Treatment Outcomes After 3 Years in Neovascular Age-Related Macular Degeneration Using a Treat-and-Extend Regimen

NADIM RAYESS, S.K. STEVEN HOUSTON III, OMESH P. GUPTA, ALLEN C. HO, AND CARL D. REGILLO

• PURPOSE: **To determine 3-year treatment outcomes after 1 to 3 years of ranibizumab or bevacizumab therapy using a treat-and-extend regimen in patients with neovascular age-related macular degeneration (AMD).**

• DESIGN: **Retrospective, interventional, consecutive case series.**

• METHODS: **We treated 212 eyes from 196 patients diagnosed with treatment-naive neovascular AMD between January 2009 and March 2013; they were treated with either ranibizumab or bevacizumab for a minimum of 1 year, using a treat-and-extend regimen. The main outcome measures were change from baseline best-corrected Snellen visual acuity (BCVA), proportion of eyes losing < 3 BCVA lines, proportion of eyes gaining ≥3 BCVA lines, change from baseline central retinal thickness, and mean number of injections at 1, 2 and 3 years of follow-up.**

• RESULTS: **The mean follow-up period was 1.88 years (median, 2 years). At baseline, mean BCVA was 20/139; it improved to 20/79 ($P < 0.001$) after 1 year of treatment and was maintained at 20/69 and 20/64 at 2 and 3 years follow-up ($P < 0.001$), respectively. At baseline, mean central retinal thickness was 351 μm and significantly decreased to 285 μm, 275 μm and 276 μm at 1, 2 and 3 years of follow-up ($P < 0.001$), respectively. Patients received, on average, 7.6, 5.7 and 5.8 injections over years 1, 2 and 3 of treatment, respectively. At final follow-up, 94% of eyes had lost < 3 lines BCVA, and 34.4% of eyes had gained ≥3 lines BCVA.**

• CONCLUSIONS: **The treat-and-extend regimen is effective in achieving and maintaining visual and anatomic improvements in patients with neovascular AMD for up to 3 years of treatment. (Am J Ophthalmol 2015;159:3–8.**

ANTIVASCULAR ENDOTHELIAL GROWTH FACTOR (VEGF) injections were first established as the primary treatment for neovascular age-related macular degeneration (AMD) in the Minimally Classic/Occult Trial of Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular AMD (MARINA) and the Anti-VEGF Antibody for the Treatment of Predominantly Classic Choroidal Neovascularization in AMD (ANCHOR) trials.[1,2] The Comparison of AMD Treatments Trials (CATT) and the Inhibit VEGF in Age-related Choroidal Neovascularization (IVAN) studies revealed similar visual outcomes in patients with neovascular AMD treated with either ranibizumab or bevacizumab over 2 years.[3,4] An inherent limitation of a monthly regimen is that patients are subjected to monthly examinations, testing (eg, optical coherence tomography [OCT] scans) and intravitreal injections, which raise long-term economic and safety concerns.

Alternative management algorithms such as quarterly injections demonstrated inferior visual acuity gains compared to monthly injections.[5,6] Individualized treatment regimens were also evaluated with patients' receiving injections only if examination or OCT findings revealed choroidal neovascularization (CNV) activity. The Prospective OCT Imaging of Patients with Neovascular AMD Treated with Intraocular Lucentis (ranibizumab) (PrONTO) study revealed that an as-needed, or pro re nata (PRN), treatment algorithm achieved good visual acuity gains with reduced injection frequency, but patients are still subjected to monthly evaluations.[7,8] Subsequently, the CATT and IVAN studies showed that the visual gains in an as-needed regimen were not equivalent to a monthly regimen at the end of 2 years of follow-up.[3,4,7,8]

The treat-and-extend regimen allows for individualized anti-VEGF treatments. Prior studies have suggested that this algorithm may have the socioeconomic benefit of potentially limiting the number of injections, office visits and ancillary tests.[9,10] Currently, the treat-and-extend regimen is the most commonly employed treatment approach in the United States, according to the American Society of Retina Specialists 2013 Membership Survey: Preferences and Trends, with approximately 77.8% of retina specialists favoring this style of treatment for neovascular AMD.[11]

Although prior published studies have demonstrated good visual outcomes in a cost-effective manner with the treat-and-extend regimen, using either bevacizumab or ranibizumab, the studies are limited in terms of numbers of patients or follow-up.[9,10,12–16] The purpose of our study was to determine 3-year visual and anatomic

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From the Retina Service of Wills Eye Hospital, Mid-Atlantic Retina, Philadelphia, Pennsylvania.

