

Treat and Extend Versus Treat and Observe Regimens in Wet Age-related Macular Degeneration Patients Treated with Ranibizumab: 3-year Surveillance Period

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Abstract

Objective: To compare the 3-year outcomes of two different dosing regimens used for wet age-related macular degeneration patients treated exclusively with ranibizumab.

Methods: A Treat and extend (TAE) dosing group (n=30) and a treat and observe (TAO) dosing group (n=30) were retrospectively recorded. Survival rates (SR) based on visual acuity (VA) outcomes were calculated and analyzed. The central retinal thickness measured with spectral domain (SD) optical coherence tomography (OCT) and number of intravitreal injections performed in both groups were also compared.

Results: At 36 months, Kaplan-Meier SRs were 90.9% for TAE and 89.7% for TAO (loss<0.3 units logMAR). VA improved in 42.4% and 24.1%, while 33.4% and 62.1% remained stable for TAE and TAO groups, respectively. No final VA differences were found between both therapeutic strategies (p>0.05, log-rank test). No differences were found in the final number of injections received: 20.31±6.6 in TAE group vs. 18.41 ± 7.1 in TAO group (p=0.19).

Conclusions: Both approaches showed similar number of injections and visual outcomes.

Keywords: Age-related macular degeneration; Antivascular endothelial growth factor; Choroidal neovascularisation; Intravitreal injection; Ranibizumab

Introduction

Since the initiation of anti-VEGF therapy for wet age-related macular degeneration (AMD), different treatment regimens have been developed. Multicentre studies such as the Minimally Classic/Occluded Treatment of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular AMD (MARINA) and Anti-VEGF Antibody for the Treatment of Predominantly Classic Choroidal Neovascularization (CNV) in AMD (ANCHOR) [1,2] have shown that monthly intravitreal injections of ranibizumab over a 2-year period not only maintained but improved best corrected visual acuity (BCVA), with a mean gain of 7.2 and 11.3 letters, respectively. Nevertheless, most centres have considerable difficulty maintaining this type of treatment schedule due to an ever-increasing patient load, stress on the patient and family members to attend monthly assessments, as well as the associated economic costs.

Alternate regimens of treatment have evolved in an attempt to provide comparable results in terms of BCVA, but with a fewer number of injections. One such treatment protocol is called pro re nata (PRN), or “treat and observe” (TAO). This is based on studies such as Prospective Optical Coherence Tomography (OCT) Imaging of Patients with Neovascular AMD Treated with Intraocular Ranibizumab (PrONTO) [3] and Safety and Efficacy of a Flexible Dosing Regimen of Ranibizumab in Neovascular Age-related Macular Degeneration: the SUSTAIN study (SUSTAIN) [4] where patients were given a loading dose of 3 monthly injections, followed by an as-needed decision to treat. Decision to treat is based on the presence of worsening BCVA, clinical evidence of disease activity on funduscopy, or optical coherence tomography (OCT) evidence of retinal thickening in the presence of intra-retinal (IRF) or sub-retinal fluid (SRF).

In an attempt to prolong the period between injections, Spaide [5,6]

suggested a different regimen called “treat and extend” (TAE), where the interval between injections is gradually increased, once stabilization of the wet AMD is achieved. The TAE is a dosing regimen designed to resolve all the IRF and SRF and keep the macula “dry” as long as possible with less injections and visits than monthly dosing.

The purpose of this study was to compare the TAE versus TAO regimens in wet AMD patients treated with ranibizumab with at least 3 years of follow-up.

Methods

Study design

Analytical, observational, retrospective, longitudinal study

Inclusion criteria

1. Patients >65 years of age
2. Choroidal neovascularization (CNV) due to AMD diagnosed by fluorescein angiography (FA) with at least 3 years of follow-up, with lesion size no more than 5400 µm in greatest linear diameter in the study eye.
3. Presence of IRE, SRF or central retinal thickness>250 microns on OCT.

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4. BCVA of 20/40 to 20/400 (Snellen equivalent determined with the use of a Snellen chart).

Exclusion criteria

1. Use of any other anti-angiogenic medication other than ranibizumab.
2. Previous treatment with verteporfin PDT, intravitreal steroids or laser.
3. Any history of uveitis, diabetic retinopathy or other retinal disease other than AMD.

