Characterising Treatment Outcomes of Patients Achieving Quarterly Aflibercept Dosing for Neovascular Age-Related Macular Degeneration: Real-World Clinical Outcomes from a large Tertiary Care Centre

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Abbreviations:

OCT – optical coherence tomography

SDOCT – spectral domain optical coherence tomography

ETDRS – Early Treatment Diabetic Retinopathy Study

VA – visual acuity

SD – standard deviation

SE – standard error

CI – confidence interval

Abstract:

Background and objective: To evaluate the proportion of patients achieving a 12 week (q12) aflibercept dosing interval in patients with neovascular age related macular degeneration (nAMD).

Patients and methods: Retrospective, comparative, non-randomised electronic medical record (EMR) database study of the Moorfields database of treatment-naïve nAMD eyes. Extraction criteria included at least 7 aflibercept injections in first year of treatment, AMD in the diagnosis field of EMR and minimum of 1 year follow up data.

Results: There were 2416 eyes of 2163 patients started on anti-vascular endothelial growth factor (anti-VEGF) between 01-11-2013 & 14-02-2020 who had received at least 7 aflibercept intravitreal injections (electronic database accessed March 2021). Of these, 1674 (68%) eyes of 1537 patients had at least one q12 dosing interval (>=84 and <=98 days between injections) during the first 2 years of treatment. This included 926 (61.8%) female patients and 856 (right eyes age at 1st injection, 936 (62.4%) Caucasian and 32 (2.1%) Afro-Caribbean patients. The median time to the first q12 injection (95% confidence interval) was 1.76 years (1.70 – 1.86) with mean (±SD) of 11.8 (±6.0) injections. Visual acuity (ETDRS letters) of the eyes without q12 injection and eyes with a q12 injection was 57.9 ± 14.7 and 56.7 ± 14.8 respectively at baseline, 61.4 ± 18.1 and 63.0 ± 15.9 respectively at 12 months and 61.2 ± 20.1 and 61.1 ± 17.8 respectively at 24 months.

Conclusion: 68% of eyes were able to achieve a q12 injection dose within the first 2 years of treatment. Eyes achieving a q12 injection in the first 2 years achieved a similar visual acuity outcome at both 1 and 2 year follow up to those unable to do so, with a fewer number of total injections.

Introduction

Anti-vascular endothelial growth factor (Anti-VEGF) treatment is well established as the standard of care for the treatment of neovascular age related macular degeneration (nAMD). In the United Kingdom, individualised treat-and-extend treatment protocols have been widely used as a proactive treatment regimen in order to manage patients with nAMD in the National Health Service, with patients achieving an extended interval between successive treatments if clinically stable in terms of visual acuity and structural assessment.[1] Understanding the proportion of patients able to achieve a longer treatment interval of 12 weeks (q12) in real-world practice is particularly important when planning the delivery of high-volume intravitreal anti-VEGF injection services. It would also allow patients to be counselled more accurately about the likelihood of achieving extended treatment intervals, by using data from real-world patient cohorts rather than trying to extrapolate from clinical trial data. However, the motivation of minimising treatment burdens through extended treatment intervals needs to be achieved without the poorer visual acuity outcomes associated with undertreatment. Data have shown that undertreatment with aflibercept is associated with poorer visual acuity outcomes both in the first and second year of treatment.[2 3] This may result from uncontrolled exudation (particularly intraretinal fluid) and/or haemorrhage leading to macula atrophy, fibrosis and/or disorganisation of retinal architecture.[4,5] Therefore, it is essential to characterise the visual acuity outcomes of patients achieving an extended treatment interval on a treat-and-extend regimen.

Previous studies have reported that the proportion of patients achieving a q12 treatment interval on a treat-and-extend regimen has ranged from 24 – 52%.[6-9] However, these smaller studies are perhaps not fully generalisable to real-world clinical practice. The change in visual outcome of those patients achieving a q12 treatment interval also need further characterisation. The VIEW studies defined the management of nAMD with aflibercept in a fixed dose regimen for the first year of treatment.[10] However, in a post-hoc analysis of the

VIEW trials, Khurana et al also observed that visual acuity outcomes in fixed interval treatment at 1 year was maintained at 2 years, both in those treated at less than 12 weeks and at least 12 weeks. This suggests that similar visual acuity outcomes may be possible with extended treatment intervals in appropriate eyes, at least in a clinical trial setting.[11]

Studies employing electronic medical record (EMR) data have been used to perform high-quality analyses of the real-world treatment outcomes of patients with nAMD and diabetic macular edema (DME).[12, 13] In the United Kingdom, analysis of the EMR database at Moorfields Eye Hospital, London has enabled the reporting of both one and two-year real-world treatment outcomes of 3357 patients, which to our knowledge remains the largest single-centre cohort of patients with treated nAMD in the world.[14] The retrospective nature of such EMR-based studies has limitations, in comparison with clinical trial data, particularly in terms of consistency of patient characterisation and data integrity. However, these studies allow high-volume analyses that are more generalisable to real-world practice.