Inquiries to Carl D. Regillo, Retina Service, Wills Eye Hospital, 840 Walnut St., Suite 1020, Philadelphia, PA 19107; e-mail: cregillo@aol.com

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outcomes in patients with neovascular AMD using a treat-and-extend regimen involving bevacizumab and ranibizumab.

METHODS

• **PATIENT SELECTION AND DIAGNOSIS:** This study was a retrospective, consecutive case series that received approval from the institutional review board at Wills Eye Hospital. Billing records for patients diagnosed with neovascular AMD between January 2009 and March 2013 were identified by using the International Classification of Diseases-9 code 362.52. Patients' charts were then reviewed for age, gender, date of diagnosis of neovascular AMD, best (available spectacle with/without pinhole) corrected (Snellen) visual acuity (BCVA) at each encounter, medical and ocular histories, anti-VEGF agent received, number of injections, and longest duration of successful extension. In addition, either Heidelberg spectral-domain optical coherence tomography (OCT) scans (Heidelberg Engineering; Heidelberg, Germany) or RTVue-100 SD-OCT scans (Optovue, Freemont, California, USA) were reviewed at the time of diagnosis and at 1-year intervals to document the presence or absence of intraretinal/subretinal fluid and to determine central retinal thickness. Due to variations in patients' individual follow-up periods, spectral-domain OCT scans were evaluated within 6 weeks of the yearly target dates.

Patients were included in the study if they had treatment-naive AMD, had a minimum of 1 year of follow-up using a treat-and-extend regimen, and received treatment with either bevacizumab or ranibizumab. Patients were excluded if they had any 1 of the following: (1) concomitant retinal diagnoses, such as diabetic retinopathy, retinal vein occlusion or myopic degeneration; (2) Anti-VEGF treatment regimen other than treat-and-extend; (3) intravitreal injections other than bevacizumab or ranibizumab (specifically, patients treated with aflibercept were excluded because of limited follow-up and the lack of head-to-head studies comparing the efficacy and durability of aflibercept to those of ranibizumab and bevacizumab); (4) any prior treatments for neovascular AMD, such as laser photocoagulation or photodynamic therapy; and (5) vitrectomy surgery in the study eye.

• **TREAT-AND-EXTEND REGIMEN:** All patients were evaluated at initial diagnosis using slit-lamp biomicroscopy and spectral-domain OCT. Patients were then treated with monthly (4–5 weeks) intravitreal injections of either bevacizumab (1.25 mg/0.05 mL; Avastin; Genentech, San Francisco, California, USA) or ranibizumab (0.5 mg/0.05 mL; Lucentis; Genentech, San Francisco, California, USA) until no signs of CNV activity were detected on slit-lamp biomicroscopy and spectral-domain OCT. (Signs of CNV activity include the presence of intraretinal or subretinal fluid according to spectral-domain OCT or hemorrhage in the macula.) Patient follow-ups and treatments were then extended by intervals of 2 weeks as long as no signs of CNV activity were present. However, if any signs of exudation (intraretinal/subretinal fluid or macular hemorrhage) were detected, treatment intervals would be subsequently shortened by 2-week intervals. Anti-VEGF treatment was administered at every visit, regardless of CNV activity.

