

Long-term Outcome of Intravitreal Aflibercept Treatment for Neovascular Age-Related Macular Degeneration Using a “Treat-and-Extend” Regimen

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Purpose: To report outcomes in patients with neovascular age-related macular degeneration (nAMD) after treatment with aflibercept for up to 4 years using a treat-and-extend (T&E) regimen.

Design: Observational study.

Participants: Patients with newly diagnosed nAMD treated with aflibercept in a T&E protocol.

Methods: Subjects received 3 injections of aflibercept at monthly intervals followed by a T&E protocol for at least 12 months. At each clinical visit after the loading phase, OCT and best-corrected visual acuity (BCVA) testing were performed to monitor disease activity.

Main Outcome Measures: Change in BCVA over time, number of injections and visits per year, and percentage of patients reaching a treatment interval of ≥ 12 weeks.

Results: Of 231 consecutive eyes (231 patients) with a mean follow-up time of 2.9 (1–5.5) years, 173 were followed up for ≥ 2 years, 112 were followed up for ≥ 3 years, and 62 were followed up for ≥ 4 years. Mean BCVA increased from 59.8 letters (20/60) at diagnosis to 65.8 letters (20/50) after the loading phase (+6.0 letters; standard deviation [SD], 11.1) and to 65.5 letters at 12 months (+5.7 letters; [SD], 17). After 4 years of treatment, mean BCVA was maintained insignificantly better than baseline (63.4 letters, +3.6 letters gain, SD, 20.6; $P > 0.05$). To achieve this, a mean of 7.7 (± 1.2) injections and 4.4 (± 1.6) clinic visits in the first year and 4.4 (± 1.9) injections and 4.3 (± 1.3) clinical visits per year thereafter were required. By 2 years of follow-up, 46.9% of patients reached a treatment interval of ≥ 12 weeks.

Conclusions: By using a T&E regimen, patients with nAMD maintained stable visual function over 4 years in a real-world setting with a reasonable treatment burden. *Ophthalmology Retina* 2019;3:393-399 © 2019 by the American Academy of Ophthalmology

Since its introduction in 2006, intravitreal anti-vascular endothelial growth factor (VEGF) therapy has been the mainstay of treatment for neovascular age-related macular degeneration (nAMD). Despite all 3 available anti-VEGF agents (bevacizumab [Avastin, Genentech, South San Francisco, CA], ranibizumab [Lucentis, Genentech], and aflibercept [EYLEA, Regeneron, Tarrytown, NY]) showing efficacy in achieving good visual outcomes,¹⁻⁴ the debate regarding the best treatment regimen is still ongoing. The first approval studies for ranibizumab were based on patients receiving fixed monthly intravitreal injections. The high burden of monthly clinic visits and injections for patients resulted in poor patient adherence to treatment and high socioeconomic costs for the healthcare systems and societies.¹ Monthly clinic visits, with most patients requiring an accompanying person, were identified as the major problem faced by patients during treatment.⁵

New treatment regimens have since emerged in clinical practice, including a pro re nata (PRN) or “as-needed” protocol and more recently a treat-and-extend (T&E)

protocol. In both treatment regimens, a loading phase comprising 3 initial consecutive monthly anti-VEGF injections has proven efficacious and has generally been accepted.⁶ In PRN, the loading phase is followed by monthly clinic visits to monitor disease activity and an intravitreal injection on an as-needed basis if any disease activity, indicated by the presence of intraretinal or subretinal fluid or progression of pigment epithelial detachment, is found. Pro re nata follows a reactive approach, with an intravitreal injection only given if disease activity is detected on the basis of visual stability and OCT assessment.