The aims of this study were to evaluate the proportion of patients treated with aflibercept for nAMD who were able to achieve a q12 treatment interval in the first two years of treatment and to characterise their visual acuity outcomes.

Materials and Methods:

Study Design:

This was a retrospective, cohort study from the EMR data at Moorfields Eye Hospital, London. This study adhered to the tenets of the Declaration of Helsinki and was approved by the local Clinical Effectiveness and Audit Committee.

Study Population

Treatment-naïve patients diagnosed with nAMD, commenced on treatment between 01-11-2013 and 01-01-2020 and treated with intravitreal anti-VEGF were included in the study. In order to extract subjects managed on a treat-and-extend regimen, patients were included who were treated with aflibercept only from 01-11-2013 when treatment with aflibercept at Moorfields Eye Hospital commenced. Subjects were included if they had completed a minimum of 7 injections in the first 12 months (± 2 months) ensuring a minimum of 1 year follow-up. Subjects with baseline visual acuity (VA) available were included.

Outcome Measures

The primary outcome measure was the proportion of eyes achieving at least one q12 retreatment interval in the first 2 years of treatment. A window of +/-7 days for defining the q12 retreatment interval was chosen in keeping with standard practice in clinical trial reporting.

The secondary outcomes measures included: mean ± SD (median, min – max) VA at baseline, 12 and 24 months; proportion of patients with VA ≥ 35 or VA ≥ 70 ETDRS (Early Treatment of Diabetic Retinopathy Study) letter score at baseline, 12 and 24 months; median (95% confidence interval) time to the first q12 injection interval; median (min – max) and mean ± SD number of injections at 12 months and 24 months since commencement of treatment. These secondary outcomes at the timepoints of 12 and 24 months were defined with a

window of +/- 60 days, as patients had varying treatment intervals on a treat-and-extend regimen.

Statistical Analysis:

All statistical analyses were conducted using the statistics software package R (https://www.r-project.org/ provided in the public domain by the R Core Team 2017 R Foundation for Statistical Computing, Vienna, Austria.

Results:

Study subjects

The number identified from the EMR dataset who were treatment-naïve and commenced treatment for nAMD between 1-10-2013 and 01-01-2020 were 3731 eyes of 3269 patients. Of these, 3240 eyes (86.7%) of 2833 patients who had been treated with aflibercept only). Of these, 2842 eyes of 2213 patients had completed a minimum of 7 injections in the first year (± 2 months) of treatment. Baseline clinical information including VA was available in 2416 eyes of 2163 patients. The final study population was these 2416 eyes; this included 1178 (48.8%) left and 1238 (51.2%) right eyes.

Subjects achieving a quarterly treatment interval

The number of eyes achieving at least one q12 treatment interval in the first two years after commencing aflibercept treatment was 16774 eyes of 1499 patients. The remaining 742 eyes of 664 patients did not achieve this. The median time until eyes achieved the first q12 interval after beginning treatment was 1.76 years (95% CI 1.70 - 1.86) with a median (min - max) number of injections 10 (6 – 50) (Figure 1).

Demographic characteristics including baseline age, ethnicity as well as laterality are shown in Table 1, separately for subjects who did and did not achieve a q12 treatment interval. There was a range of self-reported ethnicities of patients being treated, but most commonly in both groups were Caucasian patients at 936 (62.4%), 409 (61.6%) in those with and without a quarterly interval and 1345 (62.2%) overall in this study. The mean ± SD age of subjects was similar at 79.3 ± 8.1 years (without a q12), 78.3 ± 9.0 years (with a q12 and 79.0 ± 8.4 years (overall).

