UC San Diego

UC San Diego Previously Published Works

Title

Durability of every-8-week aflibercept maintenance therapy in treatment-experienced neovascular age-related macular degeneration

Permalink

https://escholarship.org/uc/item/8z2147rk

Journal

Graefe's Archive for Clinical and Experimental Ophthalmology, 257(4)

ISSN

0941-2921

Authors

Dans, Kunny C
Freeman, Sarah R
Lin, Tiezhu
et al.

Publication Date

2019-04-01

DOI

10.1007/s00417-018-04232-8

Peer reviewed

eScholarship.org Powered by the California Digital Library
University of California

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

HHS Public Access

Author manuscript

Graefes Arch Clin Exp Ophthalmol. Author manuscript; available in PMC 2020 April 01.

Published in final edited form as:

Graefes Arch Clin Exp Ophthalmol. 2019 April ; 257(4): 741–748. doi:10.1007/s00417-018-04232-8.

Durability of Every-8-week Aflibercept Maintenance Therapy in Treatment Experienced Neovascular Age-related Macular Degeneration

Kunny C. Dans, MD[1], **Sarah R. Freeman**[1], **Tiezhu Lin, MD**[1,2], **Amit Meshi, MD**[1,3], **Sergio Olivas**[1], **Lingyun Cheng, MD**[1], **Manuel J. Amador-Patarroyo, MD**[1,4], and **William R. Freeman, MD**[1]

[1]Department of Ophthalmology, Jacobs Retina Center at the Shiley Eye Institute, University of California San Diego, La Jolla, California, US

[2]Member of the Department of Ophthalmology, He Eye Hospital, He University, Shenyang, China.

[3]Member of the Department of Ophthalmology, Rabin Medical Center, Petach Tikva, Israel; Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel.

[4]Member of the Department of Ophthalmology, Escuela Superior de Oftalmologia, Instituto Barraquer de America, Bogota, Colombia.

Abstract

Purpose: To determine the proportion of treatment experienced eyes with exudative age-related macular degeneration successfully treated with every-4-week aflibercept that can be kept dry on fixed every-8-week aflibercept injections (maintenance).

Methods: In this retrospective chart review, we evaluated our cohort of patients treated with a treatment paradigm for CNV in AMD. Initially patients were treated with bevacizumab or ranibizumab and switched to every-4-week aflibercept when therapeutic responses were not

Corresponding Author: William R. Freeman, MD, Jacobs Retina Center, Shiley Eye Institute, University of California San Diego, 9415 Campus Point Drive, La Jolla, CA 92037, **Phone:** (858) 534-3513; **Fax:** (858) 534-7985, wrfreeman@ucsd.edu.

Conflict of Interest:
Kunny C. Dans declares that she has no conflict of interest.
Sarah R. Freeman declares that she has no conflict of interest.
Tiezhu Lin declares that he has no conflict of interest.
Amit Meshi declares that he has no conflict of interest.
Sergio Olivas declares that he has no conflict of interest.
Lingyun Cheng declares that he has no conflict of interest.
Manuel J. Amador-Patarroyo declares that he has no conflict of interest.
William R. Freeman declares that he has no conflict of interest.

Ethical Approval:
UCSD Institutional Review Board (IRB) approval was acquired for the review of patient data. All procedures adhered to the tenets of the 1964 Declaration of Helsinki for research involving human subjects and its later amendments. All procedures complied with the Health Insurance Portability and Accountability Act (HIPAA) regulations.
This article does not contain any studies with animals performed by any of the authors.

Informed Consent:
Each patient gave written informed consent prior to the intravitreal injections.

The study was conducted and completed in the Jacobs Retina Center at the Shiley Eye Institute, University of California San Diego, La Jolla, California.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

durable or were suboptimal. Maintenance every-8-week therapy was initiated when the retina was completely dry on every-4-week aflibercept therapy. The primary outcome measure was recurrence of exudation on optical coherence tomography (OCT) during maintenance.

Results: Thirty-six eyes of 31 consecutive patients with median age of 79 years (range, 65-89) were included. Maintenance was started after a median of 34 (range, 8-88) injections. Recurrence was observed in 20 eyes (55%). Of these, 11 eyes (31%) reactivated at 8 weeks. Median time to failure of maintenance schedule was 40 weeks by Kaplan-Meier analysis. Baseline demographic and anatomic characteristics were not associated with failure of maintenance schedule.

Conclusion: In treatment experienced eyes that respond completely to every-4-week aflibercept, maintenance therapy with every-8-week injections can only temporarily maintain anatomic success with the majority of eyes developing recurring activity. This regimen fails early in one third of eyes and has a median effective duration of 40 weeks. Aflibercept appears to be inadequate to maintain control of exudation in most eyes in at least half of eyes undergoing long-term therapy.

Keywords

aflibercept; anti-VEGF; fixed; maintenance; neovascular AMD; optical coherence tomography

INTRODUCTION

Aflibercept is the most recent anti-vascular endothelial growth factor (VEGF) drug to be used for neovascular age-related macular degeneration (AMD). Its approval for use in AMD is every eight weeks after a series of three injections given every four weeks as part of an induction regimen [1]. Our prior experience with aflibercept has been published using it as a second line drug if bevacizumab or ranibizumab either became ineffective or require multiple retreatment courses due to reactivations after discontinuing therapy using a pro re nata (PRN) treatment regimen [2]. Our PRN treatment regimen is similar to that of the Comparison of AMD Treatments Trials (CATT) and it allows determination of durability of treatment as well as disease reactivation intervals. In our experience, eyes which responded poorly to first line agents at least initially responded well to aflibercept [2-4]. Previously, we have used aflibercept every-8-weeks in eyes which responded, although incompletely, to other agents. We found that some 40% of eyes required escalation to aflibercept every-4-weeks [3]. One year outcomes of aflibercept every-4-weeks at our institution using a PRN regimen showed that after a mean of 8 injections there was improved anatomy but no corresponding improvement in visual acuity largely because of damage to the outer retinal layers [4].

