcomes between ranibizumab and aflibercept in treatment of neovascular AMD in a large US data set. *Eye* [Internet]. 2017 Dec;31(12):1697–706. Available from: http://dx.doi.org/10.1038/eye.2017.143

14. Rao P, Lum F, Wood K, et al. Real-World Vision in Age-Related Macular Degeneration Patients Treated with Single Anti-VEGF Drug Type for 1 Year in the IRIS Registry. *Ophthalmology* [Internet]. 2017 Nov 13; Available from: http://dx.doi.org/10.1016/j.ophtha.2017.10.010

15. Almuhtaseb H, Johnston RL, Talks JS, et al. Second-year visual acuity outcomes of nAMD patients treated with aflibercept: data analysis from the UK Aflibercept Users Group. *Eye* [Internet]. 2017 Nov;31(11):1582–8. Available from: http://dx.doi.org/10.1038/eye.2017.108

16. Writing Committee for the UK Age-Related Macular Degeneration EMR Users Group. The neovascular age-related macular degeneration database: multicenter study of 92 976 ranibizumab injections: report 1: visual acuity. *Ophthalmology* [Internet]. 2014 May;121(5):1092–101. Available from: http://dx.doi.org/10.1016/j.ophtha.2013.11.031

17. Kataja M, Hujanen P, Huhtala H, et al. Outcome of anti-vascular endothelial growth factor therapy for neovascular age-related macular degeneration in real-life setting. Available from: http://dx.doi.org/10.1136/bjophthalmol-2017-311055

18. Ozturk M, Harris ML, Nguyen V, et al. Real-world visual outcomes in patients with neovascular age-related macular degeneration receiving aflibercept at fixed intervals as per UK licence. *Clin Experiment Ophthalmol* [Internet]. 2017 Oct 17; Available from: http://dx.doi.org/10.1111/ceo.13085

19. Denaxas S, Direk K, Gonzalez-Izquierdo A, et al. Methods for enhancing the reproducibility of biomedical research findings using electronic health records. *BioData Min* [Internet]. 2017 Sep 11;10:31. Available from: http://dx.doi.org/10.1186/s13040-017-0151-7

20. von Elm E, Altman DG, Egger M, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Lancet* [Internet]. 2007 Oct 20;370(9596):1453–7. Available from: http://dx.doi.org/10.1016/S0140-6736(07)61602-X

21. Benchimol EI, Smeeth L, Guttmann A, et al. The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) statement. *PLoS Med* [Internet]. 2015 Oct;12(10):e1001885. Available from: http://dx.doi.org/10.1371/journal.pmed.1001885

22. Rodrigues IA, Sprinkhuizen SM, Barthelmes D, et al. Defining a Minimum Set of Standardized Patient-centered Outcome Measures for Macular Degeneration. *Am J Ophthalmol* [Internet]. 2016 Aug;168:1–12. Available from: http://dx.doi.org/10.1016/j.ajo.2016.04.012

23. Packer M. Data sharing in medical research. *BMJ* [Internet]. 2018 Feb 14;360:k510. Available from: http://dx.doi.org/10.1136/bmj.k510

24. Cohen D. Why have UK doctors been deterred from prescribing Avastin? *BMJ* [Internet]. 2015 Apr 1;350:h1654. Available from: http://dx.doi.org/10.1136/bmj.h1654

25. Hambleton D. Commentary: NHS patients should have a choice of drug for wet age-related macular degeneration, despite pressure from pharma. *BMJ* [Internet]. 2017 Oct 31;359:j5013. Available from: http://dx.doi.org/10.1136/bmj.j5013

26. Lange C, Feltgen N, Junker B, et al. Resolving the clinical acuity categories “hand motion” and “counting fingers” using the Freiburg Visual Acuity Test (FrACT). *Graefes Arch Clin Exp Ophthalmol* [Internet]. 2009 Jan;247(1):137–42. Available from: http://dx.doi.org/10.1007/s00417-008-0926-0

27. Fasler K. Fellow Eye Involvement with Neovascular Age-related Macular Degeneration in the Moorfields AMD Database. *unpublished*.

