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Efficacy of a Treat-and-Extend Regimen With Ranibizumab in Patients With Neovascular Age-Related Macular Disease
A Randomized Clinical Trial

Peter J. Kertes, MD, CM; Ivan J. Galic, MD; Mark Greve, MD; Geoff Williams, MD; Jason Baker, MSc, MBA; Marcel Lahaie, BAA; Tom Sheidow, MD, MMath

IMPORTANCE Although the Canadian Treat-and-Extend Analysis Trial With Ranibizumab in Patients With Neovascular Age-Related Macular Disease (CANTREAT) reported herein and the Treat and Extend study provided data to show noninferiority of treat-and-extend (T&E) at 12 months, to date there are few data on 24-month T&E trials compared with monthly dosing.

OBJECTIVE To compare the efficacy of ranibizumab using a T&E regimen to monthly dosing in treatment-naive patients with neovascular age-related macular degeneration (nAMD) after 24 months.

DESIGN, SETTING, AND PARTICIPANTS A randomized, open-label, multicenter, noninferiority intention-to-treat trial with a margin of −5 letters in best-corrected visual acuity (BCVA) from baseline to 12 months between groups was conducted at 27 treatment centers in Canada. Participants included 580 patients with treatment-naive choroidal neovascularization secondary to AMD. The study was conducted from May 8, 2013, to August 28, 2018, and data analysis was performed between August 29 and September 12, 2018.

INTERVENTIONS Patients with nAMD were randomized 1:1 to receive intravitreal ranibizumab, 0.5 mg, in either a T&E or monthly dosing regimen.

MAIN OUTCOMES AND MEASURES Mean change in BCVA in Early Treatment of Diabetic Retinopathy Study letters from baseline to month 24.

RESULTS Of the 580 randomized patients, 350 were women (60.3%) and 547 were white (94.3%). Mean (SD) age was 78.8 (7.8) years. By the end of month 24, 466 of the 580 randomized patients (80.3%) had completed the study and participants in the T&E arm received a mean of 17.6 injections compared with 23.5 injections for the monthly arm, for a difference of 5.9 injections and visits over 2 years (95% CI, 5.4-6.5; $P < .001$). The mean (SD) BCVA improvement was not worse with the T&E arm, 6.8 (14.1) letters vs 6.0 (12.6) letters, compared with the monthly arm (difference, 0.9; 95% CI, −1.6 to 3.3; $P = .21$). There was a gain of 15 or more letters in 25.5% of the T&E group and 23.1% of the monthly treatment group (difference, 2.4%; 95% CI, −6.8% to 11.6%; $P = .59$) and a loss of 15 or more letters in 6.5% of the T&E group and 5.8% of the monthly treatment group (difference, −0.7%; 95% CI, −9.9% to 8.5%; $P = .85$).

CONCLUSIONS AND RELEVANCE These findings suggest that change in vision from baseline is not worse with a T&E compared with a monthly regimen of ranibizumab for nAMD through 24 months, achieving clinically meaningful improvements in BCVA despite fewer injections and visits.

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Supplemental content

Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Author: Peter J. Kertes, MD, CM, The John and Liz Tory Eye Centre, Sunnybrook Health Sciences Centre, 2075 Bayview Ave, Room M1-202a, Toronto, ON M4N 3M5, Canada (peter.kertes@sunnybrook.ca).

The introduction of anti-vascular endothelial growth factor (anti-VEGF) agents to ophthalmology practice has advanced the treatment of neovascular age-related macular degeneration (nAMD), a leading cause of vision loss among elderly patients in developed nations.[1] Although a cure remains elusive, timely treatment with anti-VEGF can help achieve the nAMD treatment goals of drying the affected retinas and improving or maintaining visual acuity (VA) over long periods of time.[2-6] Despite substantial progress, gaps and challenges persist, including the cost and inconvenience associated with frequent treatments.[7]

To overcome these barriers, retina specialists have developed alternative regimens in which patients receive injections at extended fixed intervals as needed based on disease activity and/or by a treat-and-extend (T&E) strategy.[8-10] The goals of these approaches are to (1) minimize exudative disease activity, such as retinal fluid and hemorrhage, as efficiently and safely as possible; (2) maintain or improve VA; and (3) reduce the number of injections needed. Although the specifics of the T&E regimen vary among practitioners, the general approach includes a loading phase of monthly treatment followed by a maintenance phase. After the loading phase, the interval between injections is progressively shortened or lengthened depending on the presence or absence of disease activity (usually determined by optical coherence tomography [OCT]), respectively.