Patient groups

TAE group (treating physician: M.H.B.): In this cohort, initial treatment consisted of a loading dose of three intravitreal injections of ranibizumab (0.5 mg) at monthly intervals. One month after the third injection, patients underwent a full ophthalmic examination including BCVA, biomicroscopy and OCT. Disease state was considered to be still active if BCVA was worse by 5 letters, or if there was any clinical or OCT evidence of disease activity (hemorrhage, SRF or IRF). If this was the case, patients were given another series of three, monthly injections of ranibizumab followed by another full clinical and OCT evaluation.

Disease state was deemed to be inactive if BCVA was stable or improved, and there was no clinical or OCT evidence of disease activity (hemorrhage, SRF or IRF). If this was the case, patients received an injection of ranibizumab, and were instructed to return in 6 weeks for repeat full clinical and OCT assessment. If disease state was deemed to be still inactive, the re-treatment interval was increased by 2 weeks. Full assessments were repeated after each 2-week interval extension, until a 3-month interval was established. Intervals were not extended beyond 3 months. If, at any time, disease activity developed between intervals, the patient was deemed to have a recurrence of active wet AMD, and returned to a loading dose of 3 monthly injections, and continued monthly injections until disease state was deemed to be inactive. If disease state became inactive again, the interval between injections was gradually increased, until the interval was 2 weeks less than the interval ascribed to the last recurrence. This interval was maintained for one year prior to trying to extend further. This pattern was repeated over the 3-year surveillance period.

TAO group (treating physicians: R.D., W.L.): In this cohort, initial treatment consisted of a loading dose of three intravitreal injections of ranibizumab (0.5 mg) at monthly intervals. One month after the third injection, patients underwent a full ophthalmic examination including BCVA, biomicroscopy and OCT. Disease state was deemed to be still active if BCVA was worse by 5 letters, or there was any clinical or OCT evidence of disease activity (haemorrhage, SRF or IRF). If this was the case, patients were given another injection of ranibizumab, and were instructed to return in one month for another full clinical and OCT evaluation. This was repeated on a monthly basis until disease state was deemed inactive.

Disease state was deemed to be inactive if BCVA was stable or improved, and there was no clinical or OCT evidence of disease activity (hemorrhage, SRF or IRF). If this was the case, ranibizumab injections were suspended, and patients were instructed to return on a monthly basis for a full ophthalmic examination including BCVA, biomicroscopy and OCT.

If during the patient's monthly examination there was either a 5 letter decrease in BCVA, or clinical or OCT evidence of hemorrhage,

IRF or SRF, the patient was deemed to have developed a recurrence of active wet AMD. Monthly injections of ranibizumab were re-established until disease state was deemed inactive. If disease state became inactive again, ranibizumab treatment was suspended again, and the patient was monitored with clinical and OCT examination on a monthly basis until there was a recurrence. This pattern was repeated over the 3-year surveillance period.

Study procedures

The study protocol was approved by the Institutional Research Ethics Board at the University Health Network, Toronto, Canada. We retrospectively analysed the consecutive charts and FA of three vitreoretinal practices at the Toronto Western Hospital in patients with naive CNV secondary to AMD who had been treated exclusively with ranibizumab from 01/October/2008 to 01/October/2012.

For both groups, we collected baseline data: BCVA, age, gender, slit lamp examination of the anterior segment, intraocular pressure (IOP), dilated fundus examination, FA and OCT.

The following data was also collected on a quarterly basis: BCVA, CRT measured by OCT and number of ranibizumab injections.

Snellen visual acuity was measured by a certified ophthalmic technician. The Snellen value was recalculated to determine the corresponding logarithm of the minimum angle of resolution (logMAR) value for statistical analysis using a formula that reflects the relationship between the two methods [7].

Central retinal thickness (CRT) was determined using spectral-domain Cirrus OCT (Carl Zeiss Meditec, USA). Scanning with the Cirrus OCT was performed with the 512 × 128 scan pattern where a 6 × 6 mm area on the retina was scanned with 128 horizontal lines, each consisting of 512 A-scans per line (total of 65,536 sampled points) within a scan time of 2.4 seconds. All scans were performed by an experienced ophthalmic technician. Only good-quality examinations with a signal strength of 6/10 or better were retained.

Statistical analysis

BCVA, gender, age, CRT and FA were compared at baseline between the two groups (t test for quantitative variables and chi-square test for categorical variables).

The main statistical study was a survival analysis, which represents time-to-event data. Subjects were followed over time and observed at the time point at which they experienced the event of interest. The hazard ratio (HR) was the probability that an individual experienced an event at a determined time while that individual was at risk for an event.