In contrast, the T&E regimen is a proactive approach with a loading phase followed by monthly injections until any intraretinal fluid has completely resolved and subretinal fluid and pigment epithelial detachment are reduced. When this is achieved, the injection interval is extended by 2 weeks up to intervals of 12 weeks or more if no fluid recurrence is discovered. Patients on T&E protocols have achieved similar functional and anatomic outcomes over more than 12 months as those on monthly injections, but

Table 1. Reasons for Treatment Discontinuation

Reason	n	%
Treatment continuation with local ophthalmologist	24	35.8%
Stability reached	15	22.4%
Patient deceased	10	14.9%
Sickness/hospitalization	7	10.4%
No functional capacity	5	7.5%
Others	6	9%

with a reduced number of injections (−1.6 and −6.9 injections less at 12 and 24 months).⁷ It has been shown that the functional stability is better in T&E compared with PRN at 12 months, with a mean of 1.4 more injections but fewer clinical visits.⁷

The reduced treatment burden together with a good functional and anatomic performance are the main arguments for the increasing popularity and shift from PRN to the T&E regimen. There are studies showing good long-term visual acuity (VA) results after anti-VEGF treatment for up to 8 years using a T&E regimen with bevacizumab or ranibizumab.^{8,9} Outcome studies of patients with neovascular AMD treated with aflibercept in a T&E-regimen are limited to a follow-up of 2 years.¹⁰⁻¹²

The purpose of this study was to report the “real-life” long-term outcomes of treatment with aflibercept for up to 4 years following a T&E protocol in a consecutive series of treatment-naïve eyes with nAMD.

Methods

We conducted a single-center retrospective observational study. Consecutive treatment-naïve eyes with newly diagnosed neovascular AMD treated with aflibercept, since its approval in Switzerland in December 2012, at our institution (Berner Augenklinik am Lindenhofspital, Bern, Switzerland) were included. All eyes were treated following a T&E regimen that consisted of an initial loading phase of 3 injections at monthly intervals without intercurrent visits. Thereafter, patients were given an injection at all subsequent visits; the re-treatment interval (or time to next visit) was extended by 2 weeks up to a maximum of 14 weeks each time once the retina was stable, as defined by the anatomic criteria in the OCT guidance. When new disease activity was detected, the re-treatment interval was shortened by at least 2 weeks to identify the optimal re-treatment interval for each individual. If subsequently disease stability was seen in 2 consecutive visits, intervals could be extended again after the T&E regimen. If interval stability was found (i.e., after 2 consecutive intervals without options for the adoption of treatment intervals), we skipped 1 clinical visit and performed a second injection without prior examination in selected cases to further minimize the treatment burden.

The initial diagnosis was confirmed using fluorescein angiography and OCT, and OCT and VA testing were performed at every clinical visit after the loading phase to monitor disease activity. Patients who did not receive 3 monthly loading treatments or in total less than 6 injections in the first 12 months, or switched therapy for any reason, were defined as T&E protocol violators and excluded from the analysis (n = 58).

At each clinical visit, Snellen best-corrected visual acuity (BCVA), OCT (central horizontal line scan 6 mm using the Spectralis, Heidelberg Engineering, Heidelberg, Germany), and a

clinical assessment including slit-lamp examination and indirect stereo funduscopy were performed. The BCVA and functionally relevant anatomic findings such as intraretinal or subretinal fluid, central retinal thickness (CRT), and presence of new hemorrhages were retrieved from the patient’s electronic records. For the purpose of this study, BCVA values were converted to the corresponding Early Treatment Diabetic Retinopathy Study letter score. The CRT was measured from the internal limiting membrane to Bruch’s membrane, or where it was estimated if it was obscured by massive exudation or a fibrovascular complex, and was reported on a micrometer scale.

All data collected between December 2012 and August 2018 were included in this study. For each patient, if both eyes were affected during the study period, the findings from the first treated eye were included. The findings from the second eye were included if the first eye was not eligible for inclusion. Because of the retrospective nature of this study, a difference of 15% between the clinical visit and the scheduled study visit was accepted. The study was approved by the regulatory authorities (Institutional Ethics Committee, University of Bern, under the reference KEK 099/15), and all patients gave informed consent for the use of their coded data. The study was conducted in compliance with the tenets of the Declaration of Helsinki.