Over the past few years, the T&E approach for nAMD has gained acceptance among retina specialists worldwide. This individualized treatment strategy reduces the burden of monthly injections and is supported by an emerging body of evidence reporting better visual outcomes in a real-world setting when compared with the OCT-guided as-needed regimens.[11-18] As the T&E approach eliminates the need for frequent assessment-related visits, it may be more convenient for both patients and ophthalmology clinics and may also result in better retention rates and visual outcomes.

To appreciate the true value of T&E, however, one must compare visual outcomes achieved with T&E with those achieved with monthly treatments, a regimen evaluated and approved in the phase 3 registration trials.[2,3] To our knowledge, thus far, only 2 prospective, randomized trials, Neovascular Age-related Macular Degeneration Management Using Ranibizumab With Continued Treat and Extend (TREX-AMD), and Treat and Extend (TREND) have compared the T&E approach with monthly treatment.[12,19] However, TREND, a large randomized trial with more than 600 patients, was not continued beyond 1 year.[19] The TREX-AMD trial included 60 patients (2:1 randomization to T&E and monthly) and by the end of year 2, many data points were missing.[13] All other T&E trials are either prospective or retrospective single-arm trials[20-27] or noncontrolled studies looking at different T&E regimens[28,29] to determine whether VA outcomes are not worse compared with monthly treatment. Hence, there is a need for large randomized clinical trials comparing the T&E approach with monthly treatment beyond 12 months. Furthermore, it is well established that patients with AMD require continued treatment with as-needed regimens (Comparison of Age-related Macular Degeneration Treatments Trials [CATT][5] Inhibit VEGF in Age-Related Choroidal Neovascularisation [IVAN][30]). However, additional data are needed regarding the VA outcomes as well as the number of injections and visits beyond 1 year with a T&E approach compared with monthly injections and visits.

Key Points

Question Does a treat-and-extend approach with potentially less frequent anti-vascular endothelial growth factor injections and visits provide visual outcomes not worse than monthly ranibizumab injections in patients with neovascular acute macular degeneration?

Findings In this randomized clinical trial of 580 patients with treatment-naive choroidal neovascularization secondary to acute macular degeneration, at month 24, visual acuity outcomes in the treat-and-extend group were not worse than those in the monthly group. This outcome occurred despite a mean of 17.6 injections and visits in the treat-and-extend group compared with 23.5 in the monthly group.

Meaning These 2-year outcomes, combined with those of 1-year trials, appear to support the hypothesis that treat-and-extend regimens are not worse than monthly treatment with ranibizumab for patients with neovascular acute macular degeneration similar to patients enrolled and treated in this trial.

The specifics and requirements differ between these T&E trials, and there is a lack of consensus on established algorithms. The application of T&E varies among practitioners, and it is influenced by different practice-, patient-, disease-, and access-related factors; these variations indicate the need for additional country-specific research to establish benchmarks on which specific recommendations for the T&E approach can be developed.

The Canadian Treat-and-Extend Analysis Trial With Ranibizumab (CANTREAT) is a 2-year, multicenter, randomized Canadian trial designed to evaluate and compare the monthly administration of ranibizumab with the T&E approach in achieving and maintaining an optimum visual function benefit (ie, BCVA stability). CANTREAT was further extended to a third year to gather data on long-term outcomes of patients with nAMD treated with the T&E regimen. The primary end point—noninferiority in the mean change in BCVA (Early Treatment of Diabetic Retinopathy Study [ETDRS]) from baseline to month 12)—was met and previously reported.[31] Herein, we describe the 24-month, preplanned secondary outcomes from CANTREAT.

Methods

Study Design

CANTREAT is a 2-year, prospective, randomized, open-label, multicenter, postauthorization study of Canadian patients treated with ranibizumab. Before starting ranibizumab injections, patients were randomized to either a once-monthly dosing regimen (monthly arm) or an extended schedule of ranibizumab intravitreal injections (T&E arm). In-depth explanation and description of the study protocol and design were previously reported.[31] After an initial loading phase of 3

consecutive monthly intravitreal injections of ranibizumab, 0.5 mg, patients were treated according to the randomization treatment arm to which they had been assigned. The study and written informed consent form were approved by the institutional review board, independent ethics committee, or research ethics board at each site, and it was conducted in adherence to the tenets of the Declaration of Helsinki.[32] Prior to enrollment, all patients provided written informed consent; participants received reimbursement for their expenses. The trial protocol is available in Supplement 1.

