Analysing Subgroups and Treatment Discontinuation in a Finnish Cohort of Patients with Neovascular AMD

Ollila, Terhi

2022-08

Ollila , T , Silvennoinen , J , Joshi , A , Liu , J , Kulathinal , S & Immonen , I 2022 , ' Analysing Subgroups and Treatment Discontinuation in a Finnish Cohort of Patients with Neovascular AMD ' , Ophthalmologica : the journal of the European Society of retina specialists , vol. 245 , no. 4 , pp. 358-367 . https://doi.org/10.1159/000524848

http://hdl.handle.net/10138/351495
https://doi.org/10.1159/000524848

acceptedVersion

Analyzing subgroups and treatment discontinuation in a Finnish cohort of patients with neovascular AMD

Terhi Ollila[1], Juuso Silvennoinen[2], Ashwini Joshi[2], Jia Liu[2, 3], Sangita Kulathinal[2] and Ilkka Immonen[1]

Department of Ophthalmology, Helsinki University Hospital, Helsinki, Finland[1]

Department of Mathematics and Statistics, University of Helsinki, Helsinki, Finland[2]

Biological Data Science Institute, Australian National University, Canberra, Australia (current affiliation)[3]

Correspondence:

Terhi Ollila, M.D., FEBO

Department of Ophthalmology

Helsinki University Hospital

PO Box 220

00029 HUS

Helsinki, Finland

Tel: +358947173110

Fax: +358947175100

Email: terhi.ollila@hus.fi

Abstract

Purpose

To study the regional detailed visual outcome and treatment discontinuation of neovascular age-related macular degeneration (nAMD).

Methods

Clinical records of 110 patients treated for nAMD at the sole referral center in the Helsinki region were analysed retrospectively. The follow-up was up to the fourth year.

Results

The mean visual acuity (VA) at baseline was 56.3 (SD 16.2) letters. The mean last VA at the first year was 59.7 (20.2), and the corresponding values for the second, third and fourth years were 60.8 (20.6), 60.0 (19.0) and 59.7 (19.3). The mean difference from baseline was +3.39 (SD 14.6), +3.59 (17.6), +0.08 (18.9) and +3.08 (14.3). The number of patients declined each year, with only 51 % of the patients being in treatment until the fourth year. The patients with shorter duration of follow-up tended to have a lower baseline VA, lesser gains and an earlier decline in VA. The VA levels at the last visit were poorer in the shorter follow group. The initial VA response predicted later VA, whereas VA at baseline, age or sex had no effect. However, the effect vanished with a longer time in treatment.

Conclusions

Long-term VA stabilization was obtained in a regional material. Patients with neovascular AMD consists of cohorts with varying visual outcome and treatment time. Many of the patients benefit from the treatment for some time, however. When comparing real-world results, the outcome of the different follow-up time cohorts should be considered. This calls for new methods for analysing real world nAMD treatment results.

Key words: neovascular age-related macular degeneration, anti-VEGF treatment, visual acuity, real-world studies

INTRODUCTION

The use of anti-VEGF agents has revolutionized the visual prognosis of neovascular age-related macular degeneration (nAMD). The efficacy of anti-VEGF agents was initially proven in registration studies with strict inclusion criteria, and a rigid protocol of frequent intravitreal injections and follow-up visits [1, 2]. These studies generally lasted for one to two years, after which the continuation studies were generally performed according to a more flexible regimen. In these continuation studies the visual results tended to deteriorate from those obtained in the original studies [3]. Similarly, data from the results of real-world treatments for nAMD generally show visual results that are inferior to those of the registration studies [4], albeit clearly better than the natural history of nAMD [5]. The reason for this difference has been suggested to be due to a larger spectrum of AMD lesion types and sizes included and undertreatment [6].

Observational studies are especially important for the comparison of different treatment protocols and organizations, and for resource allocation. However, the evaluation of real world studies is made complicated by several issues. These include the amount of data recorded, the validity of the data, the representativeness of the study sample and the impact and statistical handling of patients lost to follow-up [7].

In this manuscript, we describe the outcome of a cohort of patients with the first anti-VEGF injection given in the year 2012, with a follow-up for up to 4 years. Since our hospital is the only organization giving public treatments for nAMD and long-term private treatments are rare in our region, we feel that this report reasonably reflects the regional outcome of nAMD treatment.

In this report we paid special attention to the course of treatment outcome in the patients dropping out before the end of the follow-up.

