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Consistent Long-Term Therapy of Neovascular Age-Related Macular Degeneration Managed by 50 or More Anti–VEGF Injections Using a Treat-Extend-Stop Protocol

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Purpose: To examine the clinical results for patients with neovascular age-related macular degeneration (nAMD) who were managed with a treat-extend-stop (TES) protocol and received 50 or more injections of anti–vascular endothelial growth factor (VEGF) agents.

Design: Retrospective case study.

Participants: Data for patients from a private retina practice meeting the following criteria were included: diagnosis of nAMD and having received 50 or more intravitreal injections of anti-VEGF agents.

Methods: The patients' baseline visual acuity (VA; obtained using Snellen charts and converted to Early Treatment Diabetic Retinopathy Study [ETDRS] letters), age, length of follow-up, anti-VEGF agents used, and interval between treatments were obtained. These data were examined through the 51st injection and at the last follow-up examination. Patients were excluded if they lost significant vision because of a diagnosis unrelated to AMD during therapy.

Main Outcome Measures: Visual acuity and complications.

Results: Seventy-one eyes of 67 patients were identified who met inclusion criteria. The mean age of patients was 83.0 years. Women made up 58.2% of the study population, whereas men constituted 41.8%. The mean initial VA was 55.6 ETDRS letters. The mean duration of follow-up at the 51st visit for an injection was 6.4 years, and the mean duration of follow-up at the last visit was 8 years. The mean number of injections at final follow-up was 63.7. The mean interval between treatments at the 51st follow-up was 5.4 weeks, and the mean follow-up at the last examination was 6.4 weeks. Mean VA at the 51st injection was 65.3 letters, and the mean change from baseline was 9.7 letters ($P < 0.001$, Student paired *t* test). The mean vision gained at last follow-up was 8.7 letters from baseline ($P < 0.001$), or 64.3 letters.

Conclusions: In this study, patients gained a mean of 2 ETDRS lines after 50 injections. This study had a mean follow-up of 8 years, and 35.2% of eyes had a 3-line or more gain in VA at the last follow-up examination. Patients who require consistent long-term anti-VEGF therapy, managed with a TES protocol, are likely able to maintain or improve their vision. *Ophthalmology 2018;■:1–7 © 2018 by the American Academy of Ophthalmology*

Age-related macular degeneration (AMD) is a leading cause of vision loss in patients older than 65 years.[1] Neovascular AMD (nAMD) accounts for 10% to 15% of cases of AMD and is responsible for more than 80% of severe vision loss and blindness attributable to AMD.[2] The natural long-term history of nAMD is poor; at 2 years, the average vision loss is approximately 4 Early Treatment Diabetic Retinopathy Study (EDTRS) lines.[2] In this study, 20% of patients had visual acuity (VA) that was 20/200 or worse at baseline, and this percentage increased to 76% after 3 years.[2] With the advent of intravitreal anti–vascular endothelial growth factor (VEGF) agents, many large randomized controlled trials (RCTs) showed improvement in VA at the 1- and 2-year analyses.[3–8] The Anti-VEGF Antibody for the Treatment of Predominantly Classic Choroidal Neovascularization in Age-Related Macular Degeneration (ANCHOR) trial was the first trial that demonstrated visual improvement in nAMD through intravitreal anti-VEGF therapy.[3] Intravitreal anti-VEGF agents now are the first-line therapy for treating nAMD.[4]

However, the effectiveness depends on the dose regimen and is variable.[5] In major RCTs, monthly injections over the course of the study typically are used and provide effective treatment. Pro re nata (PRN) dosing has been used with success, typically after a loading dose of 3 monthly injections, and has been examined in clinical trials, as well.[6,7,9] Treat-and-extend regimens, along with their variant, the treat-extend-stop (TES) protocol, have been found to achieve comparable efficacy to traditional fixed dosing.[10–12]