Statistical Analysis

Nonparametric tests were applied because the Shapiro–Wilk test showed that the data were not normally distributed. To estimate the significance of the Early Treatment Diabetic Retinopathy Study and CRT change, the Wilcoxon signed-rank test was performed. We handled the problem of missing data over time in 2 ways.

First, we applied multiple imputation. Multiple imputation as proposed by Rubin¹³ is a method of handling data missing at random. It was assumed that any systematic difference between the missing values and the observed values could be explained by differences in observed data. Multiple imputations are simulated draws from the posterior distribution of missing data. The imputations were adjusted for uncertainty. Multiple imputation was only applied to patients still in follow-up, whereas data from patients lost to follow-up were censored. Second, we also present data only from those patients with 4 years of follow-up time. Data are presented as mean ± standard deviation (SD). All statistical evaluations were performed using the SPSS software package V.23 (SPSS, Inc, Chicago, IL), with the level of significance set at $P < 0.05$.

Results

Of 318 eyes that received aflibercept therapy for nAMD, 231 eyes (from 231 patients) fulfilled the study inclusion criteria. The mean age of patients at diagnosis was 79.9 years (SD, 8.2; range 54–100), and 144 were female (62.3%) and 87 were male (37.7%). A total of 115 patients (49.8%) were phakic, and 116 patients (50.2%) were pseudophakic. The mean length of follow-up was 2.9 years (SD, 1.2; range, 1–5.5). All 231 patients had at least 1 year follow-up; of these, 173 were followed up for ≥ 2 years, 112 were followed up for ≥ 3 years, and 62 were followed up for ≥ 4 years.

Sixty-seven patients (29%) discontinued treatment before the end of the study. The reasons for treatment discontinuation are displayed in Table 1.

The mean VA increased from 59.8 letters (20/60) at diagnosis (SD, 16.9; range, 15–85 letters; median, 65 letters) to 65.8 letters (20/50) after the initial loading phase (+6.0 letters; SD, 11.1;