At the baseline visit, patients in each treatment arm underwent a standard ophthalmic examination. During the study treatment period, patients in the monthly arm had ophthalmic examinations, ETDRS BCVA assessments, and OCT every 3 months and fluorescein angiography at weeks 52 and 104. Patients randomized to the T&E arm underwent all efficacy and safety examinations, including all diagnostic procedures (eg, OCT) at each clinic visit. Lesion growth was assessed based on fluorescein angiography, with assessments performed at baseline, week 52, and week 104 visits, and at any other time at the investigator's discretion.

Outcome Measures

The primary study objective of CANTREAT was to determine whether the mean change in BCVA (ETDRS) from baseline to month 12 with a T&E regimen was noninferior (not worse) than monthly treatment within a randomized clinical trial.[31]

Preplanned secondary objectives of CANTREAT, presented herein, were to compare the mean change in ETDRS BCVA and number of injections between the 2 treatment groups from baseline to month 24 as well as to determine the proportion of patients with gains of 5 or more, 10 or more, and 15 or more letters; the proportion of patients with losses of 5 or more, 10 or more, and 15 or more letters; and the proportion of patients who achieved more than 8-week and 12-week dosing intervals. For assessment of outcomes of interest, BCVA and OCT were evaluated, where OCT images were used to measure disease stability.

Statistical Analysis

In this intention-to-treat analysis, sample size calculations were based on the change in BCVA from baseline to 12 months (noninferiority margin of −5 letters BCVA, a true difference of −1.5 letters between the 2 groups, and a common SD of 13.3 letters). Summary statistics were produced, including the mean and SD for continuous variables and counts and percentages for categorical variables. Between-group differences in the mean change in BCVA from baseline to 24 months were assessed with the Mann-Whitney test, and the total number of injections received from baseline to month 24 was evaluated with count data regression. Both BCVA and the number of injections are presented using a 2-sided 95% CI. Requests were paired or unpaired according to whether the testing was on the same group over time (paired) or 2 different treatment groups (unpaired). Analyses were performed using SAS Software, version 9.4 (SAS Institute Inc). Data analysis was performed between August 29 and September 12, 2018.

Results

Between May 8, 2013, to August 28, 2018, a total of 580 patients were enrolled (T&E, 287; monthly, 293) and included in the final analysis. Of these, 466 patients (80.3%) (T&E, 237; monthly, 229) completed the 24-month follow-up (**Figure 1**). A total of 113 discontinuations (19.5%) were reported (**Table 1**): 49 discontinuations (17.1%) in the T&E group and 64 discontinuations (21.8%) in the monthly group. Overall, the most common reason for discontinuation was withdrawal of consent (39 [6.7%] patients).

Baseline demographics and disease characteristics were similar between the treatment groups.[31] Most patients were white (547 [94.3%]), and 350 were women (60.3%). Mean (SD) age was 78.8 (7.8) years. Mean (SD) central subfield thickness at baseline was 382.7 (114.0) µm for the T&E group and 374.2 (111.9) µm for the monthly group; mean baseline BCVA in patients who completed 24 months was a letter score (approximate Snellen equivalent) of 59.6 (20/63) for the T&E group and 59.4 (20/63) for the monthly group. At 24 months, mean (SD) BCVA improvement was not worse (**Figure 2**) in the T&E treatment group (6.8 [14.1] letters) compared with the monthly treatment group (6.0 [12.6] letters; difference, 0.9; 95% CI, −1.6 to 3.3; $P = .21$). Most of the change in mean BCVA occurred during year 1 (8.5- and 6.1-letter gains for T&E and monthly, respectively).