• **STATISTICAL ANALYSIS:** Patients' BCVAs were converted into logarithm of the minimum angle of resolution (logMAR) score for statistical analysis. Data for continuous variables were recorded as mean ± standard deviation (SD). Paired 2-tailed *t* test analysis with significance set at $P < 0.05$ was used to compare mean data points at baseline with years 1, 2 and 3 of follow-up and was carried out using GraphPad Software (GraphPad, La Jolla, California, USA). BCVA was also converted into approximate Early Treatment Diabetic Retinopathy Study (approx ETDRS) scores to determine the mean gain in letters from baseline at years 1, 2 and 3.[17] The mean maximum period of successful treatment extension at each year of follow-up and the mean number of yearly injections were also calculated. Categorical variables were reported as proportions. They included data concerning spectral-domain OCT characteristics such as the presence of intraretinal or subretinal fluid, in addition to the proportion of eyes losing <3 BCVA lines and the proportion of eyes gaining ≥3 BCVA lines at yearly intervals.

RESULTS

• **BASELINE CHARACTERISTICS:** A total of 212 eyes from 189 patients (123 female, 66 male) with treatment-naive neovascular AMD were included. The minimum follow-up of 1 year was completed by 212 eyes (100%), with 121 eyes (57%) and 59 eyes (27.8%) completing 2 and 3 years of follow-up, respectively. Similarly, spectral-domain OCT characteristics were obtained for 212 eyes (100%) at 1 year follow-up, and 121 eyes (57%) and 59 eyes (27.8%) provided spectral-domain OCT data at 2 and 3 years of follow-up, respectively. The mean age of included patients was 80.3 ± 9.0 years. Baseline mean BCVA was 0.832 ± 0.57 (Snellen equivalent, 20/136; median, 20/80), with a corresponding mean central retinal thickness of 350.8 ± 116.8 μm (median, 322.5 μm) (Table). The mean follow-up period was 1.88 years (median, 2 years).

• **VISUAL ACUITY AND SPECTRAL-DOMAIN OPTICAL COHERENCE TOMOGRAPHY OUTCOMES AT YEARS 1, 2 AND 3:** Mean visual acuity significantly improved at years 1, 2 and 3 compared to baseline. After 1 year of treatment, mean BCVA was 0.601 ± 0.47 (Snellen equivalent 20/79;

TABLE. Baseline Characteristics (212 Eyes in 196 Patients) for Patients With Neovascular Age-Related Macular Degeneration Treated Using a Treat-and-Extend Regimen

Baseline Characteristics	Treat-and-Extend Regimen (n = 212 eyes)[a]
Age	
Mean ± SD	80.3 ± 9.0
Median (min, max)	82 (54, 99)
Gender (n = 189)	
Male	66 (35%)
Female	123 (65%)
Hypertension	
Yes	97 (46%)
No	115 (54%)
Diabetes mellitus	
Yes	24 (11%)
No	188 (89%)
Vision (BCVA)	
Mean	20/136
Median (min, max)	20/80 (20/23, HM)
CRT (μm)	
Mean ± SD	350.9 ± 116.8
Median (Min, Max)	322.5 (145, 869)

BCVA = best-corrected visual acuity; CRT = central retinal thickness; HM = hand motion; max = maximum; min = minimum; SD = standard deviation.

[a]At baseline, 212 eyes were included in the study. At 1, 2 and 3 years of follow-up, 212, 121 and 59 eyes, respectively, were included.

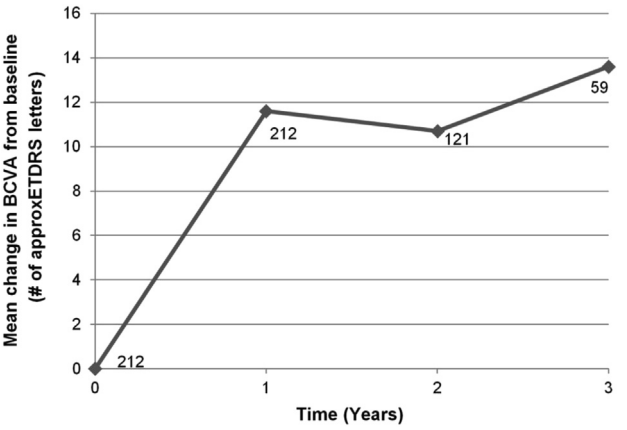

FIGURE 1. Mean change in best-corrected visual acuity (approximate Early Treatment Diabetic Retinopathy Study letters) from baseline to 3 years of follow-up in eyes with neovascular age-related macular degeneration treated with either ranibizumab or bevacizumab using a treat-and-extend regimen. The numbers of eyes at each follow-up data point are labeled. BCVA = best-corrected visual acuity; approx ETDRS = approximate Early Treatment Diabetic Retinopathy Study.