Visual Acuity outcomes

Mean ± SD (median, min-max) VA was 56.7 ± 14.8 (60.0, 0 - 92.0) ETDRS letters and 57.9 ± 14.7 (61.0, 5.00 – 85.0) ETDRS letters at baseline and 61.1 ± 17.8

(65.0, 2.00 – 90.0) and 61.2 ± 20.1 (66.0, 0 - 99.0) at 24 months for the eyes with and without a q12 intravitreal injection treatment respectively. All visual acuity outcomes at baseline, 12 and 24 months are shown in Table 1. Figure 2 shows the mean VA and mean change in VA over two years, separately for the two groups. Mean VA (and change in VA) at 12 months was numerically greater in the group that achieved a q12 interval than those that did not, but the VA outcome at 24 months was similar between the two groups.

The number of patients who achieved a q12 treatment and attain VA ≥ 70 ETDRS letters was 418 (25.0%) at baseline, 685 (40.9%) at 12 months and 685 (40.9%) at 24 months. The number of patients who do not achieve a q12 treatment and had a VA ≥ 70 ETDRS letters was 224 (30.2%) at baseline, 294 (39.6%) at 12 months and 249 (33.6%) at 24 months.

The number of patients who achieved a q12 treatment maintaining VA ≥ 35 ETDRS letters was 1538 (91.9%) at baseline, 1506 (90.9%) at 12 months and 1392 (83.2%) at 24 months. The number of patients who did not achieve a q12 treatment maintaining VA ≥ 35 ETDRS letters was 693 (93.4%) at baseline, 638 (86.0%) at 12 months and 508 (68.5%) at 24 months.

For those achieving a q12 injection treatment in the first two years the mean visual acuity was 61.6 ± 16.8 at the time of the first q12 injection.

Intravitreal Treatment Frequency

The total number of injections given for these patients are shown in Table 1. The mean number of intravitreal injections in patients who did achieve a q12 intravitreal injection treatment was 13.8 ± 2.3 (13.0, 9.00 - 24.0) at 24 months. The mean number of intravitreal injections in patients who did not achieve a q12 intravitreal injection treatment was 16.9 ± 3.3 (17.0, 8.00 – 26.0) at 24 months.

Discussion

In our cohort of 2416 eyes with nAMD receiving a minimum of 7 aflibercept injections in the first year of treatment, 67% were able to achieve at least one q12 dosing of aflibercept in the first two years of treatment. The median time until a patient achieved a q12 dosing after beginning treatment was 1.76 years (1.70 - 1.86) with a median number of injections of 10. The mean number of intravitreal injections in patients who achieved and did not achieve a q12 intravitreal injection treatment was 13.8 $\pm$ 2.3 and 16.9 $\pm$ 3.3 at 24 months.

This study indicates that a substantial proportion of eyes (67%) treated with aflibercept for nAMD were able to achieve at least one q12 injection interval in the first two years of treatment. This information can be used to advise patients about the likelihood of achieving extended intervals in the first two years of treatment. It also provides important information for planning of clinical services, in terms of estimating likely demands for patient through-put, imaging requirements, and numbers and cost of anti-VEGF drugs. However, for those eyes achieving a q12 interval, the median time of 21 months to the first q12 interval suggests that most eyes do not achieve this until close to the end of two years of treatment. Indeed, even with extension increments of two weeks, the earliest possible time-point of achieving a q12 interval is 17.5 months (i.e. with one extension from q8 to q10 and a second from q10 to q12, in the absence of significant disease activity or VA loss at either visit).

As those achieving at least one q12 interval require fewer injections, this might suggest that these patients are more stable in terms of their disease activity. Furthermore, both the mean VA outcome and the proportion of patients maintaining good VA of > 70 ETDRS letters (approximately 6/12 or better on the Snellen scale) at 24 months were similar, between groups, despite a lower number of injections in the q12 group. It is reassuring that both those with and without a q12 injection are able to achieve similar visual acuity outcomes suggesting that those with q12 dosing are receiving an appropriate number of number of injections to achieve good treatment outcomes. Baseline visual acuity was similar between the groups of patients suggesting that VA is not a predictive factor in the stability associated with achieving

a q12 treatment. Similarly, it appeared that age, sex and ethnicity was similar for those achieving and not achieving a q12 treatment interval in our study.