MATERIALS AND METHODS

Study design

We analysed patients with nAMD with a treatment naïve eye given the first injection at the Helsinki University Central Hospital between 1.1.2012 – 31.12.2012. One hundred ninety-six eyes of 196 patients were identified from the electronic medical records using the ICD10-code H35.31 for wAMD. Altogether 86 eyes were excluded. The main reasons for exclusion were the anti-VEGF injection given elsewhere (41 eyes), unconfirmed diagnosis (11 eyes) and prior vitreoretinal surgery (9 eyes) (**Table 1**). In patients, who had nAMD diagnosis of both eyes, the first treated eye was included, or if the treatment was initiated in both eyes at the same time, the right eye was chosen.

Data collection

Treatment decisions had been made by clinicians in routine practice, mostly using a PRN type of protocol, in which an injection was given only when signs of neovascular activity (intra- or subretinal fluid or bleeding) were present at a follow-up visit. Typically, the visit interval was 4 to 5 weeks. Patients received either bevacizumab (Avastin, F Hoffmann-La Roche Ltd Switzerland), ranibizumab (Lucentis, Novartis Pharma GmbH Nürnberg Germany) or aflibercept (Eylea, Bayer AG, Berlin, Germany). Baseline data included date, patient age, sex, visual acuity, ETDRS score and AMD status of the fellow eye. Fluorescein and indocyanine green angiographies were taken at baseline at discretion of the treating ophthalmologist in 59% of the cases especially if the diagnosis of wAMD was to be confirmed. Since almost half of the patients had not angiographies taken, and the selection for angiography was not random, we did not analyse the outcomes in relation to angiography results. At follow-up visits, we recorded the date, visual acuity, the drug injected, possible complication of intravitreal injection, and the cause for ending the follow-up at the last visit. Part of follow-up visits were conducted in an outsourced unit using Snellen tables, converted to ETDRS scores for analysis. Data were collected until March 2016.

The study was approved by the local ethics committee and adhered to the tenets of the Helsinki declaration.

Outcome measures

The main outcome measure was the change of visual acuity from baseline. Other measures included the number of injections with respect to completed years of follow-up, stability of visual acuity with respect to baseline visual acuity, proportion of patients with different visual thresholds at the end of follow-up in different follow-up groups; timing and severity of permanent visual loss below baseline level; and timing and causes of treatment drop-out. VA at the different corresponding time points were analysed in groups, based on the eventual total treatment time of a patient, grouped as follows: G1: dropout during the first year, G2: dropout during the second year, G3: dropout during the third year and G4: dropout or study end during the fourth year. We also measured annually the change in central foveal thickness from baseline and the presence of subretinal fluid (SRF), intraretinal fluid (IRF) and pigment epithelial detachment (PED) at baseline and at last follow-up.

Statistical methods

Visual acuity between groups were analyses using ANOVA with post hoc tests.

For the analysis of the visual outcome and the role of the initial VA response, all patients at a time point were analysed, or patients were divided into the 4 groups (G1 to G4) based on their follow-up periods for analysis. The initial VA response was taken from the closest VA value available within 6 months from the initial injection. The actual median interval from the first injection to the initial VA response time point was 22.7 weeks (5.8months), range 10.0 to 25.9 weeks. The median number of injections before the timepoint was 5 (range 2 to 7). The early and late VA responses were saved as a binary variable with 1 indicating improvement over the baseline measurement and 0 indicating VA value of equal to or worse than baseline VA. The late VA response was computed similarly at the end of each year for patients in each follow-up group. Logistic regression was performed with late VA response as dependent variable and baseline age, gender, baseline VA measurement and early VA response as covariates. Point estimates and confidence intervals of all covariates were reported for each follow-up group for every year.

Since the sample size is small with 110 patients divided into 4 groups and 4 years, there was a possibility of small sample bias while performing logistic regression. In case of small-sample bias, log-likelihood may become infinite, and estimate may not exist. Various penalties or corrections to

likelihood and score functions are suggested in literature to handle small sample bias. We used maximum penalized likelihood with powers of the Jeffreys prior as penalty to overcome the problem of infinite log-likelihood [9]. R function 'glm' was used for performing logistic regression and the R package 'brglm2' was used for applying maximum penalized likelihood when 'glm' leads to infinite loglikelihood due to small sample bias.