The CATT compared monthly with PRN treatment and showed a mild benefit of strict monthly, i.e. continuous treatment with either ranibizumab or bevacizumab, over an as needed treatment regimen. This result persisted even after the formal study closed when patients were followed for a longer period [5]. Evaluation of standard versus high dose (2 mg) ranibizumab therapy also showed that the PRN group had a slight disadvantage versus continuous treatment. In studies evaluating aflibercept PRN, there was also a small group of patients who lost more letters in the PRN dosing arm than in strict timed dosing arms [6].

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Because randomized clinical trials have studied PRN treatment thoroughly in large patient cohorts, this modality is well understood and is one of the ways neovascular AMD is treated [7]. Based on data presented by the large clinical trials evaluating the PRN strategy (CATT [5], IVAN [8], VIEW [6], and HARBOR [7]) the same regimen remains to be a satisfactory method of treating neovacular AMD to reduce office visits without largely compromising visual outcomes.

Unlike treat and extend, PRN treatment strategy permits determination of which eyes can successfully be maintained dry using a constant reduced frequency injection regimen. Prior to the approval of aflibercept, treatment strategies that aimed to reduce the frequency the office visits relied on increasing dosing intervals between injections using drugs that have been evaluated for every-4-week dosing. The VIEW study suggested that aflibercept every-8-week administration following an initial loading dose of 3 monthly injections is non-inferior to ranibizumab. This led to the approval of aflibercept use every 8 weeks, making it the only approved regimen at extended intervals to date.

Other treatment strategies that aim to extend treatment intervals are still currently under investigation or pending approval. Brolucizumab is a humanized single-chain antibody fragment that inhibits all isoforms of VEGF-A [9]. It is currently under review for regulatory approval following completion of the Phase III trials, HAWK and HARRIER, a head to head comparison of 12-weekly brolucizumab and 8-weekly aflibercept. Genentech's proprietary Ranibizumab Port Delivery System (RPDS) is an investigational refillable eye implant designed to continuously deliver ranibizumab into the vitreous cavity [10]. The phase 2 study reportedly showed promising results and is proceeding to a multicenter phase 3 study.

In this study, we reviewed our patients who were successfully treated with every-4-week aflibercept and then maintained on an every-8-week dose regimen. In these eyes, aflibercept at the standard 2 mg dose was used as a maintenance therapy given every 8 weeks. We did not change the frequency of dosing unless recurrences occurred, nor did we attempt to increase the interval beyond every 8 weeks. We wished to determine the proportion of eyes in which such a regimen was successful and study the predictive factors associated with such success.

METHODS

Study Design

This was a retrospective chart review of patients with neovascular AMD previously treated with multiple anti-VEGF injections on an as needed basis and subsequently placed on a fixed bimonthly aflibercept schedule. All patients were seen by a single experienced retina practitioner (W.R.F.) at the Shiley Eye Institute and Jacobs Retina Center (JRC), University of California San Diego (UCSD). Written informed consent was obtained for each patient prior to the intravitreal injections. UCSD Institutional Review Board (IRB) approval was acquired for the review of patient data. All procedures adhered to the tenets of the Declaration of Helsinki for research involving human subjects and complied with the Health Insurance Portability and Accountability Act (HIPAA) regulations.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Study Population

A database search of the JRC imaging reports was performed using the keywords ‘maintenance’ and ‘Eylea’. The charts of all patients with neovascular AMD receiving maintenance aflibercept every 8 weeks between November 2016 and May 2018 were gathered and reviewed. All patients previously received multiple bevacizumab or ranibizumab, and aflibercept injections given on PRN basis. The population included patients who were successfully treated with every-4-week aflibercept and subsequently maintained on fixed every-8-week aflibercept injections. Successful treatment was defined as the absence of intraretinal or subretinal fluid in the macula on optical coherence tomography (OCT) and absence of leakage on fluorescein angiography (FA).

Patients were excluded if any of the following were fulfilled: 1) choroidal neovascularization secondary to a disease other than neovascular AMD; 2) visual acuity worse than 20/400 at the beginning of maintenance; 3) presence of a large central disciform scar; (4) presence of ocular co-morbidities, including glaucoma, diabetic retinopathy and macular edema, epiretinal membrane, intraocular inflammation, optic nerve pathology; or (5) history of vitrectomy. Eyes were not included in the analysis if the duration of maintenance was less than 24 weeks (or three every-8-week injections), unless the criterion for failure was met before 24 weeks. Eyes were censored in the analysis if the patient failed to follow-up at 8 weeks after 24 weeks of starting maintenance.

Ophthalmological Examination and Retinal Imaging

All patients underwent a complete ophthalmological examination and retinal imaging at baseline (first clinic visit) and at each follow-up visit, including best-corrected visual acuity (BCVA) measurement using the Early Treatment Diabetic Retinopathy Study (ETDRS) chart, slitlamp biomicroscopy, and indirect ophthalmoscopy through dilated pupils.