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Recent studies examining the long-term effectiveness of anti-VEGF treatments have reported variable results. For example, the Comparison of Age-Related Macular Degeneration Treatments Trial (CATT) compared intravitreal injections of ranibizumab or bevacizumab given either monthly or PRN and demonstrated that the treatments were effective through month 24; however, the 5-year outcomes of this study extension using a PRN method indicate that the mean VA gains were not maintained.[8,13] Similarly, the outcomes of the Seven-Year Outcomes in Ranibizumab-Treated Patients in ANCHOR, Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab In the Treatment of Neovascular AMD (MARINA), and Open-Label Extension Trial of Ranibizumab for Choroidal Neovascularization Secondary to Age-Related Macular Degeneration (HORIZON) Study (SEVEN-UP) found an overall mean decline in vision using the PRN method.[14] By contrast, a recent report of the long-term vision outcome of the VEGF Trap-Eye: Investigation of Efficacy and Safety in Wet AMD 1 Extension Study indicates that treatment with aflibercept with fixed-interval dosing maintained visual improvement at 4 years.[15] The purpose of this retrospective case study was to examine the clinical results and treatment patterns for patients with nAMD who were managed with a TES protocol and received 50 injections or more of anti-VEGF agents.

Methods

The study was approved by a local institutional review board (IRBco) and followed the tenets of the Declaration of Helsinki. Compliance with the Health Insurance Portability and Accountability Act (HIPAA) regulations was followed. Informed consent was not required for this retrospective chart review. The clinical database of a retina-only practice was searched for patients that had a diagnosis of nAMD and were treated with anti-VEGF agents. Records of patients with nAMD who were examined in the clinic between September 2005 and January 2017 were included in the analysis. Patients were included in the study if they had received 50 or more intravitreal anti-VEGF injections. Patients with loss of vision not related to the retina, such as that resulting from ischemic optic neuropathy, and patients who initially were treated elsewhere, for whom a pretreatment VA was not available, were excluded.

The patients in the study underwent a comprehensive ophthalmic examination and either spectral-domain OCT (Spectralis; Heidelberg Engineering; Franklin, MA) after January 2008 or time-domain OCT before January 2008 (Stratus; Carl Zeiss Meditec; Ontario, CA) at each visit. Patients also underwent fluorescein angiography at initial presentation and at other time points based on the discretion of the treating physician. The anti-VEGF agents administered during this study included bevacizumab (Avastin; Genentech Pharmaceuticals, San Francisco, CA), ranibizumab (Lucentis; Genentech Pharmaceuticals; San Francisco, CA), and aflibercept (Eylea; Regeneron Pharmaceuticals, Tarrytown, NY) and were selected to treat nAMD.

The patients received treatment in accordance with a TES protocol, such that after 3 injections at a 4- to 6-week interval, the treatment period was extended if the macula was determined to be without fluid on OCT and on clinical examination. Treatments then were extended successively by 1 to 2 weeks between injections, and patients were monitored carefully for increased fluid on OCT or for decreased vision. If at any time the patient was determined to be failing a certain time interval (between 4-12 weeks per the TES protocol), which was defined as increased fluid on OCT or decreased vision related to nAMD, then either the interval between treatments was decreased or the anti-VEGF agent was changed. Patients then were rechallenged by increasing the interval by 1 week for the next 2 to 4 injections. Patients in whom the treatment again failed either would repeat the rechallenge schedule or be maintained on the interval that kept the macula without fluid. If patients showed mild fluid on OCT and the interval was in the 4- to 6-week range, the same anti-VEGF agent was continued at that interval, as long as there was a good response from the initial presentation and the vision had not worsened. As soon as the macula was free of fluid, the treatment intervals were increased successively by 1 to 2 weeks until a 12-week interval was reached. Patients then received 2 injections at 12-week intervals, and if the macula remained dry, then treatments were suspended and the patients were monitored carefully. Initial monitoring began at a 4-week interval. Subsequent times between monitoring then were increased by 2 weeks until the interval was 12 weeks between visits. At that point onward, patients were monitored quarterly for signs of recurrence. Patients also were instructed to return earlier than their scheduled appointment if they noted decreased vision or an increase in metamorphopsia. If at any point a new CNV developed or a recurrence of the previous CNV was found, treatment was reinitiated immediately.