Results reported for gain and loss of ETDRS letters in the T&E group were not worse than those in the monthly group (**Table 2**). The proportion of patients with a gain of less than 5 letters (including loss of letters) at 24 months was 38.1% (95% CI, 31.8%-44.7%) in the T&E group vs 40.4% (95% CI, 34.0%-47.2%) in the monthly group (difference, 2.4%; 95% CI, −6.8% to 11.6%; $P = .63$). A gain of 15 or more letters was experienced by 25.5% of the T&E group and 23.1% of the monthly treatment group (difference, 2.4%; 95% CI, −6.8% to 11.6%; $P = .59$); 6.5% of the T&E group and 5.8% of the monthly treatment group lost 15 or more letters (difference, −0.7%; 95% CI, −9.9% to 8.5%; $P = .85$). A gain of 10 or more letters was achieved by 42.9% of the T&E group vs 36.4% of the monthly group (difference, 6.4%; 95% CI, −2.9% to 15.5%; $P = .18$), and a loss of 10 or more letters was experienced by 9.5% and 9.8% of T&E and monthly patients, respectively (difference, 0.3%; 95% CI, −9.0 to 9.5; $P > .99$).

At month 24, a lower mean number of injections was reported for T&E (17.6) compared with the monthly dosing regimen (23.5) (difference, 5.9, 95% CI, 5.4-6.5; $P < .001$). In the T&E arm, 73.7% (95% CI, 67.6%-79.3%) of the patients were able to extend their treatment interval to 8 or more weeks during the 24 months of treatment, and 43.1% (95% CI, 36.6%-49.8%) of patients reached the 12-week maximum extension interval.

Discussion

This Canadian multicenter, prospective, randomized study confirmed the feasibility and effectiveness of the T&E

Figure 1. Flow of Study Participants

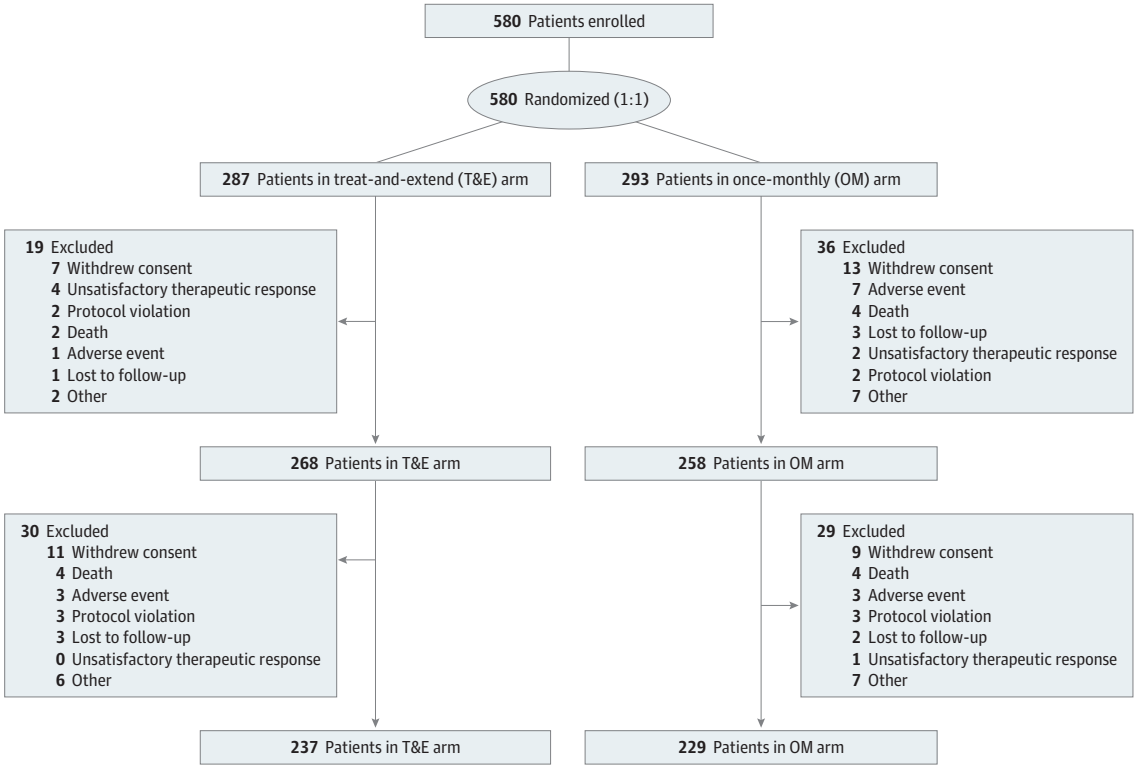
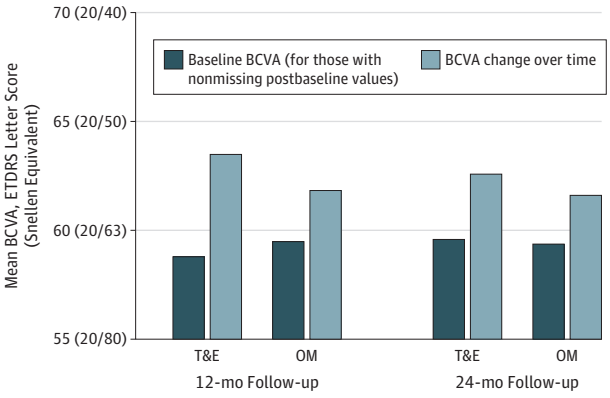