RESULTS

Baseline characteristics

At baseline, 110 eyes of 110 patients were included in the study. 71 patients (65%) were female. Median age at baseline was 80.4 years (SD 8.60). The proportion of right and left eyes as the study eye was equal, 55/55. Thirty-five patients (32%) were non-smokers, 9 patients (8%) currently smoked and 33 (30%) were ex-smokers. Data could not be obtained from 33 patients (30%).

Mean baseline ETDRS score was 56 (SD ± 16). Baseline EDTRS level was <40, 40-54, 55-70 and >70 in 22 (20%), 26 (24%), 37 (34%) and 25 (23%) patients, respectively (Fig 1).

The follow-up and injections

Mean total follow-up time per patient was 32.1 months (SD 14.1). Mean visit interval was 40.0 days (SD 12.4). Proportion of patients remaining was 91% (n=100) at 12 months, 69% (n=76) at 24 months and 49% (n= 54) at 36 months. Eleven percent (n=12) of the patients were treated during the 4^{th} year. Thus, the cumulative percentages of patients lost to follow-up were 9% at 1 year, 31% at 2 years and 51% at 3 years.

Causes for discontinuing treatment were lack of response to treatment (n=18), inactive disease for 12 months (n=15), other serious medical condition (n=9), not appearing at follow-up visits (n=3), death (n=7) or patient willing to give up treatment (n=4). In the patients discontinued for lack of response, the median baseline VA was 39 letters (range 19 to 68), and the corresponding values at the last follow-up were 21 (0 to 46) All of these patients were treated with bevacizumab. Aflibercept was not widely available at that time.

The mean number of injections (corrected to a full year value for the last year of follow-up) given was 7.7 (2.5 (SD)), 4.8 (3.8), 6.0 (3.4) and 7.5 (3.6) during the first, second, third and fourth years (**Table 2**). The proportion of anti-VEGF agents injected were: 82.5% bevacizumab, 3.5% ranibizumab and 14.0% aflibercept. The proportion of patients who had an injection with the respective anti-VEGF agents at least once were 97.0 %, 5.5 % and 30.0% for bevacizumab, ranibizumab and aflibercept. This distribution of anti-VEGF agents reflects the practice still used in Finland with bevacizumab being the primary agent and aflibercept being used if a satisfactory response is not obtained with bevacizumab. Ranibizumab is generally used in patients developing uveitis or intolerance to the two other compounds [8]. There were no cases of endophthalmitis, traumatic cataract or retinal detachment. In two injections, there was a temporary intraocular pressure elevation above 40 mmHg, with pain or acute visual decline. In both cases, the intraocular pressure elevation resolved with topical hypotensive medications.

The mean central foveal thickness (CFT) was 443 (SD 218) µ at baseline. During follow-up the difference of CFT to baseline was -130 (174) µ at one year and -146 (188) µ, -138 (160) µ and -154 (180) µ at the second, third and fourth years, respectively. At baseline 82/107 (78%) patients had subretinal fluid (SRF), 55/107 (51%) had intraretinal fluid (IRF) and 97/108 (86%) had a pigment epithelial detachment (PED, including all elevations of the pigment epithelium, with or without fluid). At the last follow-up the corresponding proportions were 25/107 (23%) for SRF, 42/107 (39%) for IRF and 93/108 (86%) for PED.

Visual outcome

The mean visual acuity of all patients at baseline was 56.3 (SD 16.2, n=110) letters. The mean last VA of the first year was 59.7 (20.2, 110). The corresponding values for the second, third and fourth years were 60.8 (20.6, 99), 60.0 (19.0, 72) and 59.7 (19.3, 54).

The mean difference between the baseline VA and the last VA measurement of each year was +3.39 (SD 14.6) in the first year, +3.59 (17.6) in the second year, +0.08 (18.9) in the third year and +3.08 (14.3) in the fourth year.

We also calculated the difference to baseline VA from the individual mean of all VA measured during each year. The letters gained were +4.14 (SD 11.0) the first year, +3.92 (15.1) the second year, +2.29 (15.7) the 3rd year and +3.01 (14.3) the fourth year.

The visual acuity changes at the different corresponding time points were also analysed in the follow-up time cohorts G1 to G4. The difference (mean) of the last VA measurement compared to baseline was -8.1 letters (SD 10.7) in G1, -1.22 letters (18.8) in G2, -7.2 letters (20.9) in G3 and +3.0 letters (14.3) in G4. Although the G4 tended to have a better VA value, the differences were not statistically significant (ANOVA). It should be noted that all the values for G1 to G3 were those obtained at dropout, whereas G4 included also values obtained at study end.