At each visit, patients underwent clinical examination and OCT. The data were examined at the 51st injection visit as well as at the last recorded examination in the data collection period. Visual acuity was assessed using Snellen vision and converted to ETDRS vision for the purpose of analysis. Statistical analysis of the study data was performed using the Student paired t test, chi-square test, and Mann−Whitney U test as appropriate. A P value of less than 0.05 was considered statistically significant.

Results

A total of 996 patients diagnosed with nAMD in our practice were examined. Seventy-one eyes of 67 patients met the inclusion criteria of receiving 50 injections or more. This group comprised 41.8% men and 58.2% women, with mean age of 82.9±6.2 years.

During the follow-up period, 4552 anti-VEGF injections were administered in 6617 patient-months (64.5% bevacizumab, 9.8% ranibizumab, and 25.7% aflibercept). The average time to the 50th injection was 77.4 months (6.5 years; range, 50−132 months). Patients received an average of 63.7 injections (range, 50−125 injections) with an average follow-up of 95.3 months (8 years; range, 52−135 months).

The average time between injections through the 51st injection was 5.4 weeks or 9.6 injections per year (range, 4−12 weeks); this increased to an average of 6.4 weeks or 8.1 injections per year (range, 4 weeks−treatment cessation) at the last examination in the data collection period. A total of 4 patients stopped treatment at the last examination (Table 1).

Before treatment, the mean VA for the group was 55.6±17.2 letters (Fig 1). The mean initial vision was 20/80. After 50 injections, average VA was 65.3±13.1 EDTRS letters (Snellen equivalent, 20/50), and the average change from baseline was 9.7±19.6 letters ($P < 0.001$; Fig 1). Specifically, 30 of 71 eyes (42.9%) demonstrated 20/40 vision or better, whereas only 5 of 71 eyes (7.0%) demonstrated VA of 20/200 or worse (Fig 2). After 50 injections, 26 of 71 eyes (36.6%) had gained 15 letters or more (average, 28.2±13.4 letters) from study baseline, 15 of 71 eyes (21.1%) had gained 5 to 14 ETDRS letters, 18 of 71 eyes (25.4%) had demonstrated a change of +4 to −4 ETDRS letters, 6 of 71 eyes (8.5%) had lost 5 to 14 ETDRS letters, and 6 of 71 eyes (8.5%) had lost 15 ETDRS letters or more (Fig 3).

Table 1. Percentage of Patients at Various Treatment Intervals

Weeks	Fifty-First Injection (%)	Final Follow-up (%)
4	33.8	15.5
5	26.8	21.1
6	18.3	26.8
7	2.8	2.8
8	15.5	14.1
9	1.4	2.8
10	0	7
12	1.4	4.2
Stop treatment	0	5.6

In this study, the average interval between injections through the fifty-first injection was 5.4 weeks. The average interval at follow-up was 6.4 weeks. Fewer patients required frequent injections over time.

Visual improvement was maintained through the last examination in the data collection period, with an average score of 64.3±14.6 EDTRS letters (Snellen equivalent, 20/50−), and an average change from baseline VA of 8.7±20.2 letters ($P < 0.001$; Fig 1). This was not significantly different compared with vision at the 50th injection ($P = 0.189$; Fig 1). At the last examination during the study period, 30 of 71 eyes (42.9%) demonstrated 20/40 vision or better, whereas 7 of 71 eyes (9.9%) demonstrated VA of 20/200 or worse (Fig 2). Additionally, 25 of 71 eyes (35.2%) gained 15 letters or more from study baseline, 16 of 71 eyes (22.5%) gained 5 to 14 ETDRS letters, 17 of 71 eyes (23.9%) demonstrated a change of +4 to −4 ETDRS letters, 6 of 71 eyes (8.5%) lost 5 to 14 ETDRS letters, and 7 of 71 eyes (9.9%) lost 15 ETDRS letters or more (Fig 3). The proportions of patients achieving these visual results were not statistically different at the last examination compared with the 50th injection ($P = 0.378$ total EDTRS letters; $P = 0.705$ EDTRS letter change from baseline; Fig 3). Visual gains and losses were not correlated significantly with the type of anti-VEGF agent used ($P = 0.721$; Table 2).