28. RPB/Academy Award [Internet]. American Academy of Ophthalmology. 2017 [cited 2018 Jun 24]. Available from: https://www.aao.org/iris-registry/data-analysis/research-to-prevent-blindness-research-grants

29. Arnold JJ, Campain A, Barthelmes D, et al. Two-Year Outcomes of “Treat and Extend” Intravitreal Therapy for Neovascular Age-Related Macular Degeneration. *Ophthalmology* [Internet]. 2015 Jun;122(6):1212–9. Available from: http://linkinghub.elsevier.com/retrieve/pii/S0161642015001244

30. Kim LN, Mehta H, Barthelmes D, et al. Metaanalysis of real-world outcomes of intravitreal ranibizumab for the treatment of neovascular age-related macular degeneration. *Retina* [Internet]. 2016 Aug;36(8):1418–31. Available from: http://dx.doi.org/10.1097/IAE.0000000000001142

31. Holz FG, Tadayoni R, Beatty S, et al. Key drivers of visual acuity gains in neovascular age-related macular degeneration in real life: findings from the AURA study. *Br J Ophthalmol* [Internet]. 2016 Dec;100(12):1623–8. Available from: http://dx.doi.org/10.1136/bjophthalmol-2015-308166

32. Sarwar S, Clearfield E, Soliman MK, et al. Aflibercept for neovascular age-related macular degeneration. *Cochrane Database Syst Rev* [Internet]. 2016 Feb 8;2:CD011346. Available from: http://dx.doi.org/10.1002/14651858.CD011346.pub2

33. Lee AY, Lee CS, Egan CA, et al. UK AMD/DR EMR REPORT IX: comparative effectiveness of predominantly as needed (PRN) ranibizumab versus continuous aflibercept in UK clinical practice. *Br J Ophthalmol* [Internet]. 2017 Dec;101(12):1683–8. Available from: http://dx.doi.org/10.1136/bjophthalmol-2016-309818

34. Velilla S, García-Medina JJ, García-Layana A, et al. Smoking and age-related macular degeneration: review and update. *J Ophthalmol* [Internet]. 2013 Dec 4;2013:895147. Available from: http://dx.doi.org/10.1155/2013/895147

35. Gregori NZ, Feuer W, Rosenfeld PJ. Novel method for analyzing snellen visual acuity measurements. *Retina* [Internet]. 2010 Jul;30(7):1046–50. Available from: http://dx.doi.org/10.1097/IAE.0b013e3181d87e04

Figure legends

Figure 1: Visual acuity (A&C) and change in visual acuity (B&D) over time for all eyes and stratified by follow-up period (black: one year completers only; grey: two year completers). Bars represent 95% confidence intervals.

Figure 2: Percentage of eyes with good VA (≥ 70 letters), intermediate VA (36-69 letters), and poor VA (≤ 35 letters) at different follow-up times (A) and comparison of cohorts of different follow-up times at one year (B). VA - visual acuity

Figure 3: Change in visual acuity stratified by baseline VA (A), baseline age (B), and injection number at two years (C). Bars represent 95% confidence intervals.

Supplementary material

Supplementary 1: Data cleaning

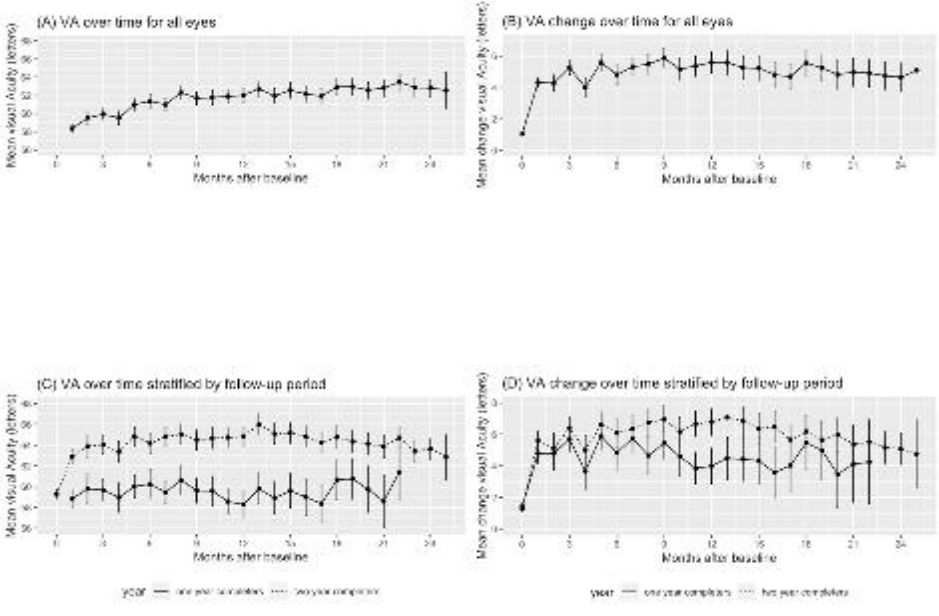
Manual data cleaning was carried out according to the following rules:

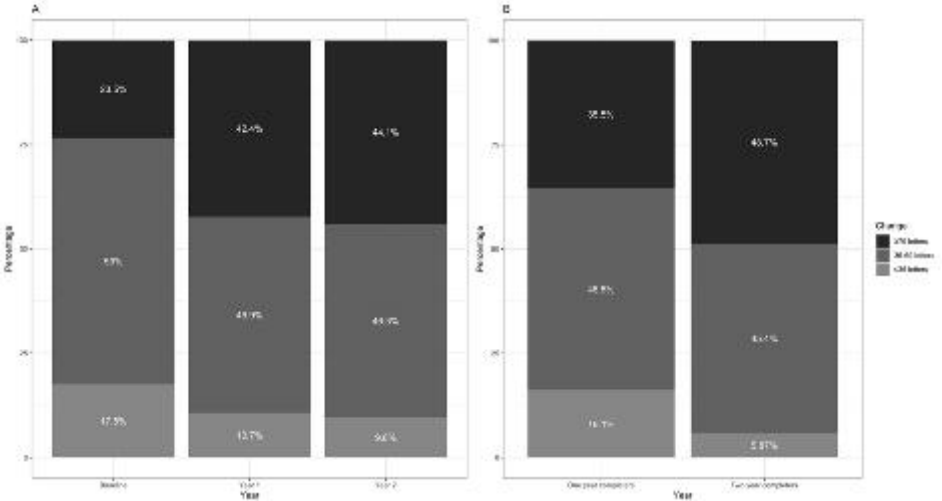
VA: Missing or zero VA entries were manually checked in paper notes. If available from within 7 days before injection date, the respective VA was manually entered. Eyes with VA < 25 letters (below National Institute for Health and Care Excellence criteria for treatment of neovascular AMD) at first presentation were checked manually. VA measured in Snellen were converted to ETDRS letters according to Gregori et. al.(35) Visual acuities below measurable ETDRS letters were converted to logMAR 2.0/-15 letters, logMAR 2.3/-30 letters and logMAR 2.7/-50 letters for count fingers, hand movements, and light perception respectively. Patient age: All patients <55 or >100 years of age at first presentation were checked manually to address misdiagnosis. Injection number: All eyes having received ≥ 50 injections were manually checked to avoid errors of manual input of legacy injection numbers.

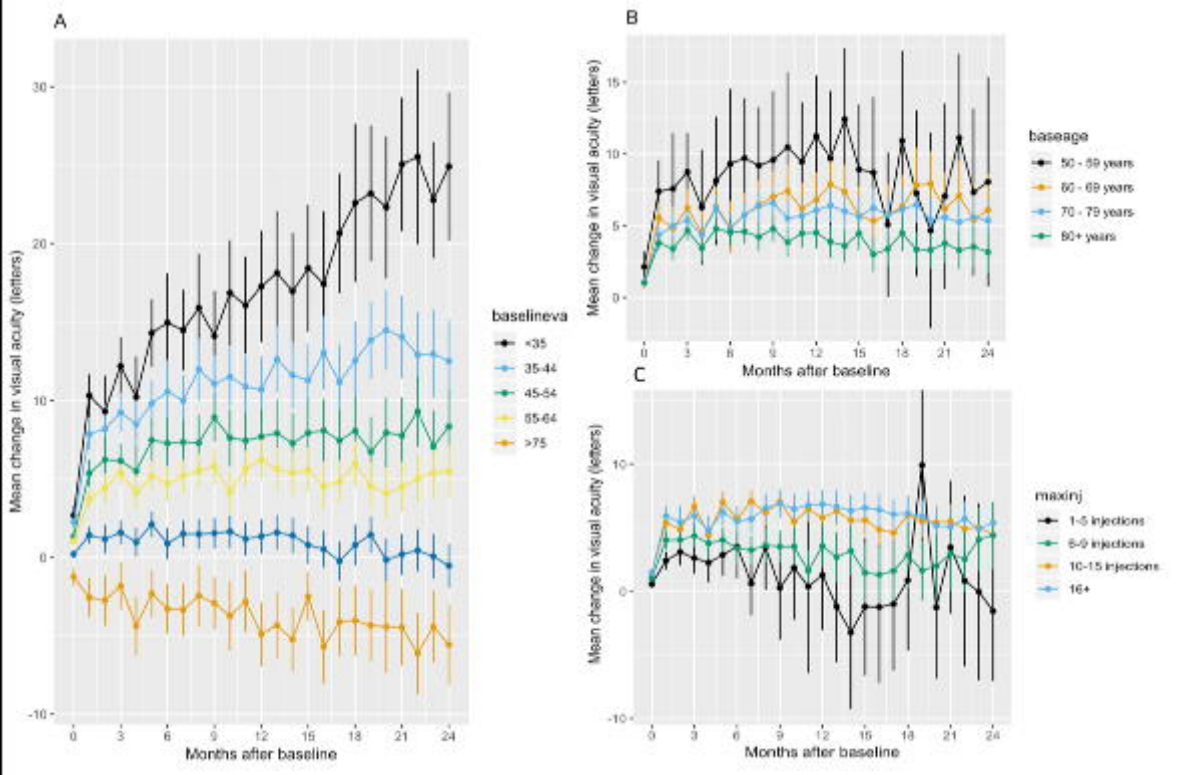
sFigure 1: Consort flow diagram data of data collection and cleaning