In this study, 3 independent survival analysis were performed: (i) the first event was considered to be a worsening of BCVA (defined as a difference of +0.3 logMAR units or more from baseline), (ii) the second event was stable BCVA (defined as ≤ 0.01 logMAR units compared with baseline) and (iii) the third event was an improvement of BCVA (defined as a difference of -0.3 logMAR units or more from baseline). Censoring occurred when either the patient attained each event or at the end of the study period (3 years).

HRs and a 95% CI were calculated for associations between groups and BCVA outcomes. Differences in the Kaplan-Meier survival plots were calculated by the log-rank test.

For all analyses, $P < 0.05$ was considered statistically significant. However, when multiple comparisons are performed, the Bonferroni correction was applied to make the level of significance $P < 0.002$.

Results

Baseline data

Of the 200 charts reviewed, 30 eyes (30 patients) in the TAE group and 30 eyes (30 patients) in the TAO group met the study inclusion criteria. Baseline demographic and ocular data for both study groups are summarized in Table 1. Patients in the TAE group had a mean age of 78.76 ± 7.14 years. Women comprised 65.15% of the cohort and the right eye was treated in 48.83% of cases. FA revealed a CNV distribution that was 18.18% predominately classic, 9.09% minimally classic and 72.73% occult. Locations of these lesions were 75% subfoveal and 25% extrafoveal. The mean baseline logMAR visual acuity was $0.73 (20/107) \pm 0.23$ and mean CRT by OCT was $318.27 \pm 95.22 \mu\text{m}$. Patients in the TAO group had a mean age of 79.72 ± 7.32 years. Women comprised 76.47% of the cohort and the right eye was treated in 44.11% of cases. FA revealed a CNV distribution that was 28.57% predominately classic, 7.14% minimally classic and 64.29% occult. Locations of these lesions were 75% subfoveal, 8.33% juxtafoveal and 6.67% extrafoveal. Mean baseline logMAR visual acuity was $0.85 (20/141) \pm 0.30$ and mean CRT by OCT was $308.95 \pm 87.43 \mu\text{m}$. All data was normally distributed. There was no significant difference found in baseline characteristics for those eyes treated with the TAE regimen versus the TAO regimen ($p > 0.05$).

Visual acuity and survival analysis outcomes

Both treatment groups experienced a statistically significant improvement in visual acuity from baseline to 3-year follow-up. BCVA for the TAE group improved from a logMAR value of 0.73 (20/107) at baseline to 0.46 (20/57) at 3 years ($p = 0.04$) while the TAO group demonstrated a logMAR improvement from 0.85 (20/141) to 0.58 (20/76) ($p = 0.0008$). However, there was no statistically significant difference in BCVA change between both groups ($p > 0.05$). Change in BCVA from baseline was also compared every 6 months up to 3 years (at 6, 12, 18, 24, 30 and 36 months) and no statistical differences were found between both groups ($p > 0.05$) at any time point (Table 2).

	TAE	TAO	p
Age (years)	78.76 ± 7.14	79.72 ± 7.32	0.52
Female (%)	65.15	76.47	0.28
Right eye (%)	48.83	44.11	0.68
Pseudophakia (%)	60.9	48.48	0.28
Glaucoma (%)	12.5	17.6	0.53
Type of CNVM (FA) (%)			
Classic	18.18	28.57	0.83
Min. Classic	9.09	7.14	
Occult	72.73	64.29	
Location of CNVM (FA) (%)			
Subfoveal	75	75	0.80
Juxtafoveal	0	8.33	
Extrafoveal	25	16.67	
IOP (mmHg)	15.58 ± 3.26	16.35 ± 3.25	0.36
BCVA LogMar (Snellen)	$0.73 (20/107) \pm 0.23$	$0.85 (20/141) \pm 0.30$	0.10
CRT (μm)	318.27 ± 95.22	308.95 ± 87.43	0.70
N	30	30	

$P < 0.05$ was considered statistically significant (in bold print)

Table 1: Demographic and Clinical Characteristics of Both Study Groups at Baseline.

TAE: Treat and Extend; TAO: Treat and Observe; FA: Fluorescein Angiogram; IOP: Intraocular Pressure; BCVA: Best Corrected Visual Acuity; LogMAR: Logarithm of the Minimum Angle of Resolution; CRT: Central Retinal Thickness; N: Number of subjects.