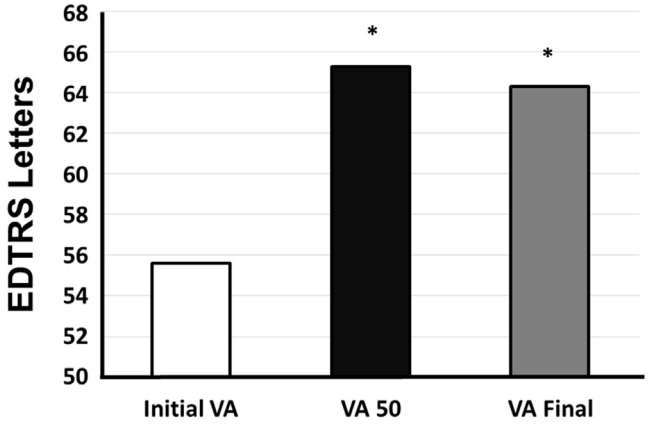

Figure 1. Bar graph showing average visual results at study time points. Average initial vision was 55.6±17.2 Early Treatment Diabetic Retinopathy Study (EDTRS) letters (Snellen equivalent, 20/80). Average vision after the 50th anti−vascular endothelial growth factor (VEGF) injection was 65.3±13.1 EDTRS letters (Snellen equivalent, 20/50; *$P < 0.001$ versus initial vision). Average vision at final follow-up was 64.3±14.6 EDTRS letters (Snellen equivalent, 20/50−; *$P < 0.001$ versus initial vision; $P = 0.189$ versus the 50th injection). VA = visual acuity.

During the data collection period, 2 episodes in 4552 injections of infectious endophthalmitis occurred, a rate of 0.044% (2/4552). Both patients' vision dropped to the counting fingers level. These patients were treated with intravitreal antibiotics and the patients resumed treatment with anti-VEGF agents as soon as the infection resolved. Their vision remained better than baseline vision as soon as the endophthalmitis resolved. Anti-VEGF injections for these 2 patients were resumed 5 weeks later. One patient's initial VA was 20/60 at baseline and was 20/40− at last follow-up, whereas the other was 20/50−2 at baseline and 20/40− at last follow-up. A single patient (1.4%) also demonstrated a large subretinal hemorrhage, decreasing his vision to 20/200. This was displaced pneumatically. Anti-VEGF injections were resumed and the VA in this patient returned to 20/25−2 at the last examination in the data collection period.

Four patients (5.6%) demonstrated central-involving geographic atrophy (GA) limiting their central vision, and they were 4 of the 7 patients (57.1%) who lost 3 lines or more of VA at final follow-up. The average number of injections received by these patients was 63.7, which is similar to the average number of injections for all patients in this study.

Discussion

Anti-VEGF therapy is the first-line treatment for nAMD.[4] Many large RCTs showed improved patient VA at the 1- and 2-year analyses.[3−8] The ANCHOR trial reported 11.3 letters gained at 1 year with monthly 0.5-mg ranibizumab injections.[3] The MARINA study reported 7.2 letters gained at 2 years, whereas HARBOR reported 9.1 letters at 2 years in the monthly arm and 7.9 letters in the PRN arm.[7,16] The VEGF Trap-Eye: Investigation of Efficacy and Safety in Wet AMD 1 and 2 Studies and CATT study[8] reported between 8.0 and 10.9 letters at the 2-year mark in the various treatment arms.[8,17] Some of these trials also have shown that there is significant variability in visual outcomes even at 2 years, depending on treatment strategy, with fixed dosing and a greater number of injections resulting in greater visual gains compared with a PRN regimen.[7,8]

Long-term studies of anti-VEGF efficacy also have been documented in both extensions of RCTs and retrospective clinical studies. Most RCTs in the extension studies switched to a PRN method, and the number of injections per year decreased significantly.[18] Although the extension studies recorded fewer injections compared with fixed dosing in the original trials, the visual results were substantially poorer.[18] In fact, greater injection numbers to maintain a fluid-free interval seem to be associated positively with maintaining visual gains.[18] Although PRN studies reported poor visual outcomes, they were still much better than the course of the untreated disease.[2]