Table 1. Discontinuation Rates Over 24-Month Period

Parameter	No. (%) T&E (n = 287)	Once Monthly (n = 293)	Total (N = 580)
Discontinuation	49 (17.1)	64 (21.8)	113 (19.5)
Reasons for discontinuation			
Withdrew consent	18 (6.3)	21 (7.2)	39 (6.7)
Death	6 (2.1)	8 (2.7)	14 (2.4)
Adverse event	4 (1.4)	8 (2.7)	12 (2.1)
Unsatisfactory therapeutic effect	4 (1.4)	3 (1.0)	7 (1.2)
Protocol violation	5 (1.7)	5 (1.7)	10 (1.7)
Lost to follow-up	4 (1.4)	5 (1.7)	9 (1.6)
Other	8 (2.8)	14 (4.8)	22 (3.8)

Abbreviation: T&E, treat-and-extend.

Figure 2. Change in Best-Corrected Visual Acuity (BCVA) Letters at 12- and 24-Month Follow-up



ETDRS indicates Early Treatment Diabetic Retinopathy Study; OM, once monthly; T&E, treat-and-extend.

approach in daily practice. The 24-month vision outcomes using the T&E approach was not worse than the monthly regimen for nAMD. To maintain visual outcomes over 24 months, patients in the T&E arm needed a mean of 17.6 injections compared with 23.5 injections in the monthly arm, for at least a mean of 5.4 fewer injections. In the T&E arm, 73.7% of the patients were able to extend their treatment interval to 8 or more weeks during the 24 months of treatment and 43.1% of patients reached the 12-week maximum extension interval. The mean gain of 6.0 letters is slightly lower than the reported 2-year improvement in VA with monthly ranibizumab in the Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular Age-Related Macular Degeneration (7.2 letters),[2] CATT (8.8 letters),[5] and Anti-VEGF Antibody for the Treatment of Predominantly Classic Choroidal Neovascularization in Age-Related Macular Degeneration[3] (10.7 letters) studies. The mean gain of 6.8 letters achieved in our study over 24 months is in line with evidence from the Australian Fight Retinal Blindness! registry; patients

Table 2. Proportion of Patients With Gain or Loss of 10 or More or 15 or More ETDRS Letters at 24 Months

Outcome	% (95% CI)		Difference (95% CI)	*P* Value
	T&E	Once Monthly		
Letters gained, % of patients				
≥10	42.9 (36.4-49.5)	36.4 (30.2-43.1)	6.4 (−2.9 to 15.5)	.18
≥15	25.5 (20.1-31.7)	23.1 (17.8-29.2)	2.4 (−6.8 to 11.6)	.59
Letters lost, % of patients				
≥10	9.5 (6.1-14.1)	9.8 (6.2-14.4)	0.3 (−9.0 to 9.5)	>.99
≥15	6.5 (3.7-10.5)	5.8 (3.1-9.7)	−0.7 (−9.9 to 8.5)	.85

Abbreviations: ETDRS, Early Treatment of Diabetic Retinopathy Study; T&E, treat-and-extend.

with nAMD receiving anti-VEGF therapy using the T&E dosing gained, on average, 5.3 letters at month 24.[17] However, when comparing the outcomes from randomized clinical studies conducted several years ago with more recent studies, one should keep in mind that differences in patient populations and baseline characteristics may contribute to differences in outcomes.