A meta-analysis investigating disease stability and extended dosing in nAMD found that 34.2% and 47.7% of subjects were extended to q12 treatment by 12 and 24 months respectively.[15] We report that a higher number of patients were able to achieve a q12 injection with aflibercept, compared with the meta-analysis performed by Garweg and Gerhardt.[15] Indeed, Garweg has noted that 43% of eyes were able to achieve at least 12-weekly dosing using aflibercept with a treat-and-extend regimen by the end of the 2 year of treatment.[16] It is important to note that, whilst similar patients were included in these studies, our study was a single-centre study where treatment decisions were based in a more uniform pattern based on local treatment protocols despite being assessed by multiple clinicians. Our study suggests that those able to achieve a q12 dose with aflibercept achieve similar visual acuity outcomes to those who did not.

Our study adhered to standardised methods for the reporting of observational studies (The Strengthening the Reporting of Observational Studies in Epidemiology – STROBE Statement). The strengths of this study include that it reports the real-world treatment patterns in a large cohort of patients treated for nAMD. This is a large cohort of patients treated over two years with the same intravitreal agent. These data can be used to help counsel patients about patterns of treatment response when using a proactive treatment regimen; this enables discussion about the possible frequency of clinic visits. The study defined the main clinical endpoints of a quarterly injection interval by a window of +/- 7days, in accordance with previous clinical trials in medical retina conditions. As patients had varying treatment intervals at 12 and 24 months, VA and intravitreal injection data endpoints were chosen with time windows of +/- 60 days at 12 and 24 months. The time window of 60 days for endpoint data collection are appropriate to this real-world clinical study using EMR to extract clinical data reflects the variability of patient appointments and attendance. We note the rate of missing data in our cohort, particularly VA data at 24 months. This reflects normal variability in follow-up intervals clinically; in the future, alternative methods including further time-to-event

analyses may be considered.[17, 18] Furthermore, the rate of this missing data is consistent with previous real-world study.[19] Although patients with regular treatment with aflibercept were extracted, it is possible that some treatment intervals might have be affected by patient non-attendance, contraindication to treatment (e.g. concurrent ocular infection or new systemic thromboembolic event) or indeed switching to treatment with ranibizumab because of limited response to treatment with aflibercept. The number of patients who were lost to follow-up or in whom we have limited information regarding VA or injection frequency is noted; indeed, this has previously been described as a limitation of large volume real-world studies using EMR data.[20]

Building on this work, future studies could consider which features of retinal morphology and OCT characteristics would permit these extended treatment intervals, with some studies suggesting small amounts of subretinal fluid may not be detrimental to visual acuity outcomes and other studies suggesting that fluctuations in structural OCT nAMD disease biomarker volume could lead to worse treatment outcomes.[21] Similar studies in those treated in both diabetic macula edema and cystoid macula edema secondary to retinal vein occlusion would be possible, with the understanding that the treatment decision may vary more widely in these conditions.

In conclusion, we utilise our large real-world cohort study to report that 67% of eyes treated with aflibercept for nAMD were able to achieve at least one quarterly injection with aflibercept in the first two years of treatment. In addition, we observed that there was a similar VA outcome at 24 months in eyes that did and did not achieve quarterly treatment, with fewer total injections in the former group, suggesting that those achieving quarterly treatment had more stable disease activity.

Figures Legends:

Figure 1: Kaplan-Meier graph showing the length of time to the first quarterly injection with aflibercept for neovascular age-related macular degeneration

Figure 2: Visual acuity of patients with neovascular age-related macular degeneration with and without a quarterly (q12) intravitreal injection treatment

Visual acuity of patients with neovascular age-related macular degeneration with and without a quarterly (q12) intravitreal injection treatment showing mean visual acuity (a) and change in visual acuity (b)

Tables

Table 1: Demographic characteristics of patients included in the study including those with and without quarterly (q12) injection treatment

	Does not have a quarterly injection N=664	Has a quarterly injection N= 1499	All Patients (n = 2163)
Age (years)			
Mean (SD)	78.3 (9.0)	79.3 (8.1)	79.0 (8.4)
Median (min, max)	79.0 (49.0, 97.0)	80.0 (53.0, 100)	80.0 (47.0, 100)
Gender, n (% female)	392 (59.0)	926 (61.8)	1318 (60.9)
Ethnicity			
Afrocarribean	7 (1.1)	32 (2.1)	39 (1.8)
Caucasian	409 (61.6)	936 (62.4)	1345 (62.2)
Chinese	5 (0.8)	5 (0.3)	10 (0.5)
Mixed	2 (0.3)	5 (0.3)	7 (0.3)
South-East Asian	48 (7.2)	151 (10.1)	199 (9.2)
Other	193 (21.1)	370 (24.7)	563 (26.0)