The 5-year follow-up of the CATT study, the HORIZON study examining the 5-year outcomes of the ANCHOR, MARINA, and FOCUS trials, as well as the Seven-Year Outcomes in Ranibizumab-Treated Patients in ANCHOR, MARINA, and HORIZON Study, which was a 2-year extension of the HORIZON study, all used a PRN method and reported vision loss at the end of the study period.[13,14,19] Vision loss in these studies ranged from 8.6 to 11.0 letters from the end of the original trials at 2 years, and some even reported 3 to 8 letters lost compared with

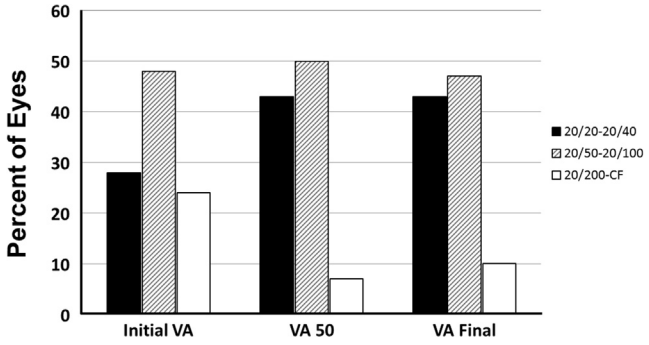

Figure 2. Bar graph showing visual proportions at study time points. Greater proportions of eyes achieved 20/40 or better after the 50th anti–vascular endothelial growth factor (VEGF) injection or at final follow-up. Likewise, fewer proportions of eyes recorded 20/200 or worse vision at the 50th anti-VEGF injection or at final follow-up. The proportions of eyes maintaining 20/50 to 20/100 vision was similar at each time point. CF = counting fingers; VA = visual acuity.

baseline.[13,14,19] In fact, 28.6% of eyes lost 3 lines or more in the 5-year follow-up of the CATT study, and similar losses were observed in 34% of eyes in the Seven-Year Outcomes in Ranibizumab-Treated Patients in ANCHOR, MARINA, and HORIZON Study.[13,14] In our study, only 9.9% of patients lost 3 lines or more of vision at an average of 8 years of follow-up. Likewise, in long-term retrospective studies, with 4 to 7 years of follow-up managed with a PRN method, only 1 study reported minimal visual gain, whereas most had average visual losses ranging from 2.4 letters to 10.3 letters.[20–25] Notably, 18% to 34% of eyes lost 3 lines or more of vision in studies conducted by Zhu et al,[23] Wecker et al,[24] and Arevalo et al.[22] However, this was not the case in our studies after the 50th injection, which showed a 9.7-letter gain at 6.5 years or an 8.7-letter gain at 8 years at the time of the final examination in the data collection period. This suggests that treatment methodology may play a role in improving and maintaining vision because our study used the same anti-VEGF agents, but instead followed a TES strategy, with most patients receiving continuous treatment.

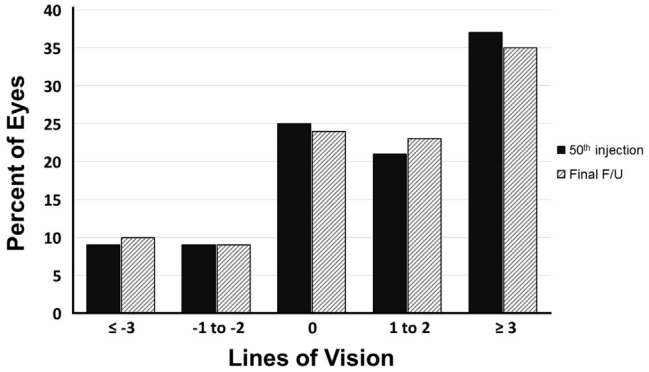

Figure 3. Bar graph showing vision change from baseline at 50th injection and final follow-up (F/U). Greater numbers of eyes gained or maintained vision after the 50th anti–vascular endothelial growth factor (VEGF) injection or at final F/U as compared with losing vision at these time points. Proportions of eyes gaining or maintaining vision at the 50th anti-VEGF injection were similar to those at final F/U.