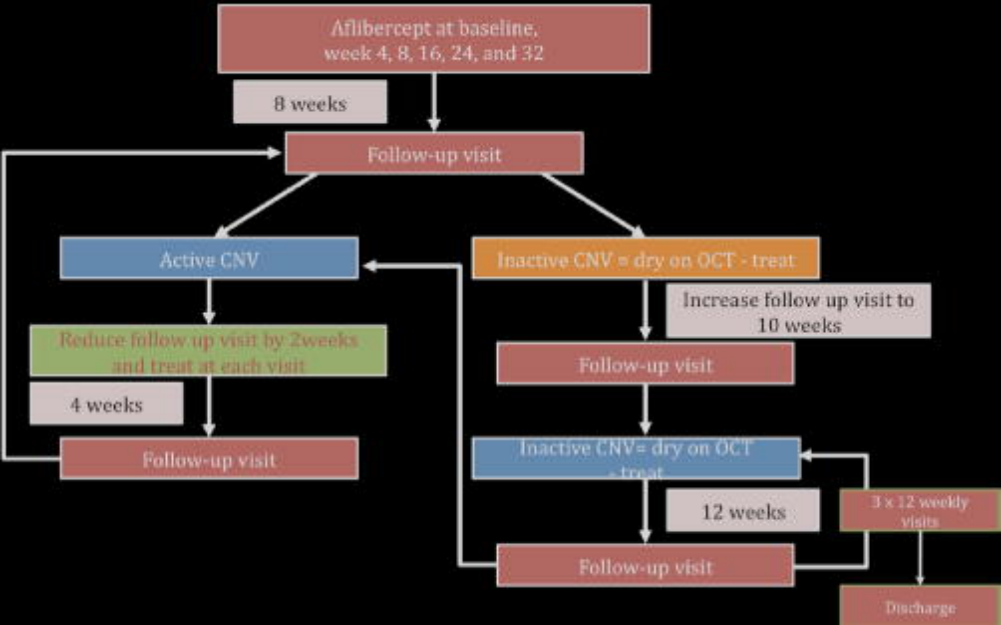
Supplementary 2: Treatment guidelines for aflibercept – figure legend