Table 2: Visual acuity and intravitreal injections of eyes treated in study with and without a quarterly (q12) injection and overall

	Does not have a quarterly injection N=742	Has a quarterly injection N= 1674	All Patients (n = 2416)
Baseline VA			
Mean (SD)	57.9 (14.7)	56.7 (14.8)	57.0 (14.8)
Median (Mix, Max)	61.0 (5.00, 85.0)	60.0 (0, 92.0)	60.0 (0, 92.0)
VA at 12 months			
Mean (SD)	61.4 (18.1)	63.0 (15.9)	62.5 (16.6)
Median (Mix, Max)	65.0 (2.00,90.0	65.0 (6.00, 98.0)	65.0 (2.00, 98.0)
Missing *n (%)*	27 (3.6)	53 (3.2)	80 (3.2)
VA at 24 months			
Mean (SD)	61.2 (20.1)	61.1 (17.8)	61.1 (18.4)
Median (Mix, Max)	66.0 (0,99.0	65.0 (2.00, 90.0)	65.0 (2.00, 99.0)
Missing *n (%)*	160 (21.6%)	126 (7.5)	286 (111.8)
VA ≥ 70 at baseline *Mean (SD)*	224 (30.2)	418 (25.0)	642 (26.6)
VA ≥ 70 at 12 months			
Mean (SD)	294 (39.6)	685 (40.9)	979 (40.5)
Missing *n (%)*	27 (3.6)	53 (3.2)	80 (3.23)
VA ≥ 70 at 24 months			
Mean (SD)	249 (33.6)	641 (38.3)	890 (36.8)
Missing *n (%)*	160 (21.6)	126 (7.5)	286 (11.8)
VA ≥ 35 at baseline	693 (93.4)	1538 (91.9)	2231 (92.3)
VA ≥ 35 at 12 months			
Mean (SD)	638 (86.0)	1506 (90.0)	2144 (88.7)
Missing *n (%)*	27 (3.6)	53 (3.2)	80 (3.3)
VA ≥ 35 at 24 months			
Mean (SD)	508 (68.5)	1392 (83.2)	1900 (78.6)
Missing *n (%)*	160 (21.6)	126 (7.5)	286 (11.8)
Total injections at 12 months			
Mean (SD)	8.7 (1.3)	8.1 (0.9)	8.3 1.1)
Median (Mix, Max)	9.00 (6.00, 14.0)	8.00 (6.00, 15.0)	8.00 (6.00, 15.0)
Missing *n (%)*	87 (11.7)	145 (8.7)	232 (9.6)
Total injections at 24 months			
Mean (SD)	16.9 (3.3)	13.8 (2.3)	14.7 (3.0)
Median (Mix, Max)	17.0 (8.00, 26.0)	13.0 (9.00, 24.0)	14.0 (8.00, 26.0)
Missing *n (%)*	32.5 (43.8)	669 (40.0)	994 (41.1)