Other retrospective studies and extension trials that used a fixed dosing regimen or treatments of greater frequency over the long term demonstrated better visual results.[15,26-28] In the retrospective study performed by Peden et al,[28] 44 patients managed with an average of 10.5 injections per year showed an average VA gain of 12.1 letters at the 7-year mark using a fixed dosing schedule. Likewise, in the extension trial of the VEGF Trap-Eye: Investigation of Efficacy and Safety in Wet AMD 1 Study, a fixed dose interval was used. Treatment with aflibercept with fixed intervals at 12 weeks, then changed to at least every 8 weeks through week 212, maintained improved vision, with a mean 5.6-letter vision increase from baseline and only 8.2% losing 15 letters or more.[15] Although we followed a TES protocol with our patients, the average time between injections was 5.4 weeks through the 51st injection and 6.4 weeks at final follow-up of 8 years. Therefore, these patients likely preserved their improved vision because of the greater frequency of injections that allowed for consistent suppression of disease activity and prevention of fluid breakthrough as opposed to the PRN treatment, which likely allowed for multiple recurrences of exudation that caused recurrent damage to the photoreceptors, ultimately leading to visual loss.[18]

The treat-and-extend protocol has been used widely because of its efficacy for improving vision and reducing the treatment burden. However, relatively few studies examining its long-term efficacy for maintaining visual gains exist. Engelbert et al[29] demonstrated eyes improving from an average baseline of 20/80 to 20/40 at 1 month, and maintaining this average out to 36 months using a mean total of 20 injections. Rayess et al[30] likewise examined visual gains at 3 years using a treat-and-extend method with ranibizumab and bevacizumab and demonstrated mean best-corrected VA improvement from an average of 20/139 at baseline to steadily improving over 3 years to a final average of 20/64. At final follow-up, 94% of eyes had lost fewer than 3 lines, and 34.4% of eyes had gained more than 3 lines.[30] To our knowledge, our current study using a TES protocol, which is a modification of the treat-and-extend protocol, is the longest to date, with an average follow-up time of 8 years. The patients in this study who received consistent long-term anti-VEGF treatment had an average baseline vision of 20/80 that improved to 20/50, including 35.2% of participants with a 3-line gain over the entire 8 years (Fig 3)—a figure that is reported by many RCTs within 2 years, but that is lost later during extension studies. These visual gains were unrelated to the type of anti-VEGF agent used (Table 2). Only 9.9% of eyes (7/71) showed 3 lines or more loss of vision, and 4 of 7 eyes showed a decrease because of central-involved GA. Four patients were able to achieve cessation of therapy during this study.

Geographic atrophy is the end stage of macular degeneration and is a significant factor for vision loss refractory to anti-VEGF therapy. At the end of the CATT study, monthly anti-VEGF injections were associated significantly with greater frequency of GA than PRN

Table 2. Visual Gains and Losses by Anti–Vascular Endothelial Growth Factor Agent

Vision (No. of Lines)	Bevacizumab	Ranibizumab	Aflibercept
≤−3	4	1	1
−2 to −1	3	1	2
−1 to +1	7	1	7
+1 to +2	6	1	10
≥+3	12	5	10
Total	32	9	30

In this study, more patients received bevacizumab and aflibercept compared with ranibizumab. However, the choice of anti–vascular endothelial growth factor agent did not affect visual gains or losses significantly ($P = 0.721$).