When the difference to baseline was calculated from the mean of all VA: s measured each year the difference was -6.9 (SD=10.2) in G1, +0.18 (16.3) in G2 -4.85 (18.2) treated in G3 and +3.3 (14.4) in G4.

The actual last VA: s and the change from baseline show a trend of VA values being lower in the shorter follow-groups and tending to be worst at the time of the final VA assessment (**Figure 1**).

The last VA improved above baseline level in only 2.7% of patients with a baseline VA of <35 letters. The corresponding percentages for patients with baseline visual acuity of <59, <70 and <80 were 17.3%, 22.7% and 10.9%, respectively. Most of the improvements occurred in the patients within the longer follow-up groups (**Table 3**).

Length of follow-up seems to correlate with permanent visual acuity worsening. Patients with shorter follow-up times had earlier drops under the thresholds (baseline, >5 letter loss and >15 letter loss). Vice versa, patients with >3 years' follow-up time had smallest proportions in each category, as shown in **Figure 2.**

When all patients were analysed, the early VA response was associated with later VA outcome during the first 3 years (**Table 4**). Baseline VA, sex or patient age did not significantly predict the outcome. A similar pattern was observed when the different follow-up groups were analysed separately, but the effect attenuated during a longer follow-up (**Figure 3**).

DISCUSSION

The Helsinki-Uusimaa hospital district is the sole payor of publicly funded nAMD treatments in the region. Comprehensive private health insurance is uncommon, and practically all nAMD patients

ultimately enroll into our program. However, some patients are willing to take the first injection privately in order to ensure an earlier start of the treatment regimen. Such patients contributed to the 41 subjects excluded from the study due to having received anti-VEGF injections elsewhere. It is possible that their treatment outcome was different to those of the included subjects. With this reservation, we feel, however, that our material reasonably describes the nAMD treatment results in our region.

The baseline mean visual acuity of 56.3 (16.2) letters was typical for real-world studies, although also higher values have been described Gillies et al [10].

Our overall visual results of VA +3.39, +3.59, +0.08 and +3.08 letters above baseline at years 1, 2,3 and 4, respectively, are in the range reported earlier in studies on real-life AMD treatments. Kim et al. [11] reported in a meta-analysis a mean improvement of +5.0, +3.0 and +1.1 letters above baseline after years 1,2 and 3, respectively. The large UK EMR users group study [4] reported a change from a baseline +2, +1 and -2 at the same time-points, starting from a baseline value of 55 letters, close to our baseline value of 56 letters. A recent large Danish study by Brynskov et al [12] reported VA improvement of +0.7, -1.0, -1.8 and -2.4 letters, at year 1, 2, 3 and 4, respectively, after PRN treatment with ranibizumab or aflibercept. However, in the recent Moorfields cohort study, VA improvement of +5.5, and +4.9 letters above baseline after the first and second years were reported [15]. These differences may reflect baseline lesion variations, the drugs used or injection protocols. We do not have representative data on angiographic types of choroidal neovascularisation (CNV) in our patients. However, a previous study on Finnish AMD patients showed a lesion type distribution similar to other reports on caucasian subjects (Seitsonen et al [13], Invernizzi et al[14]).

We performed multiple logistic regressions to study the effect of initial VA response on later response after 1 , 2 , 3 and 4 years.

We observed that patients with an early improvement of VA were more likely to retain a VA value better than that before treatment, in agreement with earlier reports [16]. However, this effect appeared to be attenuated during longer follow-up as shown by the coefficients of initial response in the later logistic regressions. This fading of the initial response effect with the longer follow-up

time may be due to late recoverers [17] or due to tissue changes such as atrophy or fibrosis developing in a longer follow-up, and not directly related to excess VEGF.

During the four year follow-up, a significant number of patients dropped out of treatment, with the cumulative percentage of patients terminating follow-up and treatment being 9% at 1 year, 31% at 2 years and 51% after three years, findings in agreement with the report by Brynskov et al [12]. In previous studies, dropout rates from 17% up to 34% have been reported after 1 year [4, 18, 19], 16 % up to 47 % after 2 years [6, 20, 21], up to 47% after 4 years [22] and up to 54% after 5 years [10]. Twelve of our patients (15%) were not followed further after having an inactive lesion for 12 months. This in agreement with Amarakoon et al [23], who raported 19% of lesions to be inactivated with one-year PRN treatment to keep inactive for at least 12 months. The extended course of these patients in our material is not known.