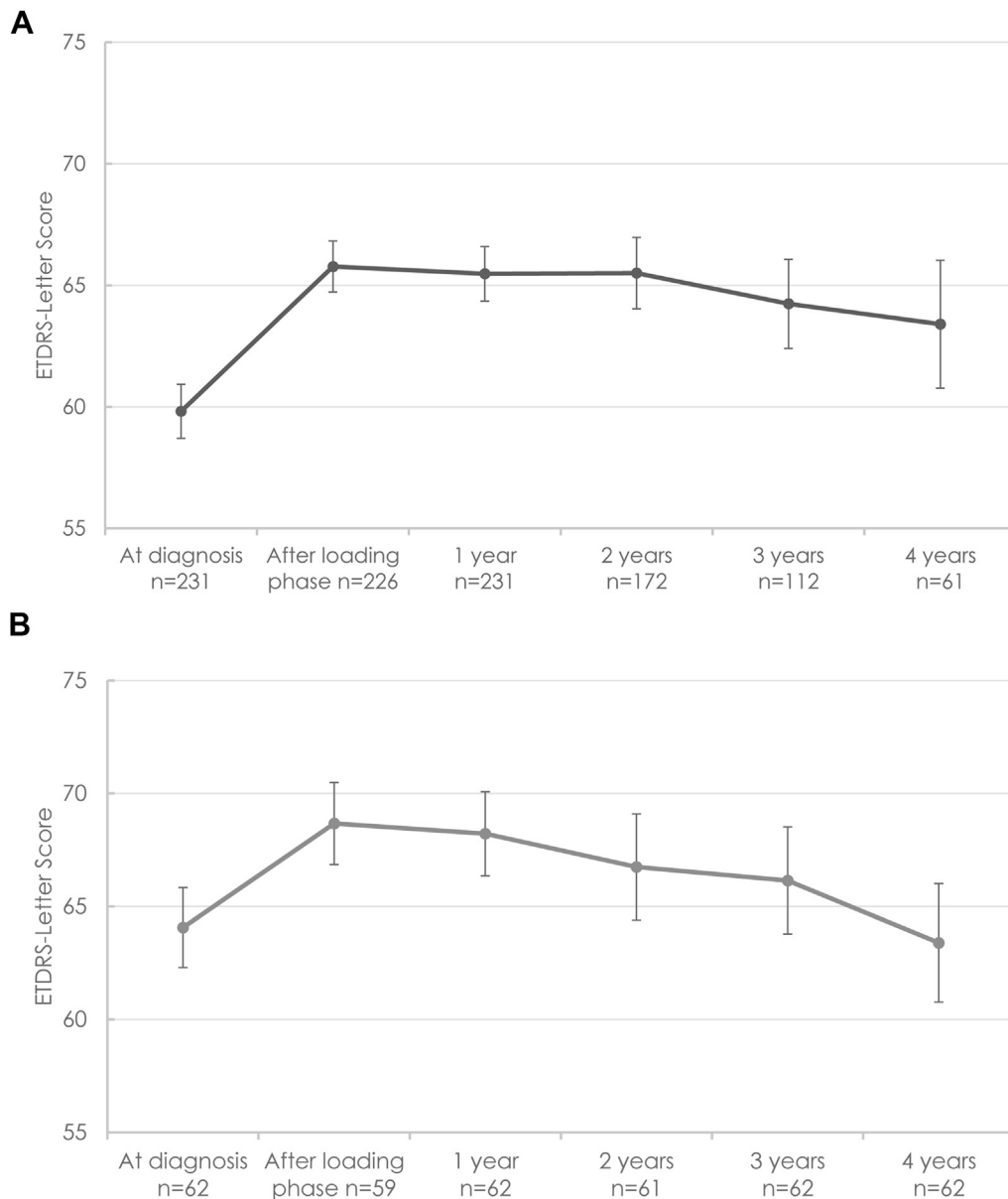


Figure 1. A, Total sample; visual acuity (VA) over time. B, Subsample of patients with 4 years follow-up, VA over time.

$P = 0.0005$; median, 70 letters) and to 65.5 letters at 12 months (+5.7; SD, 17.0; median, 70 letters).

At years 2 and 3, VA was still significantly better than at baseline (65.5 letters, +5.7; SD, 19.3; median, 70 letters; 64.2 letters, +4.4; SD, 19.4, median, 70 letters, respectively).

After 4 years of treatment, VA was 63.4 letters (20/50) with a gain of +3.6 letters (SD, 20.4; $P = 0.35$; median, 70 letters) compared with baseline (Fig 1A). These differences were no longer significant. When multiple imputation was used to account for missing data, results were comparable. The mean VA increased from 59.8 letters at diagnosis (SD, 16.9; range, 15–85 letters) to 65.8 letters after the initial loading phase (+6.0 letters, SD, 15.1, $P = 0.0005$). After 4 years of treatment, VA remained stable at 59.9 letters (+0.1 letters, SD, 33.6, $P = 0.35$). The results for the subgroup of patients with 4 years of follow-up data ($n = 62$)

were similar, although the initial VA was better at 64.1 letters (20/50), which increased to 68.7 (20/40) after the initial loading phase (+4.6, SD, 9.7; $P = 0.001$). Again, after 4 years of treatment VA remained stable at 63.4 letters (20/50) compared with the initial VA (−0.7, SD, 20.4; $P = 0.35$; Fig 1B).