Retinal imaging including fluorescein angiography (FA) and high-resolution spectral-domain optical coherence tomography (SD-OCT) were performed using a device coupled with a simultaneous scanning laser ophthalmoscope (cSLO) (Spectralis HRA+OCT, Heidelberg Engineering, Carlsbad, CA, USA). As a routine imaging protocol, raster SD-OCT scans along with horizontal and vertical B-scans through the fovea as well as through other areas where CNV activity was most pronounced were obtained.

Treatment Protocol

We previously reported our standard protocol for the treatment of neovascular AMD [2-4, 11]. A fixed regimen of strict monthly bevacizumab (Avastin , Genentech, San Francisco, CA, USA) or ranibizumab (Lucentis, Genentech, San Francisco, CA, USA) intravitreal injections was started until the retina becomes completely dry, after which 1 to 2 bonus injections were given before going to an observation phase. Eyes were observed clinically and by multimodal retinal imaging initially every 8 weeks then every 12 weeks if there was no macular exudation evident on clinical examination and imaging studies. The same treatment regimen was started when recurrence was observed. Recurrence was defined as new IRF and/ or SRF on SD-OCT and/ or leakage on FA accompanied by symptoms of worsening vision, including decline in ETDRS BCVA or presence of metamorphopsia.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Resolution was defined as absence of leakage on FA and complete absence of IRF and SRF on SD-OCT.

Patients who developed treatment resistance to either bevacizumab or ranibizumab were switched to aflibercept (Regeneron, Tarrytown, NY, USA) injections on PRN basis since 2012, when aflibercept became available [2-4, 11]. Treatment resistance was defined as having multiple recurrences (minimum of 2 recurrences after the eyes have been completely dry following a series of at least 3 monthly injections per treatment cycle) or persistence of exudation (poor response to monthly ranibizumab or bevacizumab for at least 5 months) as evident on clinical examination and on imaging studies (leakage on FA, or fibrovascular PED with IRF or SRF on SD- OCT) while on monthly ranibizumab or bevacizumab monotherapy.

A fixed dosing regimen of aflibercept given every 8 weeks in eyes which received every-4-week aflibercept and had a complete response as demonstrated by absence of fluid on OCT prior to starting the maintenance schedule. The beginning of maintenance therapy was when the every-8-week regimen was initiated. Failure was defined as recurrence of retinal exudation on OCT with or without visual loss at 8 weeks following the last injection of aflibercept.

Intravitreal injections were carried out under aseptic conditions in the clinic. Preservative-free lidocaine gel was instilled in the superior fornix at least 5 minutes prior to the injection. A lid speculum was placed and 5% povidone iodine solution was instilled on the conjunctiva and fornix prior to injection. The pars plana was marked externally 3.5 to 4.0 mm from the limbus, depending on the lens status. The intravitreal injection was performed using a 30-gauge needle in the superotemporal or superonasal quadrant. Following the injection, eyes were checked for hand motion vision and then thoroughly irrigated with sterile balanced salt solution.

Data Collection

The baseline demographic data collected from each patient’s record included age, sex, laterality of involved eye, duration of disease and follow-up, and number of anti-VEGF injections prior to maintenance. The primary outcome measure was time to recurrence while on maintenance every-8-week aflibercept treatment. Change in visual acuity (ETDRS letters) from the start to failure of the maintenance regimen was the secondary outcome measure. Imaging parameters were measured by two experienced retina specialists (K.D. & T.L.) who reached concensus in collaboration with two image readers (S.F. & S.O.), taking note of the choroidal neovascularization (CNV) type (type 1, type 2, or type 3), lesion area, central foveal thickness (CFT), and subfoveal choroidal thickness. Data was entered by two readers (S.F. & S.O.). Lesion area was measured as the maximum size of hyperfluorescence on late phase FA. All measurements were done using the built-in caliper function of the Heidelberg Spectralis software.

Statistical Analysis

The Shapiro-Wilk test was used to test normality of distribution. Wilcoxon signed rank test was used for paired comparisons. Letters read on the ETDRS chart were used for statistical

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

analysis. Kaplan–Meier survival curves were generated for survival analysis of time to failure while on maintenance aflibercept therapy. Cox proportional hazard model was used to determine covariates that affect failure of the maintenance schedule. *P* values represent results for two-sided tests, with values less than 0.05 considered statistically significant. Statistical analyses were conducted using SPSS v24.0 (IBM Corp., Armonk, NY, USA).

RESULTS

During the study period, a total of 108 eyes of 88 patients were treated with aflibercept injections for neovascular AMD. Twelve eyes of 12 patients had previous vitrectomy and were excluded. Twenty-eight eyes of 24 patients were likewise excluded due to ocular comorbidities, including glaucoma (4 eyes of 4 patients) and epiretinal membrane (24 eyes of 20 patients). Of the remaining 68 patients that met the inclusion criteria, 36 eyes (52.9%) of 31 consecutive patients were placed on maintenance aflibercept therapy demonstrating after a complete response to every-4-weeks aflibercept. Patient characteristics are summarized in Table 1. The median age was 76 years (range, 65-89). The median number of intravitreal anti-VEGF injections prior to changing to maintenance aflibercept was 34 (range 8-88). The median duration of follow-up from onset of neovascular AMD to initiation of maintenance therapy was 254 weeks (range, 33-427). A median of 9.5 bevacizumab or ranibizumab injections (range, 3-63) in a median of 2 treatment cycles (range, 2-6) over a median of 52 weeks (range, 12-330) was given prior to switching to aflibercept. Prior to initiating maintenance therapy, a median of and 16 aflibercept injections (range, 3-33) in a median of 4 cycles (range, 2-8) was given over 180 weeks (range, 12-276).