The TREND study did not extend follow-up beyond 12 months. The mean change from baseline in BCVA at 12 months was 6.2 in the T&E group vs 8.1 in the monthly group.[11] In the TREND study, patients in the T&E group received 2 initial monthly ranibizumab injections at baseline (day 1) and at month 1. After 1 month, visits in the T&E group were scheduled based on disease activity as assessed by VA and OCT criteria. This difference in the loading dose—2 in the TREND study and 3 in CANTREAT—with potential to continue with monthly injections if continuous gain in VA was observed, might have contributed to the small differences in outcomes between the 2 studies. In the TREND study, after 12 months of treatment, there was an approximate 2-letter difference in favor of monthly injections. Our results were the opposite: after 12 months of treatment, there was a 2-letter difference favoring T&E. It is possible that the additional monthly injections included in the loading phase and the CANTREAT treatment algorithm led to better resolution of underlying subclinical pathologic changes, which translated into better control once patients were switched to the T&E schedule. However, differences in relevant characteristics of patients enrolled could account for the differences reported. Regardless of these variations, patients in both the TREND study and our study achieved a similar and rapid gain in BCVA, with most of the improvement occurring during the first 6 months. Improvements in vision were generally maintained afterward. However, the true long-term effect of the T&E dosing approach in the TREND trial cannot be fully recognized because the trial was not continued beyond 12 months. To our knowledge, the only other randomized clinical trial that compared the T&E regimen with monthly treatment is the TREX-AMD study. Because this trial included 60 patients (only 20 in the monthly control group), 10 of whom discontinued by the 24-month mark, the small sample size is its major limitation.

The results of CANTREAT can also be compared with the as-needed dosing regimen in the 2 large clinical trials (CATT[5] and IVAN[30]). In the CATT and IVAN trials, the as-needed dosing regimen was not worse compared with monthly dosing. In the IVAN trial the mean difference in BCVA after 2 years of treatment was 1.63 letters (95% CI, −4.01 to 0.75; *P* = .18) with a mean of 13 (range, 8-17) injections in the as-needed arm.[30] In the CATT trial the difference in VA, averaged over 2 years of follow-up in patients treated with as-needed vs monthly ranibizumab, was 1.7 letters (95% CI, −0.1 to 3.4; *P* = .07).[5] The mean (SD) number of ranibizumab injections through year 2 in the CATT trial in the as-needed group was 12.6 (6.6). Similarly, the HARBOR study demonstrated that as-needed dosing of ranibizumab could achieve clinically meaningful BCVA improvements: +8.2 letters from baseline to month 12 and +7.9 letters to month 24.[33] These results highlighted the efficacy and durability of ranibizumab with less-frequent dosing, despite the fact that the HARBOR study did not meet the noninferiority end point compared with monthly injections.[33]

In our study, at 24 months, proportions of T&E patients experiencing gains of 10 or more or 15 or more letters were not worse than in the monthly arm (≥10-letter gain: 42.9% in the T&E arm vs 36.4% in the monthly arm; ≥15 letter gain: 25.5% in the T&E arm vs 23.1% in the monthly arm). In the T&E arm, 6.5% of patients lost 15 or more letters vs 5.8% in the monthly arm. These results are not worse compared with the CATT trial results where, after 2 years of treatment, less than 10% of patients treated with monthly or as-needed ranibizumab lost 15 or more letters. These data imply that the criteria for the T&E regimen in our study did not result in an additional risk of sudden, substantial visual loss (loss of ≥15 letters) due to events, such as the development of a large subretinal hemorrhage or a substantial increase in exudation, compared with the monthly regimen. According to the Fight Retinal Blindness Study Group, the risk of substantial vision loss is higher when treatment intervals are extended beyond 16 weeks.[34]

Our results suggest that after reaching clinical stability with monthly injections, the timing between treatments can be extended in a stepwise fashion with vision outcomes, on average, that are no worse than continuing monthly treatments through 2 years. Most patients responded well to the stepwise extension regimen. At 24 months, 73.7% of patients were able to extend the treatment interval to 8 or more weeks and 43.1% to 12 weeks. Similarly, Berg et al[28] reported that in the Lucentis Compared to Avastin Study (LUCAS), 10.6% and 37.1% of patients were able to extend the treatment interval with ranibizumab to 10 and 12 weeks, respectively. When using a T&E regimen with bevacizumab, treatment intervals were extended to 10 weeks in 7.2% of the patients and to 12 weeks in 25.1% of the patients. The design of the LUCAS was similar to that of our study; monthly

injections were given until inactive disease was achieved. The patients were then followed up with a gradual extension of the treatment interval in 2-week increments to a maximum of 12 weeks. If signs of recurrent disease appeared, the treatment interval was shortened by 2 weeks at a time. The retreatment criteria in our study, however, were different for patients who reached an extended interval of 10 or 12 weeks. If there were signs of a return of disease activity, the treatment interval for these patients was shortened by 4 weeks until disease stability was regained.