The CRT decreased from a mean of 430 μm (SD, 195; range, 156–1290) at baseline to 285 μm (−145; SD, 149) after the initial loading phase ($P = 0.0005$) and remained stable thereafter (Fig 2A). When multiple imputation was used to account for missing data, the results were almost identical. The CRT decreased from a baseline mean of 430 μm (SD, 195; range, 156–1290) to 284 μm (−146; SD, 151) after the initial loading phase ($P = 0.0005$) and remained stable thereafter. The results were also similar for the 62 patients with 4 years of follow-up data. The initial CRT decreased from 420 μm (SD, 190; range,

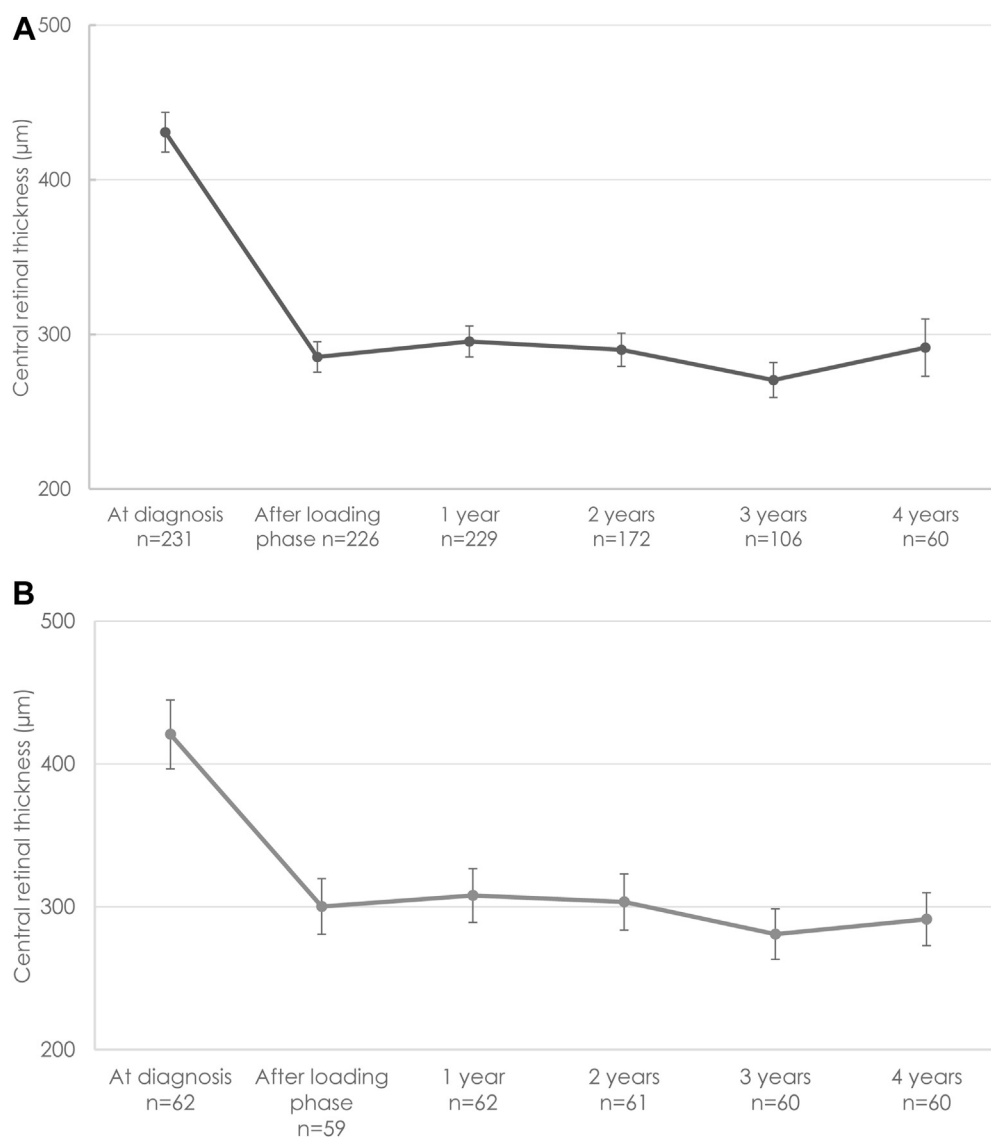


Figure 2. A, Total sample; central retinal thickness (CRT) over time. B, Subsample of patients with 4 years follow-up; CRT over time.