Twenty eyes (55%) of 18 patients failed the maintenance therapy with evidence of recurrence of subretinal and/or intraretinal fluid on OCT. Of these, 11 eyes (31%) reactivated at 8 weeks, the first evaluation period following initiation of maintenance therapy. Figures 1 and 2 illustrate the retinal imaging and clinical course of two patients included in the study population. Kaplan-Meier Analysis showed that the median time to reactivation using the maintenance regimen in eyes previously responsive to every-4-week aflibercept was 40 weeks (Figure 3). Three eyes of three patients were censored at 24, 40, and 48 weeks due to missed follow-up visits.

Cox proportional hazard regression analysis was performed to identify risk factors for time to reactivation. Covariates included age, sex, duration of disease, number of injections, baseline BCVA, lesion area, CNV type, CFT, and subfoveal choroidal thickness. None of the covariates were found to be significantly associated with time of reactivation. The results are summarized in Table 2. To ensure independence of data points, one eye of each of the 5 patients with bilateral measurements was randomly excluded. There was no meaningful change in results.

The median BCVA was 72 ETDRS letters (range 34-85, ≅20/36 Snellen) at baseline, and 70 ETDRS letters (range 28-83, ≅20/40 Snellen) at the beginning of maintenance (p=0.928). In eyes that failed every-8-weeks aflibercept anatomically, there was a significant median 4-letter drop (p=0.050) in BCVA at the time of fluid recurrence to 66 ETDRS letters (range 20-83, ≅20/48). The median CFT was 194 μm (range, 80-315) at the beginning of

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

maintenance. As expected, there was an increase in CFT to 254 (range, 90-361), a 60 μm increase (p=0.002) at the time of reactivation.

No ocular or systemic adverse events were observed during the course of treatment.

DISCUSSION

The ability to reduce the frequency of visits and burden of disease in the management of neovascular AMD remains a challenge. The VIEW studies have established the efficacy and non-inferiority of aflibercept to ranibizumab in treatment naive neovascular AMD and have suggested that injection of every 8 weeks as a maintenance after a series of three every-4-week injections is a useful regimen. In our experience, aflibercept may initially be highly effective in eyes that have developed resistance or tachyphylaxis to ongoing bevacizumab or ranibizumab injections [3-4]. Aflibercept prescribing information states that the recommended dose is 2 mg/0.05 mL delivered by intravitreal injection every 4 weeks for the first three months, then every-8-weeks [1]. In this investigation [8], we aimed to evaluate the durability of an 8-weekly fixed schedule of aflibercept in previously treated eyes with neovascular AMD who had responded completely to every 4 weeks aflibercept.

Based on the VIEW studies, neovascular AMD can be successfully treated using an every-8-week schedule of aflibercept injections without compromising visual acuity outcomes [12]. The prolonged duration of action of aflibercept has been attributed to its higher binding affinity for $VEGF_{165}$. While it has been established that visual acuity can be gained and maintained with treatment, reports have also shown that a proportion of anti-VEGF treated eyes with AMD and CNV will have persistent retinal exudation despite ongoing therapy. Heier described fluctuating central retinal thickness in the joint evaluation of VIEW 1 and 2 patients receiving every-8-week aflibercept. At the end of the 52-week study, the proportion of eyes with a dry retina in the every-8-week group was 63.4% and 71.9% in VIEW 1 and 2, respectively [12]. In a post hoc analysis of eyes included in the VIEW trials, Jaffe, et al described sustained dryness defined as absence of fluid for 2 consecutive visits in 73.8% of eyes receiving every-8-week aflibercept [13].

Khanani et al evaluated eyes previously treated with ranibizumab and/or bevacizumab that were switched to aflibercept. They found that after three loading doses the majority of their patients had recurrent fluid 8 weeks later. They did not treat until dry and then attempt every-8-week treatment as we did [14].

In a retrospective review, Chatziralli et al reported the 12 month outcomes of 535 previously treated eyes that demonstrated inadequate response to monthly ranibizumab (median of 6 injections, range 3-36) [15]. Aflibercept was given every 8 weeks without a loading dose for one year. Unlike our study they did not attempt every-8-week aflibercept therapy after a retina had completely responded to aflibercept every 4 weeks.

Thus, there have been no prior studies of maintenance every-8-weeks aflibercept after a complete response to every-4-week aflibercept. Our goal was to determine whether aflibercept could be used to maintain a dry macula in eyes that were treated with longer term anti-VEGF therapy and which were clearly completely responsive to every 4-week

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

aflibercept. Our cohort included eyes that have been treated successfully, i.e. completely dry macula, with every-4-week aflibercept who were then switched to a maintenance regimen of fixed every-8week aflibercept injections. Maintenance using every 8-week therapy was initiated only when the macula was completely dry on OCT with simultaneously confirmed lack of FA leakage. We found that in such patients, despite the complete response to every-4-week aflibercept, eyes failed every-8-week maintenance with a median time to failure of 40 weeks. Of note, one third failed early, i.e. by week number 8. This suggests that such treatment extension fails almost immediately in one third of patients. Interestingly, in the VIEW study even with maintenance every 4 or 8-week injections, one third of eyes developed recurrent fluid. While peak efficacy has been shown to be similar when using aflibercept or ranibizumab for neovascular AMD, the half-life of aflibercept (7.13 days) is slightly longer than that of ranibizumab (4.75 days) [16-17].