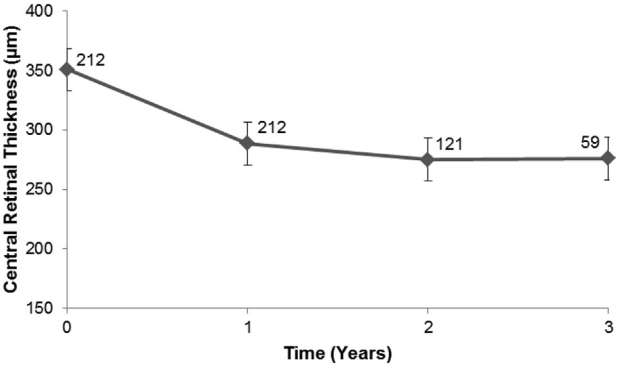

FIGURE 2. Mean change in central retinal thickness from baseline to 3 years of follow-up in eyes with neovascular age-related macular degeneration treated with either ranibizumab or bevacizumab using a treat-and-extend regimen. The number of eyes at each follow-up data point is labeled.

median, 20/56; $P < 0.001$). For the 121 eyes that completed 2 years of follow-up, mean baseline BCVA improved from 0.749 ± 0.51 (Snellen equivalent 20/112) to 0.536 ± 0.40 (Snellen equivalent 20/69; median, 20/52; $P < 0.001$) at 2 years. Similarly, baseline BCVA was 0.777 ± 0.55 (Snellen equivalent 20/120) for the 59 eyes that completed 3 years of follow-up and reached 0.505 ± 0.37 (Snellen equivalent 20/64; median, 20/52; $P < 0.001$) following 3 years of anti-VEGF therapy. The mean change in BCVA corresponded to a gain of +11.6 ± 5.7 approx ETDRS letters at 1 year of follow-up, which was maintained at +10.7 ± 8.0 approx ETDRS letters at 2years and +13.6 ± 11.4 approx ETDRS letters at 3 years of follow-up (Figure 1).

Spectral-domain OCT measurement of the mean central retinal thickness was significantly decreased at years 1, 2 and 3 compared to baseline. Patients had mean baseline central retinal thicknesses of 351 ± 116.8 μm (median, 323 μm), which decreased to 285 ± 84.8 μm (median, 273 μm) following 1 year of treatment ($P < 0.001$). Mean central retinal thicknesses at 2 years of follow-up was 275 ± 74.7 μm (median, 268 μm; $P < 0.001$) and remained stable at 3 years of follow-up (276 ± 70.8 μm) (median, 268 μm; $P < 0.001$) (Figure 2).

At 1 year of follow-up, 94.8% of patients had lost <3 BCVA lines. Similarly, 95.9% and 91.5% of patients lost <3 BCVA lines at 2 and 3 years of follow-up, respectively. The percentages of patients who gained ≥3 BCVA lines following 1, 2 and 3 years of treatment were 36.3%, 30.6% and 35.6%, respectively. Active CNV, defined as the presence of subretinal/intraretinal fluid according to spectral-domain OCT, was assessed at the yearly spectral-domain OCT scans. At year 1, 52.4% of patients had persistent CNV activity based on spectral-domain OCT findings. Following 2 and 3 years of treatment, 52.1% and 52.5% of patients, respectively, had signs of CNV activity.