Anyhow, it can be questioned, whether it is meaningful to consider the longer term annual VA reports as a treatment outcome, since the population being treated e.g. at the first year is quite different to that treated during the fifth year.

We analyzed our patients as subcohorts based on the eventual follow-up. We found the early and late treatment responses to be generally worse in those dropping out, compared to patients treated for more than three years, findings in agreement with the one and two year follow-up results of Fasler et al [15].

In observational study materials the recorded VA seems to fluctuate from one visit to another. This may be due to the patients' state of alertness at the recording of the VA, and the time allowed for the patient to recognize the letters. To evaluate the timing or significant changes in visual acuity we also looked at the timing of permanent major changes in VA. The rate of permanent visual loss was linear in all groups up to the last months before dropping out. The follow-ups seemed to terminate in each group when 30 to 40 percent of subjects had reached a major visual acuity decline treshold. We could also confirm the predictive value of early VA response to treatment on later course of visual acuity, in accord with earlier studies [16].

Since the time-points of VA evaluation vary in real-life treatment, the time point chosen for analysis also has significance. We chose the last value in the time interval to be reported, to get a value closest to end of the period. Another possibility would have been to use annual means, which we employed for comparison for some reporting, with possibly more stable values. It appeared

especially in the groups dropping out early that the last value was much worse than the annual mean. This phenomenon makes the overall results look worse and affects the whole follow-up especially if 'the last observation carried forward'-procedure is used in reporting.

The treatment protocol used in our patients was generally a modified PRN, widely used in our country at the time of the study. The visit intervals were adjusted according to the previous interval and response, in which an injection was given only when activity was present. It is conventional to give loading dose of three monthly injections, but it is at the discretion of each clinician. Currently, our center follows a modified treat-and extend strategy requiring somewhat less frequent patient visits. It is difficult to tell whether the results would have been different had a more strict treat and extend protocol been employed. Nevertheless, the injection protocol resembled those reported in treat-and extend protocols.

CONCLUSIONS

Our results show that data from real world nAMD treatment consist of subpopulations with differing visual courses and treatment times. This highlights the challenges in comparing different treatment protocols, treatment centers and medications. The patients with shorter duration of follow-up had lower baseline VA and earlier decline in VA. Final visual acuity scores were also lower in groups with shorter follow-ups. The initial VA response predicted later VA. New methods, taking also into account patients with interrupted treatment, need to be developed for these comparisons.

Acknowledgement

Dr Jia Liu contributed to the study while staying at The Department of Mathematics and Statistics, University of Helsinki. We are grateful for advice and discussions with Docent Dario Gasparra, Ph.D, The Department of Mathematics and Statistics, University of Helsinki.

Statement of Ethics

The study protocol was reviewed and approved by the Operative Ethics Committee of the Helsinki University Hospital (approval number 6/13/03/02/2014). Consent to participate statement was not required, because data were collected from patient record only. The study was conducted ethically in accordance with the Declaration of Helsinki.

Conflict of Interest Statement

Terhi Ollila has given one presentation, which was paid by Bayer in 2017. All other authors have no conflicts of interest to declare.

Funding Sources

Supported by grants from The Finnish Eye Foundation, Helsinki, Finland (Ollila); The Eye and Tissue Bank Foundation, Helsinki, Finland (Ollila); Finnish Ophthalmological Society, Helsinki, Finland (Ollila); The Evald and Hilda Nissi Foundation, Helsinki, Finland (Ollila, Silvennoinen, Immonen); Helsinki University Hospital (HUS) research funds (Immonen, Liu, Silvennoinen); Academy of Finland, Research mobility grant (Joshi) and Professor Sangita Kulathinal's start-up grant (Silvennoinen).

Author Contributions

Terhi Ollila: data collection, interpretation of data, literature review, writing the article

Juuso Silvennoinen: analysis and interpretation of data, drafting of the article

Ashwini Joshi: analysis and interpretation of data, drafting of the article

Jia Liu: analysis and interpretation of data, drafting of the article

Sangita Kulathinal: analysis and interpretation of data, drafting of the article

Ilkka Immonen: design of the work, analysis and interpretation of data, drafting of the article

Data Availability Statement

Data are not available publicly to avoid compromising the privacy of the patients. Enquiries regarding the data can be directed to the corresponding author.