We could not identify any baseline anatomic features that predicted risk of failure or the time to onset of recurrent fluid. It is of note that recurrent fluid in our study caused vision loss (p=0.050). However, our sample size and duration of follow up after recurrences were limited and the effect of recurrent fluid on long term visual acuity needs further study. Some have suggested that fluid may be compatible with acuity of 20/40 or better [18]. Both 1- and 2-year results of the CATT study showed that persistent or residual intra-retinal cystic fluid adversely affected visual acuity, whereas subretinal or sub-RPE fluid had did not have a similar effect [19]. This has also been corroborated by recent studies [20]. In our study, ten (50%) patients had intra-retinal fluid at the time of failure.

This study is limited by its retrospective nature and small sample size. Strengths of this study include a standardized PRN treatment algorithm which allows determination of duration of remission. While visual outcomes of fixed every-8-week dosing has been previously reported, to the best of our knowledge, this is the first review showing the anatomic durability of a maintenance schedule in previously treated eyes that showed complete response to aflibercept. Frequent SD-OCT with raster scans were used in our study which allowed high sensitivity to detect recurrent disease. We used the eye as the unit of analysis but if we eliminated one eye of each of the five patients who contributed two eyes to the study, there was no difference in the outcome.

We therefore conclude that in previously aflibercept-responsive eyes which had undergone therapy with other anti-VEGF injections initially (every-4-week injections) efficacy of an every-8-week aflibercept maintenance regimen begins to be lost quickly in one third (before 8 weeks) and in half of the patients by 40 weeks. Baseline features were not associated with failure of maintenance therapy. It is important to note that our cohort includes treatment experienced but aflibercept responsive patients with a long-standing history of prior multiple recurrences with other anti-VEGF drugs. In this real-world situation, durability of the every-8-week maintenance schedule was seen in nearly half of the patients. Caution must be exercised when extending treatment intervals as one third of patients demonstrate early failure. Aflibercept appears to be required more frequently than every 8 weeks in at least half of eyes undergoing long-term anti-VEGF therapy.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Acknowledgments

Funding:

This study was supported by the UCSD Vision Research Center Core Grant P30EY022589, an unrestricted fund from Research to Prevent Blindness, NY (WRF). The funding organization had no role in the design or conduct of this research.

REFERENCES

1. Regeneron Pharmaceuticals (2011) Highlights of prescribing information. https://www.regeneron.com/sites/default/files/EYLEAFPI.pdf. Accessed 01 February 2017.
2. You Q, Meshi A, Ramkumar HL, et al. (2017) Aflibercept for recalcitrant neovascular age-related macular degeneration. Retina 38(6):1156–65. doi:10.1097/IAE.0000000000001726.
3. Arcinue CA, Ma F, Barteselli G, Sharpsten L, et al. (2015) One-year outcomes of aflibercept in recurrent or persistent neovascular age-related macular degeneration. Am J Ophthalmol 159(3):426–436. doi:10.1016/j.ajo.2014.11.022. [PubMed: 25461263]
4. Muftuoglu IK, Arcinue CA, Tsai FF, et al. (2016) Long-term results of pro re nata regimen of aflibercept treatment in persistent neovascular age-related macular degeneration. Am J Ophthalmol 167:1–9. doi:10.1016/j.ajo.2016.03.038. [PubMed: 27049000]
5. Martin DF, Maguire MG, Fine SL, et al. (2012) Ranibizumab and bevacizumab for treatment of neovascular age-related macular degeneration: 2-year results. Ophthalmology 119(7):1388–1398. doi:10.1016/j.ophtha.2012.03.053.Ranibizumab. [PubMed: 22555112]
6. Richard G, Monés J, Wolf S, et al. (2015) Scheduled versus pro re nata dosing in the VIEW trials. Ophthalmology 122(12):2497–2503. doi:10.1016/j.ophtha.2015.08.014. [PubMed: 26477840]
7. Ho AC, Busbee BG, Regillo CD, et al. (2014) Twenty-four-month efficacy and safety of 0.5 mg or 2.0 mg ranibizumab in patients with subfoveal neovascular age-related macular degeneration. Ophthalmology 121(11):2181–2192. doi:10.1016/j.ophtha.2014.05.009. [PubMed: 25015215]
8. Chakravarthy U, Harding SP, Rogers CA, et al. (2013) Alternative treatments to inhibit VEGF in age-related choroidal neovascularization: 2-year findings of the IVAN randomised controlled trial. Lancet 382(9900):1258–1267. doi: 10.1016/S0140-6736(13)61501-9. [PubMed: 23870813]
9. Dugel PU, Jaffe GJ, Sallstig P, et al. (2017) Brolucizumab versus aflibercept in participants with neovascular age-related macular degeneration: a randomized trial. Ophthalmology 124(9):1296–1304. doi: 10.1016/j.ophtha.2017.03.057. [PubMed: 28551167]
10. Regillo C (2018). Port Delivery Phase 2 LADDER Study Results presented in Medical Retina Part 1 Session of the Annual Meeting of the American Academy of Ophthalmology at McCormick Place, Chicago, IL, USA.
11. Muftuoglu IK, Alam M, You Q, et al. (2018). Long-term remission of neovascular age-related macular degeneration with as-needed anti-vascular endothelial growth factor therapy. Retina 38(3): 516–522. doi: 10.1097/IAE.0000000000001572. [PubMed: 28221254]
12. Heier JS, Brown DM, Chong V, et al. (2012) Intravitreal aflibercept (VEGF trap-eye) in wet age-related macular degeneration. Ophthalmology 119(12):2537–2548. doi:10.1016/j.ophtha.2012.09.006. [PubMed: 23084240]
13. Jaffe GJ, Kaiser PK, Thompson D, et al. (2016) Differential response to anti-VEGF regimens in age-related macular degeneration patients with early persistent retinal fluid. Ophthalmology. 123(9):1856–1864. doi:10.1016/j.ophtha.2016.05.016. [PubMed: 27369111]
14. Khanani A (2015) Clinical experience with fixed bimonthly aflibercept dosing in treatment-experienced patients with neovascular age-related macular degeneration. Clin Ophthalmol 9:1315–20. doi: 10.2147/OPTH.S88624 [PubMed: 26229424]
15. Chatziralli I, Nicholson L, Vrizidou E, et al. (2016) Predictors of outcome in patients with neovascular age-related macular degeneration switched from ranibizumab to 8-weekly aflibercept. Ophthalmology 123(8):1762–1770. doi: 10.1016/j.ophtha.2016.05.002. [PubMed: 27289179]
16. Stewart MW (2018) Extended duration vascular endothelial growth factor inhibition in the eye: failures, successes, and future possibilities. Pharmaceutics 10(21):1–12. doi:10.3390/pharmaceutics10010021.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