• **TREAT-AND-EXTEND REGIMEN:** Patients received on average 7.6 ± 1.8 injections (median, 7.4; range, 5–13;

40% bevacizumab, 60% ranibizumab) during the first year of treatment, and over years 2 and 3 received 5.7 ± 2.3 (median, 5; range, 3–13; 31% bevacizumab, 69% ranibizumab) and 5.8 ± 2.1 (median, 5; range, 3–10; 28% bevacizumab, 72% ranibizumab) injections, respectively. Finally, the average longest duration of successful extension between injections during year 1 was 11.4 ± 4.3 weeks (median, 11; range, 6–16). During years 2 and 3, patients' average longest duration of successful extension was 13.7 ± 5.3 weeks (median, 13; range, 7–18) and 13.9 ± 5.1 weeks (median, 13; range, 7–18), respectively.

DISCUSSION

THE AIM OF THIS STUDY WAS TO EVALUATE 3-YEAR TREATment outcomes for patients with neovascular AMD treated with anti-VEGF agents using a treat-and-extend regimen. Our results demonstrate significant improvements in vision from baseline that are maintained for up to 3 years of follow-up. Likewise, central retinal thickness significantly decreased from baseline through 3 years follow-up.

Short-term treatment outcomes using a treat-and-extend regimen have been reported in the literature. Gupta and associates demonstrated visual improvements from 20/135 at baseline to 20/85 ($P < 0.001$) at 1 year of follow-up and was 20/83 ($P = 0.002$) at final follow-up in patients treated with ranibizumab only.[9] Another study by Shienbaum and associates demonstrated visual improvements from 20/230 at baseline to 20/109 ($P < 0.001$) and 20/106 ($P < 0.001$) at 12 months and final follow-up, respectively, in patients treated with bevacizumab only.[12] These studies demonstrated that a treat-and-extend algorithm using bevacizumab or ranibizumab can achieve visual outcomes comparable to those of monthly treatments, with the benefit of having fewer injections, office visits and OCT testing.

Engelbert and associates reported 3-year outcomes using a treat-and-extend regimen for 11 eyes with type 3 neovascular AMD, 8 of which completed 3 years of follow-up.[14] Mean VA improved from 20/80 at baseline to 20/40, which was maintained for the 3 years of follow-up ($P < 0.04$).[14] Another study by Engelbert and associates evaluated 3 year treatment outcomes using a treat-and-extend regimen for 18 eyes with type 1 neovascular AMD.[13] In this study, median baseline logMAR VA was 0.53, and at 3 years, it remained stable at 0.52 ($P = 0.68$).[13] Despite having 3 years of follow-up, these 2 studies have very small numbers of patients, which limits the confidence in drawing conclusions.

One of the disadvantages of a PRN regimen is the possibility of there being prolonged durations between consecutive anti-VEGF treatments. In fact, maintenance injections are considered to be a valuable attribute of the treat-and-extend algorithm so as to ensure disease stability and minimize structural damage that may result from recurrence of CNV activity, which includes both lesion growth and exudation. Levine and colleagues revealed recurrent CNV activity and even submacular hemorrhages shortly after normal OCT findings.[18] In their study, the 6 patients who developed submacular hemorrhage had prolonged average intervals of 16.8 weeks from the last anti-VEGF injection they had received to the development of submacular hemorrhage.[18] In our study, there were 2 cases of submacular hemorrhage. One of the patients improved from 20/200 to 20/60 over 3 years, while the other patient improved from 20/200 to 20/60 over 1 year. In an as-needed, OCT-guided treatment algorithm, patients can be left for extended intervals without receiving anti-VEGF injections. As a result, patients receiving maintenance injections may be less susceptible to developing these severe adverse events.[14]

We provide the largest series, to our knowledge, that documents 3-year treatment outcomes for patients with neovascular AMD who have been treated with a treat-and-extend algorithm. In our study, patients received, on average, 7.6 injections (median, 7) in the first year, 5.7 injections (median, 5) in the second year, and 5.8 injections (median, 5) in the third year. In comparison, the 37 patients included in the PrONTO study received, on average, 3 fewer injections (average, 9.9) than those in our study over a 2-year period. Of note, however, is that patients treated using the treat-and-extend regimen (a median of 17 injections over 3 years) had the added benefit of approximately 50% fewer examinations and OCT testings than did patients treated with PRN regimens.