REFERENCES

1. Rosenfeld PJ, Brown DM, Heier JS, Boyer DS, Kaiser PK, Chung CY, Kim RY & Group MS (2006): Ranibizumab for neovascular age-related macular degeneration. N Engl J Med 355: 1419–1431.

2. Brown DM, Kaiser PK, Michels M, Soubrane G, Heier JS, Kim RY, Sy JP, Schneider S & Group AS (2006): Ranibizumab versus verteporfin for neovascular age-related macular degeneration. N Engl J Med 355: 1432–1444.

3. Singer A, Awh CC, Sadda S, Freeman W, Antoszyk A, Wong P & Tuomi L (2012): HORIZON: an open-label extension trial of ranibizumab for choroidal neovascularization secondary to age-related macular degeneration. Ophthalmology 119: 1175-1183.

4. Writing Committee for the UK Age-Related Macular Degeneration EMR Users Group (2014): The neovascular age-related macular degeneration database: multicenter study of 92 976 ranibizumab injections: report 1: visual acuity. Ophthalmology 121: 1092–1101.

5. Wong T, Chakravarthy U, Klein R, Mitchell P, Zlateva G, Buggage R, Fahrbach K, Probst C & Sledge I (2008): The natural history and prognosis of neovascular Age-Related Macular Degeneration. A systematic review of the literature and meta-analysis. Ophthalmology 115:116–126.

6. Holz FG, Tadayoni R, Beatty S, Berger A, Cereda MG, Hykin P, Staurenghi G, Wittrup-Jensen K, Altemark A, Nilsson J, Kim K & Sivaprasad S (2016): Key drivers of visual acuity gains in neovascular age-related macular degeneration in real life: findings from the AURA study. Br J Ophthalmol 100: 1623–1628.

7. Mehta H, Tufail A, Daien V, Lee AY, Ngyen V, Ozturk M, Barthelmes D & Gillies M (2018): Real-world outcomes in patients with neovascular age-related macular degeneration treated with intravitreal vascular endothelial growth factor inhibitors. Prog Retin Eye Res 65: 127-146.

8. Tuuminen R, Uusitalo-Järvinen H, Aaltonen V, Hautala N, Kaipiainen S, Laitamäki N, Ollila M,Rantanen J, Välimäki S, Sipilä R, Laukkala T, Komulainen J, Tommila P, Immonen I, Tuulonen A & Kaarniranta K The Finnish national guideline for diagnosis, treatment and follow-up of patients with wet age-related macular degeneration (2017): Acta Ophthalmol 95 Suppl i1-i9.

9. Kosmidis I & Firth D (2020). Jeffreys-prior penalty, finiteness and shrinkage in binomial-response generalized linear models. Biometrika doi: 10.1093/biomet/asaa052.

10. Gillies MC, Campain A, Barthelmes D, Simpson JM, Arnold JJ, Guymer RH, McAllister IL, Essex RW, Morlet N, Hunyor AP & Fight Retinal Blindness Study Group (2015): Long-term outcomes of treatment of neovascular age-related macular degeneration: data from an observational study. Ophthalmology 122: 1837–1845.

11. Kim LN, Mehta H, Barthelmes D, Nguyen V & Gillies MC (2016): Meta-analysis of real-world outcomes of intravitreal ranibizumab for the treatment of neovascular age-related macular degeneration. Retina 36: 1418–1431.

12. Brynskov T, Munch I, Larsen T, Erngaard L & Sorensen T (2020): Real-world 10-year experiences with intravitreal treatment with ranibizumab and aflibercept for neovascular age-related macular degeneration. Acta Ophthalmol 98: 132–138.

13. Seitsonen S, Järvelä I, Meri S, Tommila P, Ranta P & Immonen I (2007): Complement factor H Y402H polymorphism and characteristics of age-related macular degeneration lesion. Acta Ophthalmol 86:390-394

14. Invernizzi A, Barthelmes D, Fung A, Vincent A & Gillies M Five-Year Real-World Outcomes of Occult and Classic Choroidal Neovascularization (2019): Data From the Fight Retinal Blindness! Project. Am J Ophthalmol 204: 105-112

15. Fasler K, Morales G, Wagner S, Kortuem KU, Chopra R, Faes L, Preston G, Pontikos N, Fu DJ, Patel P, Tufail A, Lee AY, Balaskas K & Keane PA (2019): One- and two-year visual outcomes from the Moorfields age-related macular degeneration database: a retrospective cohort study and an open science resource. BMJ Open 9:e027441. doi:10.1136.