17. Stewart MW (2011) What are the half-lives of ranibizumab and aflibercept (VEGF Trap- eye) in human eyes? Calculations with a mathematical model. Eye Reports 1(5):12–14. doi:10.4081/eye.2011.e5.

18. Bhavsar KV, Freund KB (2014) Retention of good visual acuity in eyes with neovascular age-related macular degeneration and chronic refractory subfoveal subretinal fluid. Saudi J Ophthalmol 28(2):129–133. doi:10.1016/j.sjopt.2014.03.001. [PubMed: 24843306]

19. Sharma S, Toth CA, Daniel E, et al. (2016) Macular morphology and visual acuity in the second year of the comparison of age-related macular degeneration treatments trials. Ophthalmology 123(4):865–875. doi:10.1016/j.ophtha.2015.12.002 [PubMed: 26783095]

20. Kodjikian K, Decullier E, Souied E, et al. (2017) Predictors of one-year visual outcomes after anti-vascular endothelial growth factor treatment for neovascular age-related macular degeneration. Retina 38(8):1492–99. doi: 10.1097/IAE.0000000000001736.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

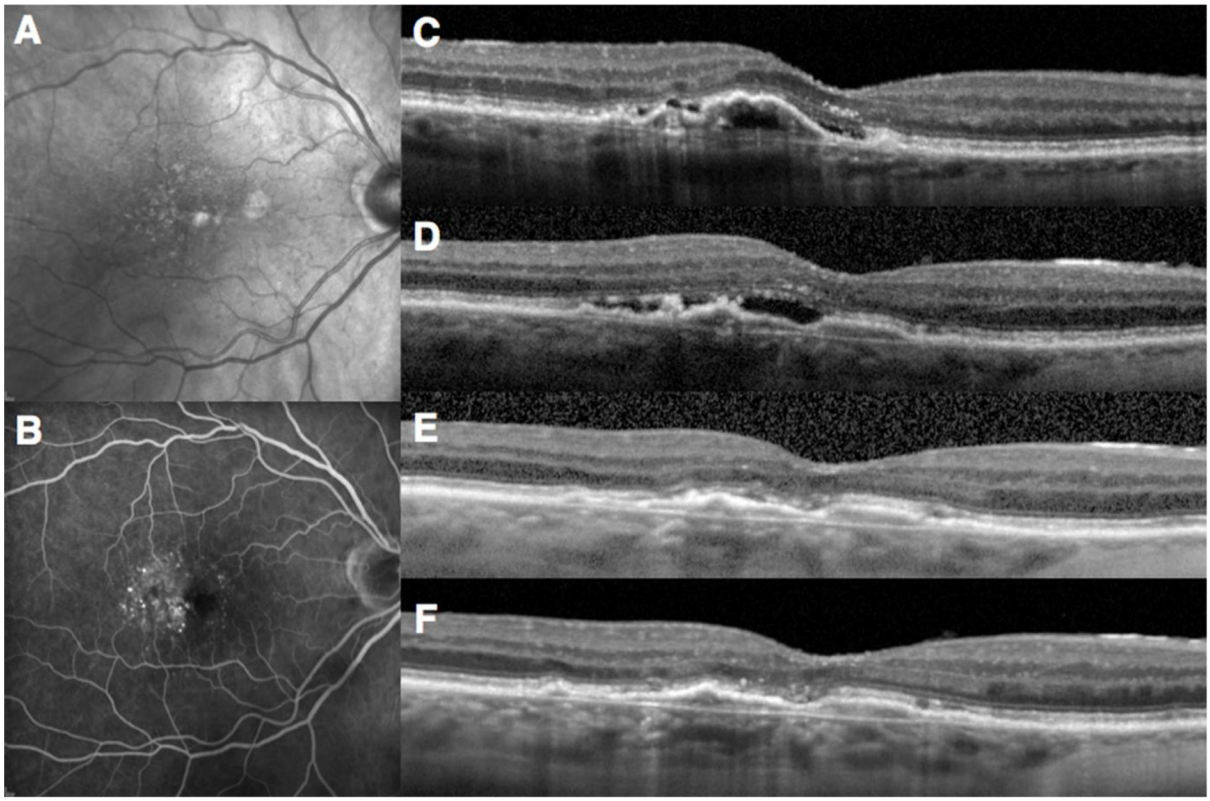

Figure 1.