156–1080; Fig 2B) at baseline to 300 μm (–120; SD, 130) after the initial loading phase ($P = 0.0005$) and remained stable thereafter.

On average, 7.7 injections (SD, 1.2; range, 6–11) were given per patient during the first year of follow-up. Furthermore, on average 4.4 injections (SD, 1.9; range, 0–9) were administered per patient per year during the second to fourth year of follow-up. Patients had on average 4.5 clinic visits during the first year (SD, 1.5; range, 3–10) and 4.3 clinic visits per year during the second to fourth year of follow-up (SD, 1.3; range, 2–10; Fig 3).

At the end of the first year of follow-up, the treatment interval (i.e., maximal disease-free interval defined by at least 2 consecutive intervals of the same length) for 81.8% of patients could be extended to ≥ 8 weeks, and for 28.6% of patients this could be extended to ≥ 12 weeks. The proportion of patients with a treatment interval of ≥ 12 weeks remained stable at 46.9% to 49.2% after year 2 (Fig 4). In 52 patients (22.5%), we were able to stop

therapy because of disease stability; 3 patients refused therapy continuation.

An insufficient therapeutic response induced a treatment switch in 5.9% of patients. Of the 62 patients on treatment for 4 years, 28 (45.2%) maintained driving vision ($BCVA \geq 0.5$). A severe vision loss, defined as a VA loss of ≥ 15 letters, occurred in 5.6% of patients despite continued treatment (central subretinal fibrosis [$n = 7$], extensive subretinal hemorrhage [$n = 1$], central geographic atrophy [$n = 5$]).

Discussion

In a real-world setting, patients treated with aflibercept over a 4-year period under a T&E protocol achieved a visual gain that was not remarkably below 4-year data from controlled clinical trials.¹⁴ The reduced burden on

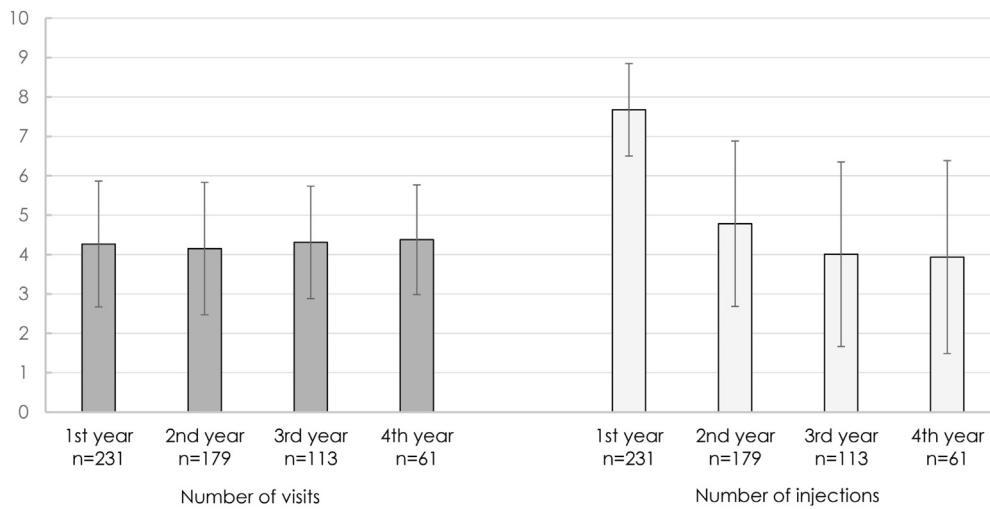


Figure 3. Mean number of visits and injections per year.