The Comparison of Ranibizumab and Aflibercept for the Development of Geographic Atrophy in (Wet) AMD (RIVAL), using an identical T&E regimen, further demonstrated that a treatment tailored to patients' individual characteristics led to clinically meaningful improvements in BCVA. In the RIVAL study, the estimated mean change in BCVA letter scores from baseline to month 12 was 7.2 for ranibizumab and 4.9 for aflibercept (estimated letter score difference, 2.3; 95% CI, −0.1 to 4.7; P = .06). The mean number of injections from baseline to month 12 (9.7 in both treatment arms) and from baseline to month 24 (17.7 for ranibizumab and 17.0 for aflibercept) were similar between the treatment arms.[35,36]

We believe that the CANTREAT 24-month follow-up results confirm not only that the T&E regimen was not worse than monthly treatment but also that the rates of improvement are in line with results achieved in other randomized clinical studies and real-world registries.

Limitations

Limitations of our study are those common to all T&E trials and include open-label design and selection of treatment based on clinician judgment, which might introduce some bias. No adjustments for multiple comparisons were made; thus, the conclusions regarding the effect and contribution of different factors cannot be made. In addition, to date it is unknown whether other commonly used anti-VEGF agents administered using the T&E approach would have the same results (eg, bevacizumab T&E compared with monthly ranibizumab or monthly bevacizumab; or aflibercept T&E compared with monthly ranibizumab or monthly aflibercept) in regard to VA or difference in injections and visits.

Conclusions

In this study, CANTREAT demonstrated that the T&E regimen resulted in clinically meaningful improvement in BCVA that was not worse than monthly treatment. The T&E dosing regimen with ranibizumab attained these results with fewer injections and visits, which has the potential to increase convenience and reduce cost to the health care system compared with monthly dosing. The study has been extended to 36 months, with participants from both study arms receiving ranibizumab with a T&E dosing regimen, to better understand the long-term outcomes of this regimen.

ARTICLE INFORMATION

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Author Affiliations: The John and Liz Tory Eye Centre, Sunnybrook Health Sciences Centre, Toronto, Ontario, Canada (Kertes); Department of Ophthalmology and Vision Sciences, University of Toronto, Toronto, Ontario, Canada (Kertes); Montreal Retina Institute, Montreal, Québec, Canada (Galic); Department of Ophthalmology & Visual Sciences, McGill University, Montreal, Québec, Canada (Galic); Alberta Retina Consultants, Edmonton, Alberta, Canada (Greve); Department of Ophthalmology & Visual Sciences, University of Alberta, Edmonton, Alberta, Canada (Greve); Calgary Retina Consultants, Calgary, Alberta, Canada (Williams); Department of Surgery, Section Ophthalmology, University of Calgary, Calgary, Alberta, Canada (Williams); Novartis Pharmaceuticals Canada Inc, Dorval, Québec, Canada (Baker, Lahaie); Ivey Eye Institute, London, Ontario, Canada (Sheidow); Western University, London, Ontario, Canada (Sheidow).

Author Contributions: Drs Kertes and Sheidow had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Kertes, Galic, Greve, Williams, Sheidow.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Galic.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Baker, Lahaie.
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Supervision: All authors.

Conflict of Interest Disclosures: Dr Kertes reported receiving grants, personal fees, and nonfinancial support from Novartis during the conduct of the study; personal fees and nonfinancial support from Bayer, grants from Allergan, and grants from Roche outside the submitted work; and holds stock in ArcticDx. Dr Greve reported receiving grants from Novartis during the conduct of the study and Shareholder Secure Diagnostic Imaging (tele ophthalmology company, with no direct conflict). Dr Williams reported receiving grants and personal fees from Novartis during the conduct of the study, grants and personal fees from Bayer and Allergan, and grants from Roche and Chengndu Kanghong Biotech outside the submitted work. Drs Baker and Lahaie are employees of Novartis Pharmaceuticals Canada Inc. Dr Sheidow reported serving as an advisory board member for Novartis, Bayer, and Allergan, for which he received honoraria. No other disclosures were reported.

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