Infrared photo, FA, and SD-OCT of the right eye of an 89 year-old female. At baseline, RPE changes are evident on IR photo (A) with corresponding temporal leakage and staining on FA (B). On horizontal scan OCT, subretinal fluid is present overlying a mixed type PED (C) accompanied by pigment migration and extrafoveal RPE changes. Intravitreal anti-VEGF injections were given on as needed basis. A total of 9 bevacizumab injections given over 144 weeks was given in 3 cycles prior to switching to aflibercept. Prior to maintenance therapy, 15 aflibercept injections were given. Recurrence was observed for the 8th time after a 75-month follow-up period as shown by subretinal fluid on OCT (D). The retina was made completely dry (E) with two monthly aflibercept injections, after which maintenance every-8-week aflibercept therapy was initiated. The retina remains dry at week 48 since maintenance was begun as exemplified by the absence of intra- or subretinal fluid on OCT (F).

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

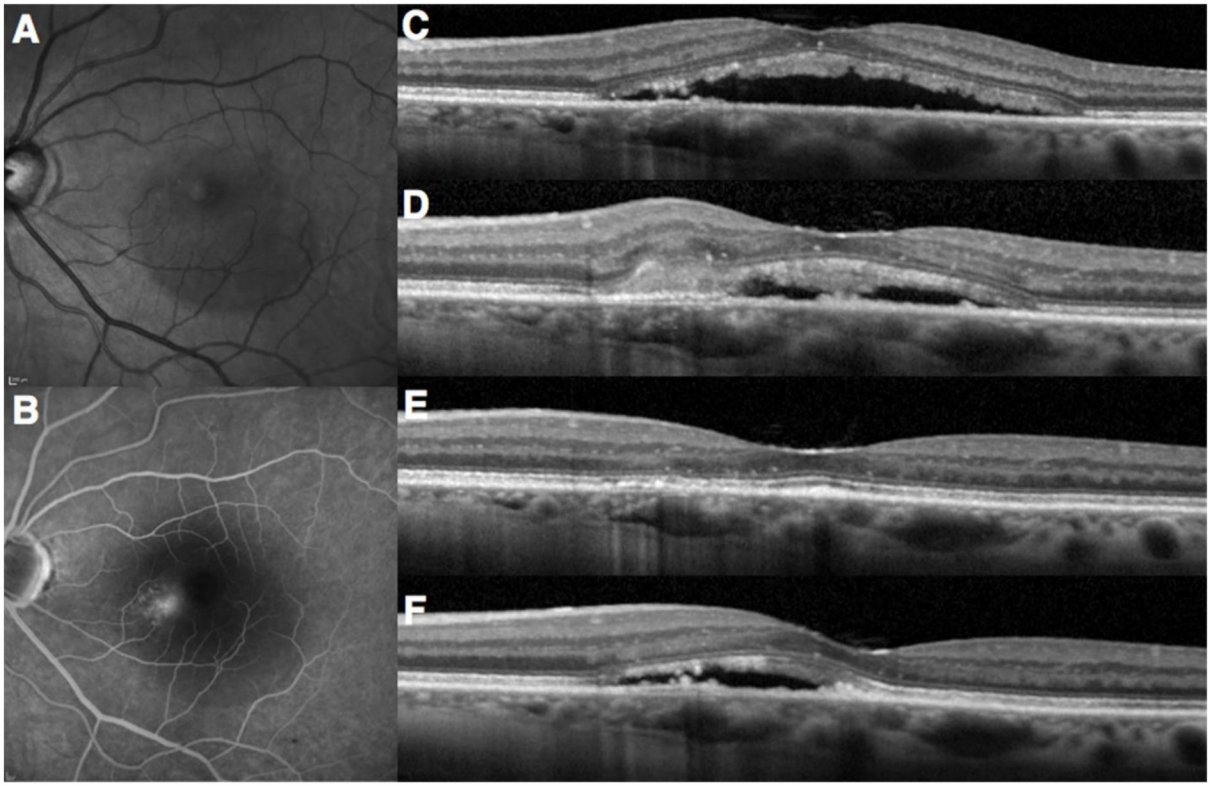

Figure 2.

Infrared photo, FA, and SD-OCT of the left eye of a 69 year-old female. Subretinal fluid was evident on IR photo (A) and SD-OCT (C) at baseline. FA (B) shows the source of leakage. Intravitreal anti-VEGF injections were given on as needed basis. A total of 9 bevacizumab injections given over 46 weeks was given in 3 cycles prior to switching to aflibercept. Prior to maintenance therapy, 18 aflibercept injections were given. Recurrence was observed for the 8th time after a 177-week follow-up period as shown by subretinal fluid and subretinal hyperreflective material on OCT (D). The retina was made completely dry (E) with 3 monthly aflibercept injections, after which maintenance every-8-week aflibercept therapy was initiated. Recurrence of subretinal fluid was noted at 8 weeks following the first maintenance injection (F).