patients associated with the treatment of nAMD under T&E resulted in 71% treatment adherence in our institution. The majority of the remaining patients did not hold therapy, but went back to their private ophthalmologists to proceed with treatment closer to their homes. This study showed that a treatment interval extension to ≥ 12 weeks was possible in approximately half of cases (46%–49%). This number is slightly lower than that in the recently presented outcomes for brolocizumab with approximately 50% of patients reaching 12 weeks intervals.¹⁵ However, our study may be prone to a positive selection bias because 29% of patients had been lost to follow-up. On the other hand, results did not change after replacing missing data using the multiple imputation method. An insufficient therapeutic response and high treatment demand (injection interval < 2 months) were rare events (5.9%).

Compared with aflibercept given every 2 months in the registration trials, the visual gain at 12 months in our cohort was slightly worse (+7.9 letters/+8.9 letters vs. +5.7 letters).¹⁴ However, baseline VA was better in our patients. This fact might explain the larger visual gain at 4 years in the VIEW 1 extension study, because the final VA in both studies is comparable (63.4 letters in our study vs. 62.8 letters in VIEW 1 extension study). The mean number of active injections in the first year were similar in our study and the VIEW study (7.7 injections vs. 7.5 active and 5 sham injections in the registration trials). In the VIEW extension study, the mean number of injections was higher compared with our sample (5.8 injections vs. 4 injections per year).

Mean baseline VA in our cohort tended to be better than in other recently published “real-life studies” with follow-up times of up to 24 months (59.8 letters vs. 55.9 letters and

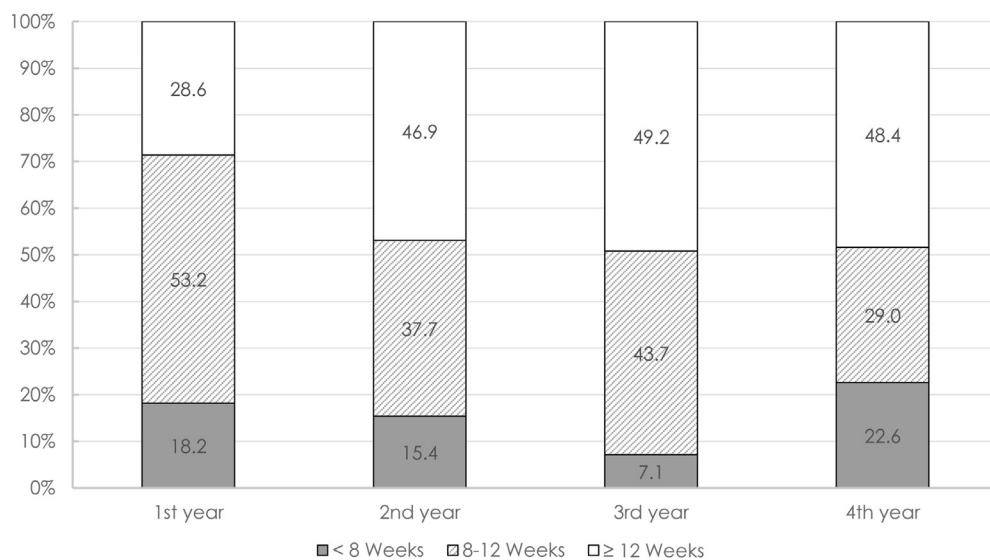


Figure 4. Percentage of eyes and their mean treatment interval over time.