T (months)	BCVA LogMar (Snellen)			CRT (μm)		
	TAE	TAO	P	TAE	TAO	P
6	$0.54 (20/70) \pm 0.24$	$0.60 (20/80) \pm 0.27$	0.48	284.25	298.65	0.73
12	$0.50 (20/63) \pm 0.28$	$0.53 (20/67) \pm 0.34$	0.67	260.25	274.76	0.53
18	$0.48 (20/60) \pm 0.30$	$0.58 (20/76) \pm 0.37$	0.29	238.75	245.35	0.64
24	$0.45 (20/56) \pm 0.31$	$0.57 (20/74) \pm 0.34$	0.18	228.67	256.07	0.14
30	$0.47 (20/59) \pm 0.28$	$0.60 (20/79) \pm 0.34$	0.14	229.28	238	0.49
36	$0.46 (20/57) \pm 0.34$	$0.53 (20/67) \pm 0.33$	0.45	224.43	234.42	0.38

$P < 0.05$ was considered statistically significant (in bold print)

Table 2: BCVA (LogMar) and CRT (microns) in both groups.

T: Time; TAE: Treat and Extend; TAO: Treat and Observe; BCVA: Best Corrected Visual Acuity; LogMAR: Logarithm of the Minimum Angle of Resolution; CRT: Central Retinal Thickness.

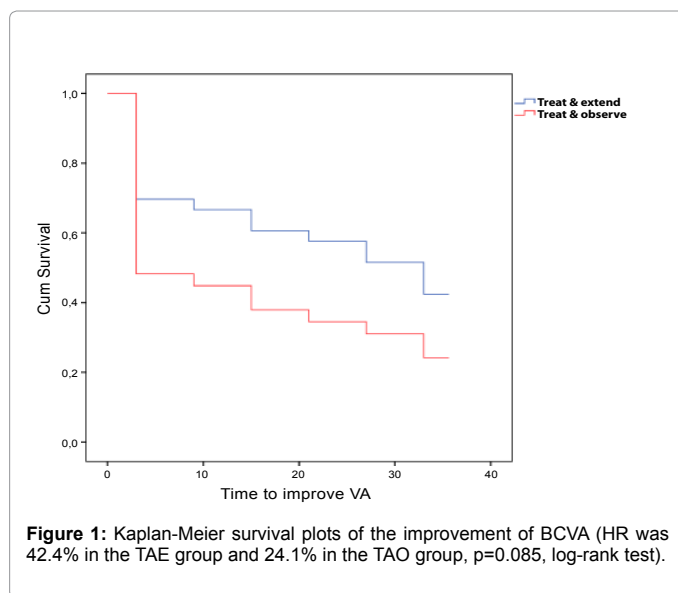


Figure 1: Kaplan-Meier survival plots of the improvement of BCVA (HR was 42.4% in the TAE group and 24.1% in the TAO group, $p = 0.085$, log-rank test).

We calculated the survival and HR for the worsening of BCVA (increase of more than 0.3 logMAR units) with respect to baseline. Survival rate was 90.9% in the TAE group and 89.7% in the TAO group ($p = 0.84$; log-rank test) at 3 years.

The survival rate calculated for BCVAs that remained stable (decrease of 0.01 logMAR units or more) from baseline was 75.8% for the TAE group and 86.2% for the TAO group ($p = 0.34$; log-rank test) at 3 years.

Improvement of BCVA (decrease of more than 0.3 logMAR units) from baseline survival rates were calculated as 42.4% in the TAE group and 24.1% in the TAO group ($p = 0.085$; log-rank test) at 3 years (Figure 1).

CRT measured with SD OCT

Both groups significantly improved CRT compared to baseline. Mean change in CRT was $-94 \mu\text{m}$ in the TAE group and $-74 \mu\text{m}$ in the TAO group from baseline to 3-year follow-up ($p < 0.001$). However, between groups, there was no statistically significant difference ($p > 0.05$) in CRT at the 6, 12, 18, 24, 30 or 3-year follow-up points (Table 2).

Number of injections

The total number of injections at 6 and 12 months was 5.44 ± 1.56 and 9.27 ± 2.3 in the TAE group vs. 4.16 ± 1.17 and 7.07 ± 1.9 in the TAO group ($p < 0.05$). However, at the end of the 3-year follow-up, no differences were found in the total number of injections received by

each group (20.31 ± 6.6 in the TAE group vs. 18.41 ± 7.1 in the TAO group, $p=0.19$).