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

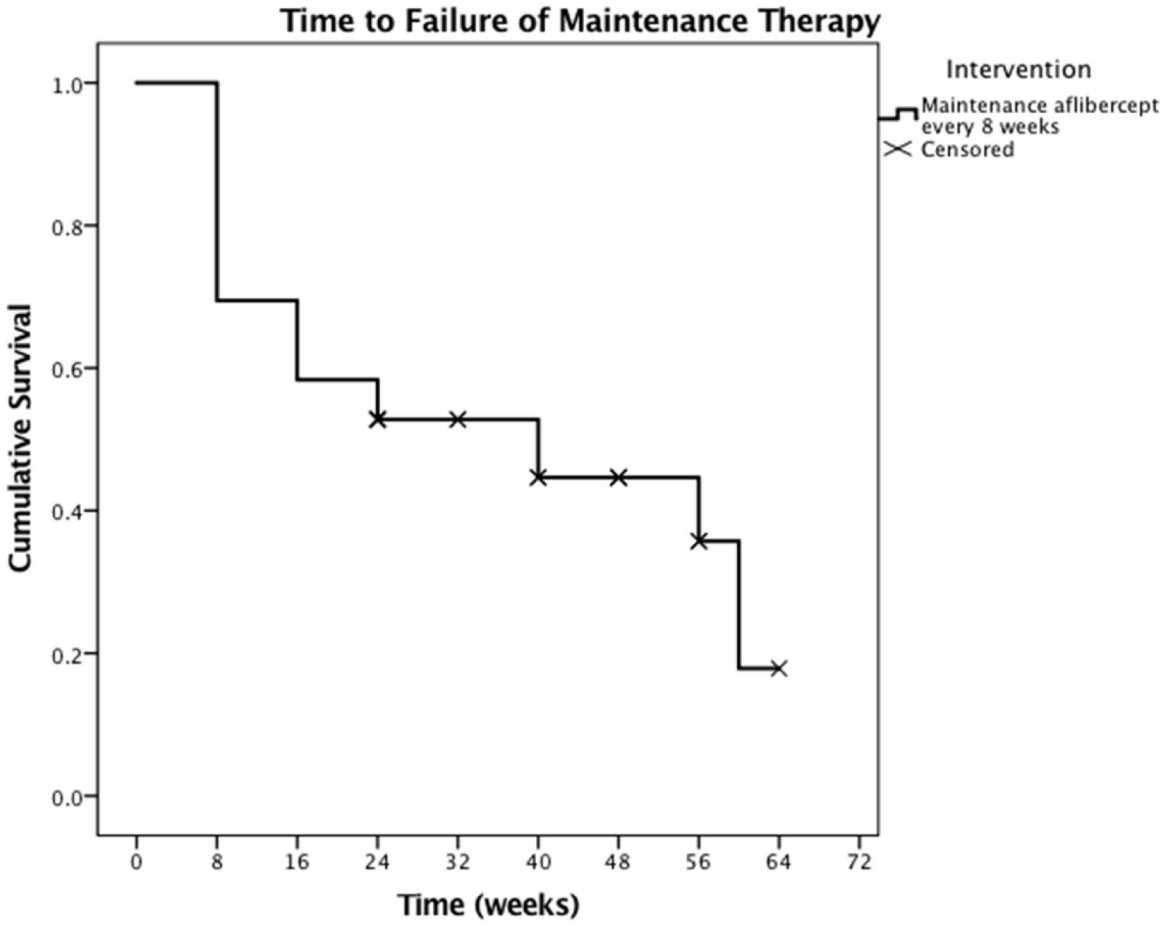

Figure 3.

Kaplan-Meier curve showing the proportion of eyes successfully treated with maintenance every-8-week aflibercept regimen.

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Table 1.

Patient characteristics at baseline.

	(n=36)
Median age, years (range)	79 (65-89)
Female, n (%)	20 (55.6)
Left eye, n (%)	18 (50.0)
Pseudophakic, n (%)	25 (69.4)
CNV type	
Type 1 (sub-RPE)	20 (55.6)
Type 2 (subretinal)	14 (38.9)
Type 3 (RAP lesion)	2 (5.5)
Median lesion size, mm^2 (range)	3.52 (0.30-9.47)
Median central foveal thickness, μm (range)	321.50 (160-528)
Median subfoveal choroidal thickness, μm (range)	215.50 (79-424)

CNV=choroidal neovascularization; RPE=retinal pigment epithelium; RAP=retinal angiomatous proliferation.

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Table 2.

Cox regression analysis to determine baseline covariates that determine duration of successful every-8-week maintenance aflibercept.

Covariate	*P* Value	Hazard Ratio	95% CI
Age	0.981	0.999	0.932-1.071
Sex (Male)	0.220	1.745	0.717-4.245
Duration of the disease	0.232	0.997	0.993-1.002
Total number of injections	0.878	1.002	0.976-1.029
BCVA at diagnosis	0.850	0.996	0.961-1.034
CNV type			
Type 3 vs. Type 1	0.638	1.651	0.204-13.328
Type 3 vs. Type 2	0.916	0.891	0.106-7.474
Type 1 vs. Type 2	0.231	0.540	0.197-1.479
Lesion area	0.276	0.904	0.753-1.084
CFT	0.276	1.003	0.998-1.007
Subfoveal CT	0.598	1.001	0.996-1.007

CI=confidence interval; BCVA=best corrected visual acuity; CNV=choroidal neovascularization; CFT=central foveal thickness; CT=choroidal thickness.