injections.[8] However, in the 5-year follow-up of the CATT study, these differences were no longer significant.[13] In retrospective studies, such as those performed by the Pan-American Collaborative Retina Study Group, the average number of anti-VEGF infections likewise was not associated with the development of GA.[22] Although the evidence and mechanism of GA relating to anti-VEGF therapy remains unclear, Qin et al[18] posit that these findings suggest that the development of GA may be the result of increased periods of exudation. Close monitoring to achieve exudative-free periods, usually requiring greater numbers of injections, is what is suggested to maintain visual gains.[18] In this data set, over the course of therapy, there was a low incidence of central-involved GA, and concern for limiting injections because of GA is not warranted. In fact, the 4 eyes (5.6%) in which GA developed on average had the same number of injections (63.7 injections) compared with the rest of the eyes in the study. Also, by including patients with 50 injections or more, this excluded most patients whose vision was stabilized using a TES protocol from fibrovascular scarring resulting from nAMD.[12]

Long-term analyses of anti-VEGF efficacy for nAMD are emerging. Both the extension trials and the retrospective studies that used the PRN treatment method reported decreased vision over time, yet the visual results were still better than the natural course of the disease. In the current study, broad inclusion criteria were used, making our visual outcomes generalizable to a standard retina clinical practice. Patients with variable VA, small and large areas of CNV, and with and without complicating factors such as concomitant dry AMD, presence of subretinal hemorrhage, or RPE tears, were included in this study. Of note, patients also were included if they showed good initial VA to start. Twenty-eight percent of patients in this study showed 20/40 or better VA at baseline, which may have limited some of the visual improvement results, and these patients are not included in the vast majority of RCTs. Moreover, although our practice uses a TES protocol, most of these patients' treatments could not be significantly extended. They required 9.6 injections per year at the 51st injection visit, and 8.1 injections per year at final follow-up.

Limitations in this study included its method of VA measurement; the nature of the study design; the sample size, which limits subgroup analysis; and the analysis of VA at the last examination in the data collection period. The vision recorded was Snellen vision and not best-corrected ETDRS vision. Additionally, this was a retrospective study, and there may be limitations in the standardization of treatment regimen and heterogeneity in treatment patterns with multiple providers, even while following the TES protocol. However, the significant number of patients and long follow-up period make this data set an extremely valuable addition to the literature. Nevertheless, the overall sample size is still relatively small compared with major RCTs, and thus limits subgroup analysis, for example, in comparisons between different anti-VEGF agents. Future studies with greater numbers of participants will be required to strengthen the statistical power and allow for subgroup analysis. On evaluation, there were no statistically significant differences between the agents used. Thus, the agent used at the 50th injection was associated with the VA obtained at the 50th injection for purposes of analysis. Finally, reporting of VA at final follow-up has the inherent bias that VA may continue to change past the variable time points for each individual patient.[31] However, one point of constancy was the examination of data after 50 injections were administered, at which point average VA and length of time of improved or preserved vision were recorded. Future studies with greater numbers of patients and a set end point may reveal findings not otherwise described in this study.

Patients in this study receiving consistent long-term anti-VEGF treatment using a TES regimen showed an average visual gain of 8.7 letters, with only 9.9% of eyes losing more than 3 lines of VA. Moreover, 35.2% of participants showed a 3-line gain over an average of 8 years of treatment, with an average of 64 injections, and an average vision of 20/50− overall. This study demonstrated that consistent long-term anti-VEGF treatment for nAMD is effective and safe and can improve or maintain visual outcomes.

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Abbreviations and Acronyms:
ANCHOR = Anti-VEGF Antibody for the Treatment of Predominantly Classic Choroidal Neovascularization in Age-Related Macular Degeneration; **AMD** = age-related macular degeneration; **CATT** = Comparison of Age-Related Macular Degeneration Treatments Trial; **CNV** = choroidal neovascularization; **ETDRS** = Early Treatment Diabetic Retinopathy Study; **GA** = geographic atrophy; **HORIZON** = Open-Label Extension Trial of Ranibizumab for Choroidal Neovascularization Secondary to Age-Related Macular Degeneration; **HIPAA** = Health Insurance Portability and Accountability Act; **MARINA** = Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab In the Treatment of Neovascular AMD; **nAMD** = neovascular age-related macular degeneration; **PRN** = pro re nata; **RCT** = randomized controlled trial; **RPE** = retinal pigment epithelium; **TES** = treat-extend-stop; **VA** = visual acuity; **VEGF** = vascular endothelial growth factor.

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