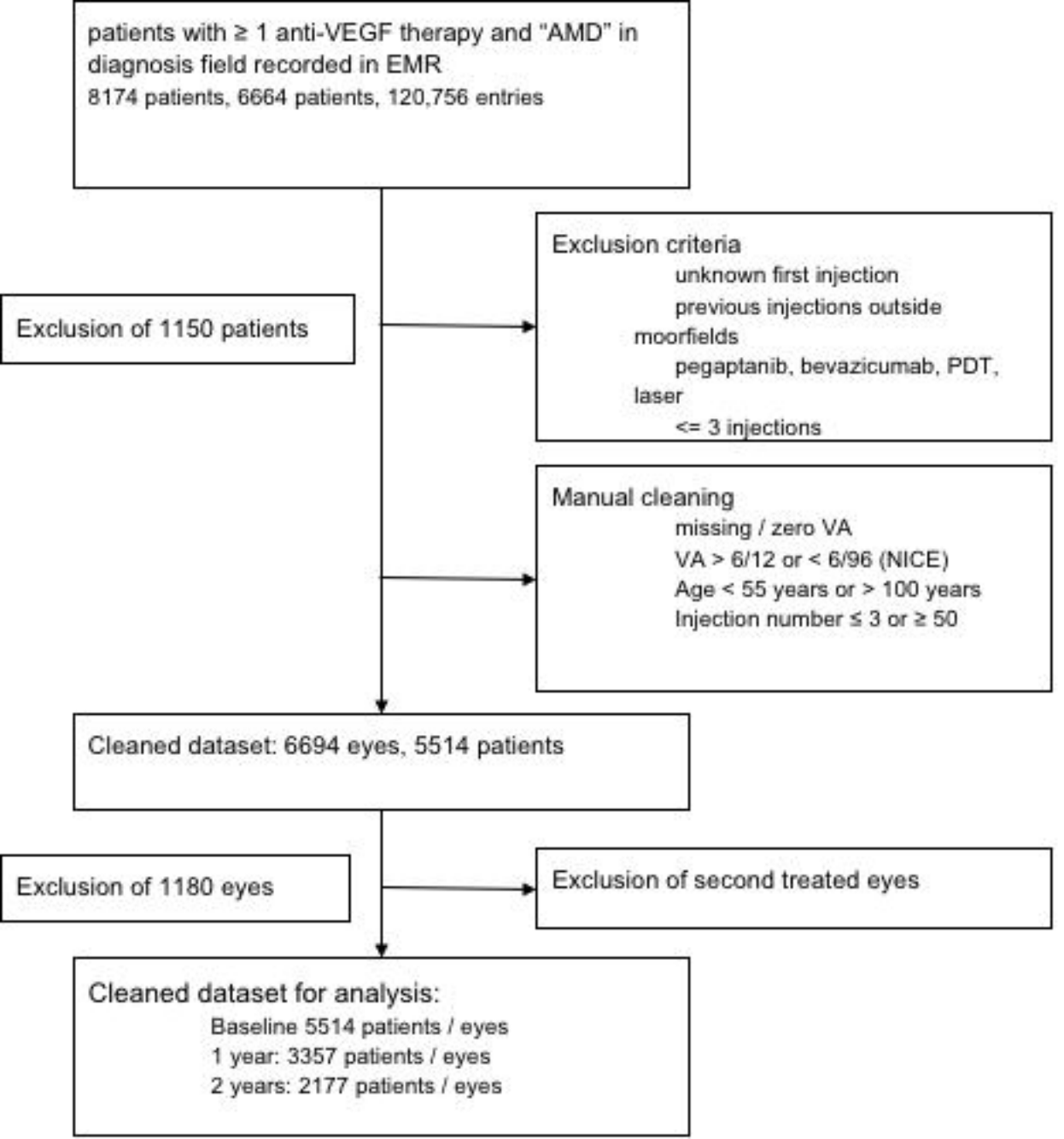
sFigure 2: Treatment flow chart for aflibercept treatment in new cases of neovascular AMD at Moorfields Eye Hospital. Derived from *Guidelines for the intravitreal service for the treatment of age-related macular degeneration (version 2.0)*. AMD - Age related macular degeneration


(A) VA over time for all eyes
Mean visual Acuity (letters)
Months after baseline
(B) VA change over time for all eyes
Mean change visual Acuity (letters)
Months after baseline
(C) VA over time stratified by follow-up period
Mean visual Acuity (letters)
Months after baseline
year
(D) VA change over time stratified by follow-up period
Mean change visual Acuity (letters)
Months after baseline
year


A
B
Percentage
Year
Year
Change


A
Mean change in visual acuity (letters)
Months after baseline
baselineva
<35
35-44
45-54
55-64
>75
B
Mean change in visual acuity (letters)
Months after baseline
baseage
50 - 59 years
60 - 69 years
70 - 79 years
80+ years
C
Mean change in visual acuity (letters)
Months after baseline
maxinj
1-5 injections
6-9 injections
10-15 injections
16+


Aflibercept at baseline,
week 4, 8, 16, 24, and 32
8 weeks
Follow-up visit
Active CNV
Inactive CNV = dry on OCT - treat
Increase follow up visit to
10 weeks
Reduce follow up visit by 2weeks
and treat at each visit
4 weeks
Follow-up visit
Follow-up visit
Inactive CNV= dry on OCT
- treat
12 weeks
3 x 12 weekly
visits
Follow-up visit
Discharge


patients with ≥ 1 anti-VEGF therapy and "AMD" in diagnosis field recorded in EMR
8174 patients, 6664 patients, 120,756 entries
Exclusion of 1150 patients
Exclusion criteria
unknown first injection
previous injections outside moorfields
pegaptanib, bevazicumab, PDT, laser
<= 3 injections
Manual cleaning
missing / zero VA
VA > 6/12 or < 6/96 (NICE)
Age < 55 years or > 100 years
Injection number ≤ 3 or ≥ 50
Cleaned dataset: 6694 eyes, 5514 patients
Exclusion of 1180 eyes
Exclusion of second treated eyes
Cleaned dataset for analysis:
Baseline 5514 patients / eyes
1 year: 3357 patients / eyes
2 years: 2177 patients / eyes