References

1. McKibbin M, Devonport H, Gale R, et al. Aflibercept in wet AMD beyond the first year of treatment: recommendations by an expert roundtable panel. *Eye (Lond)*. Jul 2015;29 Suppl 1(Suppl 1):S1-s11. doi:10.1038/eye.2015.77
2. Hsu J, Regillo CD. Poorer Outcomes in Real-World Studies of Anti-Vascular Endothelial Growth Factor Therapy for Neovascular Age-Related Macular Degeneration. *Ophthalmology*. Sep 2020;127(9):1189-1190. doi:10.1016/j.ophtha.2020.03.034
3. Almuhtaseb H, Johnston RL, Talks JS, Lotery AJ. Second-year visual acuity outcomes of nAMD patients treated with aflibercept: data analysis from the UK Aflibercept Users Group. *Eye (Lond)*. Nov 2017;31(11):1582-1588. doi:10.1038/eye.2017.108
4. Little K, Ma JH, Yang N, Chen M, Xu H. Myofibroblasts in macular fibrosis secondary to neovascular age-related macular degeneration - the potential sources and molecular cues for their recruitment and activation. *EBioMedicine*. Dec 2018;38:283-291. doi:10.1016/j.ebiom.2018.11.029
5. Okeagu CU, Agrón E, Vitale S, Domalpally A, Chew EY, Keenan TDL. Principal Cause of Poor Visual Acuity after Neovascular Age-Related Macular Degeneration: Age-Related Eye Disease Study 2 Report Number 23. *Ophthalmol Retina*. Jan 2021;5(1):23-31. doi:10.1016/j.oret.2020.09.025
6. Richard G, Monés J, Wolf S, et al. Scheduled versus Pro Re Nata Dosing in the VIEW Trials. *Ophthalmology*. Dec 2015;122(12):2497-503. doi:10.1016/j.ophtha.2015.08.014
7. 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*. Dec 2018;7(2):361-368. doi:10.1007/s40123-018-0139-5
8. Traine PG, Pfister IB, Zandi S, Spindler J, Garweg JG. Long-term Outcome of Intravitreal Aflibercept Treatment for Neovascular Age-Related Macular Degeneration Using a "Treat-and-Extend" Regimen. *Ophthalmol Retina*. May 2019;3(5):393-399. doi:10.1016/j.oret.2019.01.018
9. 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*. Jan 2018;38(1):20-28. doi:10.1097/iae.0000000000001496
10. Heier JS, Brown DM, Chong V, et al. Intravitreal aflibercept (VEGF trap-eye) in wet age-related macular degeneration. *Ophthalmology*. Dec 2012;119(12):2537-48. doi:10.1016/j.ophtha.2012.09.006
11. Khurana RN, Rahimy E, Joseph WA, et al. Extended (Every 12 Weeks or Longer) Dosing Interval With Intravitreal Aflibercept and Ranibizumab in Neovascular Age-Related Macular Degeneration: Post Hoc Analysis of VIEW Trials. *Am J Ophthalmol*. Apr 2019;200:161-168. doi:10.1016/j.ajo.2019.01.005
12. Egan C, Zhu H, Lee A, et al. The United Kingdom Diabetic Retinopathy Electronic Medical Record Users Group, Report 1: baseline characteristics and visual acuity outcomes in eyes treated with intravitreal injections of ranibizumab for diabetic macular oedema. *Br J Ophthalmol*. Jan 2017;101(1):75-80. doi:10.1136/bjophthalmol-2016-309313
13. The neovascular age-related macular degeneration database: multicenter study of 92 976 ranibizumab injections: report 1: visual acuity. *Ophthalmology*. May 2014;121(5):1092-101. doi:10.1016/j.ophtha.2013.11.031
14. Fasler K, Moraes G, Wagner S, et al. 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*. Jun 21 2019;9(6):e027441. doi:10.1136/bmjopen-2018-027441
15. Garweg JG, Gerhardt C. Disease stability and extended dosing under anti-VEGF treatment of exudative age-related macular degeneration (AMD) - a meta-analysis. *Graefe's archive for clinical and experimental ophthalmology = Albrecht von Graefes Archiv fur klinische und experimentelle Ophthalmologie*. Feb 2 2021;doi:10.1007/s00417-020-05048-1
16. Garweg JG. Twelve-week dosing with Aflibercept in the treatment of neovascular age-related macular degeneration. *Clin Ophthalmol*. 2019;13:1289-1295. doi:10.2147/opth.S185756

17. Fu DJ, Keenan TD, Faes L, et al. Insights From Survival Analyses During 12 Years of Anti-Vascular Endothelial Growth Factor Therapy for Neovascular Age-Related Macular Degeneration. *JAMA ophthalmology*. Jan 1 2021;139(1):57-67. doi:10.1001/jamaophthalmol.2020.5044
18. Bunce C, Fu DJ, Stratton I. Survival Analysis vs Longitudinal Modeling With Multiple Imputation-a False Dichotomy-Reply. *JAMA ophthalmology*. May 1 2021;139(5):588-589. doi:10.1001/jamaophthalmol.2021.0518
19. Fasler K, Fu DJ, Moraes G, et al. Moorfields AMD database report 2: fellow eye involvement with neovascular age-related macular degeneration. *Br J Ophthalmol*. May 2020;104(5):684-690. doi:10.1136/bjophthalmol-2019-314446
20. Farmer R, Mathur R, Bhaskaran K, Eastwood SV, Chaturvedi N, Smeeth L. Promises and pitfalls of electronic health record analysis. *Diabetologia*. Jun 2018;61(6):1241-1248. doi:10.1007/s00125-017-4518-6
21. Chakravarthy U, Havilio M, Syntosi A, et al. Impact of macular fluid volume fluctuations on visual acuity during anti-VEGF therapy in eyes with nAMD. *Eye (Lond)*. Nov 2021;35(11):2983-2990. doi:10.1038/s41433-020-01354-4