Our results also demonstrate significant visual improvements of over 10 approx ETDRS letters that were maintained through 3 years of follow-up. In comparison, the treat-and-extend studies by Gupta and associates and Shienbaum and associates did not gain visual acuity to the same extent as the patients in this study.[9,12] In our study, spectral-domain OCT was used to assess CNV activity, whereas time-domain OCT was used in the earlier studies. This may have enhanced our ability to detect CNV activity and guide therapy more accurately. Furthermore, the study by Shienbaum and associates included subjects with worse mean baseline visual acuities of 20/230, compared with 20/136 in this study.[12] These patients may represent a population group with more advanced disease than was included in our study, and this may have limited their potential to achieve visual improvements to the same extent that we observed.

Similar to our study, patients treated with a PRN regimen as in the PrONTO study[8] or a monthly regimen as in the ANCHOR study[2] gained an average of 11.3 letters after 24 months of follow-up. In our study, at 3 years of treatment, 74.5% of eyes gained ≥0 BCVA lines, while 8.5% of eyes lost ≥3 BCVA lines. Conversely, visual outcomes at 4 years of follow-up in the HORIZON trial[19] were inferior, with only 53.7% of eyes having gained

≥0 lines and 19.6% of eyes losing ≥15 ETDRS letters. However, it is difficult to compare our study directly with the HORIZON trial[19] because their patients were not treated using a standard algorithm and had a longer follow-up of 4 years' duration. In addition, unlike the prospective studies, vision was obtained using Snellen charts in our study and did not use the standard ETDRS letters chart. This potentially limits the extent to which we can compare visual gains across the studies.

Other limitations of this study include the inherent biases of a retrospective study and the lack of including a control group with which to compare treatment outcomes. There is a large difference in the number of patients who completed 1 year of follow-up and the number of patients who completed 2 or 3 years of follow-up. This can be attributed largely to differences in the dates on which patients were included in the study; patients included in 2013 had a maximum of 1 year of follow-up. However, this difference could also be attributed to patients' being lost to follow-up. These patients could represent a subgroup that was not responding to anti-VEGF injections, which would skew the outcomes of this study in the long term toward patients who were more likely to be responders. Similarly, the percentage of patients who lost >3 BCVA lines may be biased toward better outcomes, as nonresponders may have been lost to follow-up. In addition, we report our results as a combination of both bevacizumab and ranibizumab therapy. However, prior studies have demonstrated similar treatment outcomes when comparing the drugs using a monthly regimen, a PRN regimen and a treat-and-extend regimen.[3,4,9,12] Furthermore, patients were excluded if they had received aflibercept, which may or may not have a greater durability of effect than bevacizumab and ranibizumab. Finally, retrospective studies are limited in their ability to report on safety information. However, our clinical experience with ocular and systemic safety appears similar to that reported in prospective clinical trials of neovascular AMD.

This study is unique in that we are reporting treatment outcomes in patients who received up to 3 years of anti-VEGF therapy. With anti-VEGF therapy, now the standard of care for treating neovascular AMD, it is critical to determine whether the vision improvements reported after short-term follow-up are maintained in the long run, without there being an increased risk for long-term complications. In addition, there is no consensus on a particular standard regimen. As of today, the literature has reported comparable visual outcomes with monthly treatments, as-needed therapy, and treat-and-extend regimens. However, we do not know whether a difference in treatment outcomes would surface beyond 2 years of therapy.

In conclusion, our study suggests that the treat-and-extend algorithm is an effective and efficient method for treating patients with neovascular AMD for up to 3 years following diagnosis. Patients are able to maintain significant anatomic and visual improvements of greater than 2 lines of visual acuity, on average, during this period. This can be accomplished with fewer patient visits, injections and ancillary testing than needed by patients receiving monthly treatments. Head-to-head studies are now needed to compare outcomes in patients with neovascular AMD receiving treat-and-extend regimens with outcomes resulting from other regimens so as to determine their relative efficacies.

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Biosketch

Nadim Rayess, MD is currently a post-doctoral research fellow at Wills Eye Hospital. He received his undergraduate degree in Biological Sciences from the University of California at Irvine, followed by medical school training at the American University of Beirut.