Discussion

Since the discovery of ranibizumab for the treatment of wet AMD, marked improvements in BCVA of patients have been demonstrated in the breakthrough trials MARINA and ANCHOR following a fixed monthly dosing schedule for intravitreal injections over a two-year period. Despite these impressive results, the demand on patients, their families and clinicians to sustain monthly visits can cause a great deal of physical and emotional stress to those involved, not to mention the economical burden of resources used. Additional concern that patients unwilling to continue with injections may drop out of the practice has incited the development of more individualized treatment plans [8].

The TAE regimen described by Spaide aims to achieve and maintain a “dry” macula by gradually increasing the length of time between injections in the absence of macular fluid [5,9]. Growing use of the TAE method with ranibizumab for wet AMD has been described in recent studies with favorable improvements in visual acuity while reducing the number of office visits and injections [10-12].

Alternatively, the TAO regimen supports injections only if signs of macular exudation are present at monthly visits (i.e. treat as-needed) and has been studied in several prospective trials [3,4,13,14]. Most notably, the PrONTO trial demonstrated improved visual acuity comparable to MARINA and ANCHOR while the larger SUSTAIN study showed slightly lesser gains.

Increasing popularity for the TAE and TAO approaches can be attributed to their success at improving visual acuity while reducing the number of injections, thereby decreasing the associated burden on patients and clinicians. The 2012 American Society of Retinal Specialists Preferences and Trends survey revealed the majority of Retinal Specialists members have turned to non-monthly regimens, with 66.7% using TAE and 23.7% TAO [15].

To our knowledge of currently available data, this is the first study to compare retrospective results of treatment with ranibizumab for 3 years in two widely accepted treatment protocols for wet AMD: TAE versus TAO. Although the study is limited by its retrospective nature and small number of patients, the lengthy follow-up period allowed us to obtain enough data to make meaningful interpretations, especially considering this study was conducted in normally run vitreoretinal practices, reflecting a “real-life” clinical setting.

Our study groups were comparable in that no significant differences in baseline demographic and clinical (i.e. type of lesion, location of lesion, BCVA CRT) characteristics were found. The findings from our study confirm that intravitreal ranibizumab not only preserved but also improved BCVA after 3 years of follow-up. Only 9.1% of TAE and 10.3% of TAO patients lost 3 or more lines (15 letters) of VA from baseline ($p=0.84$; LogRank test). VA stability was achieved in 75.8% of TAE and 86.2% of TAO patients with respect to baseline ($P=0.32$; LogRank test). Probably more important to the patient is the fact that 42.4% of patients in the TAE group and 24.1% in the TAO group had VA improvement (<0.3 LogMAR units) from baseline ($P=0.085$; LogRank test). Similar outcomes were reported by Gupta et al. [12], from a retrospective study comparing 92 eyes using a TAE protocol exclusively with 96% of patients losing fewer than 3 lines and 32% gaining 3 lines or more.

Katz et al. [16] who compared monthly ranibizumab injections

versus TAO, published less than 5% of patients losing 3 or more lines and 79% preserving or gaining visual acuity in the TAO group after a treatment period of 1 year.

Oubraham et al. [17] who directly compared TAE ($N=38$) and TAO ($N=52$) regimens for 1 year, reported greater VA improvement in the TAE group than the TAO group ($+10.8 \pm 8.8$ versus $+2.3 \pm 17.4$ letters, $p=0.036$). In contrast, our results didn't find VA differences ($p>0.05$) between groups comparing data every 6 months up to 3 years (at 6, 12, 18, 24, 30 and 36 months).

In our study, only during the first 12 months did the TAE group receive more injections (9.27 ± 2.3 and 7.07 ± 1.9 , $p<0.05$) which is notably higher than the totals for either group in Oubraham's study [17] (7.8 ± 1.3 injections in TAE versus 5.2 ± 1.9 injections in TAO, $p<0.001$). This difference may be due to the treatment protocol used for TAE, which required another series of three, monthly injections of ranibizumab if disease state was considered to be still active after the initial loading dose of 3 monthly injections. We observed no differences in the total number of injections received by each group (20.31 ± 6.6 in TAE vs. 18.41 ± 7.1 in TAO) at the end of the 3-year follow-up.

The trend toward better results in the TAE group is consistent but not statistically significant in the comparisons we made between the groups. However, it is important to note the improvement in BCVA in the TAE group after 3-year follow-up was almost double than the TAO group (42.4% vs. 24.1%, $p=0.08$).

In conclusion, our study shows both regimens result in similarly good visual outcomes and number of injections over a 3 year treatment period. With a growing number of clinicians choosing to employ modified dosing regimens such as TAE and TAO, further investigation in the form of a prospective head-to-head trial is needed to recommend one over the other.

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