53.7 letters).^{16,17} Despite a possible ceiling effect, mean VA in our study group improved during the initial loading phase and the first year of treatment (+6.0 letters), which is in agreement with the outcomes reported in these other published studies (+5.4 and +5.1 letters, respectively). In the following 4 years, mean VA remained stable after the loading phase but improvements were no longer significant. Thus, a T&E regimen with aflibercept, analogous to the experience with ranibizumab, is able to maintain stable VA for up to 4 years^{8,9} and to prevent severe vision loss, defined by a loss of 3 lines (≥ 15 letters), in 94% of patients. This has not been shown before. Our OCT data, in line with the functional stability, showed a stable retinal thickness over the whole period, which again confirms published evidence for shorter time intervals.^{11,18}

Compared with long-term studies using ranibizumab, but different treatment protocols on an as-needed basis (PRN, SEVEN-UP Study, Comparison of AMD Treatments Trials [CATT] Study),^{19,20} we see similar tendencies: The VA gained until 2 years started to decline thereafter. However, the decline rate is considerably different. Although we saw a decline in VA of approximately 1 letter per year in years 3 and 4 in our study, the decline rate was approximately 4.75 letters per year in the SEVEN-UP study and approximately 3 letters in the CATT study in the respective time periods. A decline over time has certainly to be expected because of a physiologic progression of the dry AMD component, but we think that the mentioned differences are explained by qualitative differences between treatment protocols.⁷

In our cohort, a mean of 7.7 aflibercept injections administered per patient in the first year in our cohort is comparable to the treatment demand reported in other aflibercept studies.^{10,11} A mean of 4.4 injections administered per patient in the second year in our study was lower than the 5.7 injections per year reported by another comparable study.¹⁰ In the following years, the number of injections in our study remained stable at approximately 4 injections per year. A long-term study with ranibizumab reported a slightly higher number of annual injections for the 5-year time period with 8.0, 6.3, 5.9, 5.4, and 4.0 injections per year for years 1 to 5, respectively.⁹ This indicates a slightly higher mean treatment demand for ranibizumab, which is in line with our clinical experience.²¹

At 12 months, more than 80% of patients reached a treatment interval of more than 8 weeks and approximately one third of patients had a treatment interval of 12 weeks or more. During the second to fourth year, approximately half of patients reached a treatment interval of 12 weeks or more. These numbers are higher when compared with those from other aflibercept studies.^{10,11} This might be explained by the more consequent exclusion of T&E protocol violators in our study.

A strength of our study is that it reports real-world and long-term experience of aflibercept for a time period of up to 4 years using a T&E regimen. Because the study is a single-center study, all patients were treated by the same (few) clinicians ensuring standardized execution of the T&E regimen. An inherent limitation of our real-world study is its retrospective nature.

Conclusions

We found that patients with nAMD treated with aflibercept using a T&E regimen achieved a visual gain over the 4-year period with a supportable burden of disease. In addition, 45% of patients maintained driving vision (vision ≥ 0.5), a tremendous achievement in the treatment of this formerly debilitating disease.

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Footnotes and Financial Disclosures

Originally received: November 29, 2018.

Final revision: January 25, 2019.

Accepted: January 28, 2019.

Available online: February 2, 2019. Manuscript no. ORET_2018_462.

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Financial Disclosure(s):

The author(s) have made the following disclosure(s): J.G.G.: Consultant—Novartis, Bayer, Allergan, Alcon. This manuscript is independent of these activities.

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Analysis and interpretation: Traine, Pfister, Zandi, Spindler, Garweg

Data collection: Traine, Pfister, Zandi, Spindler, Garweg

Obtained funding: N/A

Overall responsibility: Traine, Pfister, Zandi, Spindler, Garweg

HUMAN SUBJECTS: Human subjects were included in this study. The human ethics committees at the University of Bern (KEK 099/15) approved the study. All research adhered to the tenets of the Declaration of Helsinki. All participants provided informed consent.

No animal subjects were used in this study.

Abbreviations and Acronyms:

BCVA = best-corrected visual acuity; **CRT** = central retinal thickness; **nAMD** = neovascular age-related macular degeneration; **PRN** = pro re nata; **SD** = standard deviation; **T&E** = treat-and-extend; **VA** = visual acuity; **VEGF** = vascular endothelial growth factor.

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