16. Ying G, Maguire MG, Daniel E, Ferris FL, Jaffe GF, Grunwald JE, Toth C, Huang J, Martin DF & Comparison of Age-Related Macular Degeneration Treatments Trials (CATT) Research Group (2015): Association of Baseline Characteristics and Early Vision Response with Two-Year Vision Outcomes in the Comparison of AMD Treatments Trials (CATT). Ophthalmology 122: 2523–2531.

17. Stoller GL, Kokame GT, Dreyer RF, Shapiro H & Tuomi L (2016). Patterns of early and delayed response to ranibizumab treatment for neovascular age-related macular degeneration. JAMA Ophthalmol 134: 545-553.

18. Gupta OP, Shienbaum G, Patel AH, Fecarotta C, Kaiser RS & Regillo CD (2010): A treat and extend regimen using ranibizumab for neovascular age-related macular degeneration: clinical and economic impact. Ophthalmology 117: 2134–2140.

19. Hjelmqvist L, Lindberg C, Kanulf P, Dahlgren H, Johansson I & Siewert A (2011): One-year outcomes using ranibizumab for neovascular age-related macular degeneration: results of a prospective and retrospective observational multicentre study. J Ophthalmol 2011: 405724.

20. Abedi F, Wickremas S, Islam AF, Inglis KM & Guymer RH (2014): Anti-VEGF treatment in neovascular age-related macular degeneration: a treat-and-extend protocol over 2 years. Retina 34: 1531–1538.

21. van Asten F, Evers-Birkenkamp KU, van Lith-Verhoeven JJ, de Jong-Hesse Y, Hoppenreijs VP, Hommersom RF, Scholten AM, Hoyng CB, Klaver JH & HELIOS study group (2015): A prospective, observational, open-label, multicentre study to investigate the daily treatment practice of ranibizumab in patients with neovascular age-related macular degeneration. Acta Ophthalmol 93: 126–133.

22. Pushpoth S, Sykakis E, Merchant K, Browning AC, Gupta R &Talks SJ (2012): Measuring the benefit of 4 years of intravitreal ranibizumab treatment for neovascular age-related macular degeneration. Br J Ophthalmol 96: 1469–1473.

23. Amarakoon S, Martinez-Ciriano J, Baarsma S, van den Born I, & Missotten T (2021): Reactivation of CNV after discontinuation of Bevacizumab treatment of age-related macular degeneration. Ophthalmologica 244: 200-207.

LEGENDS TO FIGURES

Legend to Figure 1:

Shorter follow-up time seems to be associated with lower visual acuity at baseline and at follow-up visits. Mean visual acuity calculated from the last year's follow-up visits, appears lower than in the preceding years.

ANOVA indicated a difference in year 1 (p = 0,002), year 2 (p = 0.01) and year 3 (p = 0.03) scores compared to baseline. Post hoc analysis suggested a groupwise difference to baseline of the <1 year and >3 years treated groups at the first year (p 0.005); and 2-3 years and >3 years treated groups at the second (p 0.03) and third years (p 0.03).

462 Red asterisk represents mean, black transversal line median and grey dots outliers.

463

464 Legend to Figure 2:

465 Patients in the longest follow-up group tend to have less permanent visual acuity loss in all
466 categories (visual acuity worsening below baseline level, at least five ETDRS letter loss, or least 15
467 ETDRS loss). Up to 30 % of patients followed up for > 3 years had permanent loss of visual acuity
468 below baseline level. Up to 20 % experienced loss of >5 letters and 15 % > 15 letters. The
469 proportions are higher in other groups, especially within patients of <1 year follow-up. Permanent
470 visual acuity loss is defined as ETDRS score permanent decrease below a threshold, and not
471 improving above the threshold during follow-up.

472

473 Legend to Figure 3:

474 Initial response to treatment shows correlation with better outcome. Sex or patient age seem not
475 to have strong effect on good outcome, which was here defined as patients with VA above baseline
476 at last visit. Initial VA response was defined as improvement of VA above baseline at six months.
477 The graphs present annual results of different follow-up groups. Interpretation; to the right of 0:
478 association with better results for females (sex) and associated with a better final VA (other
479 parameters).

480

481

482 Word count: 3520 words