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Treat-and-Extend Regimen for Macular Edema Secondary to Central Retinal Vein Occlusion: 12-Month Results

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Purpose: To determine treatment outcomes after 12 months of bevacizumab and ranibizumab therapy using a treat-and-extend regimen in patients with macular edema resulting from central retinal vein occlusion (CRVO).

Design: Retrospective, interventional, consecutive case series.

Methods: Sixty eyes of 58 patients diagnosed with CRVO and associated macular edema between May 2010 and June 2014 were included. Eyes were treated with bevacizumab and/or ranibizumab for a minimum of 1 year, using a treat-and-extend regimen.

Main Outcome Measures: Outcome measures were change from baseline visual acuity (VA), proportion of eyes gaining/losing $\geq$3 VA lines, change from baseline central retinal thickness (CRT), mean number of injections administered, and the longest treatment-free interval attained between injections.

Results: At baseline, mean logMAR VA was 1.18$\pm$0.71 (Snellen equivalent: 20/302), which improved to 0.85$\pm$0.71 (Snellen equivalent: 20/142) after 12 months of therapy ($P = 0.018$). During this period, 44.9% of eyes had gained $\geq$15 letters, while 10.2% had lost $\geq$15 letters. The mean CRT improved from 564.7$\pm$219.3 μm at baseline to 302.8$\pm$115.8 μm at 12-month follow-up ($P < 0.001$). Patients received, on average, 8.1 injections during the first year of treatment, and the mean longest duration of successful extension between injections during year 1 was 9.3$\pm$4.4 weeks. Multivariable analyses revealed that change in CRT over the first 3 months of therapy was significantly associated with the ability to extend injection intervals to at least 8 weeks' duration ($P < 0.05$).

Conclusions: The treat-and-extend regimen is effective in achieving visual and anatomic improvements in patients with macular edema secondary to CRVO through the first year of therapy. Change in CRT during the first 3 months of treatment may help predict which patients will respond more favorably to an extension phase at or beyond 8 weeks. *Ophthalmology Retina 2016;■:1–6 © 2016 by the American Academy of Ophthalmology*

Retinal vein occlusion (RVO) is the second most common retinal vascular disease after diabetic retinopathy, with a 15-year cumulative incidence of 2.3% reported by the Beaver Dam Eye Study.[1] The advent of intravitreal pharmacotherapy agents, primarily driven by the class of selective vascular endothelial growth factor (VEGF) inhibitors, has revolutionized the management of macular edema secondary to RVO.

Validated through the CRUISE phase III trial, ranibizumab (Lucentis; Genentech, South San Francisco, CA) became the first VEGF inhibitor approved by the US Food & Drug Administration for the treatment of macular edema resulting from central retinal vein occlusion (CRVO) in 2010.[2,3] Shortly thereafter, in 2012, aflibercept (Eylea; Regeneron, Tarrytown, NY) also gained Food & Drug Administration approval for this indication with the GALILEO and COPERNICUS phase III studies.[4–7] Although anti-VEGF therapy is a very effective option in the management of CRVO, the protocols from these pivotal studies dictated that monthly injections be administered for the first 6 months of the study period, followed by monthly clinic visits for the next 6 months with injections administered on a *pro re nata* (PRN) basis. In clinical practice, however, a number of flexible dosing strategies are being increasingly utilized to optimize the cost-effectiveness and risk-benefit ratio of intravitreal anti-VEGF therapy.

Perhaps the most popular of these alternatives is the treat-and-extend regimen, which entails fixed treatment intervals until the edema is under control, as determined by complete or near-complete resolution of fluid on spectral-domain optical coherence tomography (SD-OCT) imaging, followed by progressively increasing both encounter and injection intervals together as permitted. Recent studies have demonstrated excellent short-term and long-term visual outcomes using a treat-and-extend algorithm with bevacizumab or ranibizumab comparable to those of monthly or PRN treatments in the treatment of neovascular age-related macular degeneration (AMD).[8–15] Additionally, this approach offers the potential socioeconomic benefit of limiting the overall number of injections, office visits, and ancillary tests for patients while aiming to optimize visual outcomes.[16]

According to the American Society of Retina Specialists 2015 Membership Survey: Preferences and Trends, the

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treat-and-extend regimen is also the most commonly employed approach to managing RVO-related macular edema in the United States, with approximately 56.3% of retina specialists favoring this style of treatment vs. 40.2% opting for PRN retreatment with monthly clinic visits.[17] However, despite the majority of retina specialists utilizing a treat-and-extend strategy, there is an appreciable lack of published data supporting its efficacy in this setting.[18] The purpose of our study, therefore, was to determine functional and anatomic outcomes in patients with CRVO after 12 months of a treat-and-extend regimen using bevacizumab and ranibizumab.

Methods

This study was a retrospective, consecutive case series that received approval from the institutional review board at Wills Eye Hospital. Electronic billing records of all patients with CRVO (International Classification of Diseases 9 code: 362.35) seen between May 2010 and June 2014 at the Retina Service of Wills Eye Hospital and the outpatient offices of Mid Atlantic Retina were reviewed. Research adhered to the tenets of the Declaration of Helsinki and was conducted in accordance with regulations set forth by the Health Insurance Portability and Accountability Act.

Eligible patients were 18 years of age or older with treatment-naïve macular edema following CRVO diagnosis. Additional inclusion criteria consisted of a minimum of 12 months follow-up after using a treat-and-extend regimen, and therapy with intravitreal bevacizumab (1.25 mg) and/or ranibizumab (0.5 mg) injections. Patients were excluded if they had any 1 of the following: (1) macular edema in the study eye attributable to causes other than CRVO, such as diabetic retinopathy, neovascular AMD, or uveitis; (2) anti-VEGF treatment regimen other than treat-and-extend; (3) intravitreal injections other than bevacizumab or ranibizumab (patients treated with aflibercept were excluded due to limited longer-term follow-up and the lack of head-to-head studies comparing the efficacy and durability of aflibercept in CRVO with those of ranibizumab and bevacizumab); (4) any prior or adjunct treatments for CRVO, such as focal/grid laser photocoagulation, panretinal photocoagulation (PRP), or intraocular/periocular corticosteroid injections (eg, intravitreal triamcinolone or dexamethasone implant); and (5) vitrectomy surgery in the study eye.

Treat-and-Extend Regimen

All patients were evaluated at the initial diagnosis with a dilated funduscopic examination in conjunction with SDOCT imaging (Heidelberg Engineering, Heidelberg, Germany). Patients were then treated with monthly intravitreal injections of either bevacizumab (1.25 mg/0.05 mL; Avastin; Genentech, San Francisco, CA) or ranibizumab (0.5 mg/0.05 mL; Lucentis; Genentech) until no signs of fluid (intraretinal or subretinal) were detected on slit-lamp biomicroscopy and SDOCT. Patient follow-ups and treatments were then extended by intervals of 2 weeks as long as no sign of fluid was present. However, if any signs of recurrent exudation (intraretinal/subretinal fluid) were detected, treatment intervals would be subsequently shortened by 1- to 2-week intervals at the discretion of the investigator. Anti-VEGF treatment was administered at every visit, regardless of disease activity.

Statistical Analysis

Pertinent patient demographic, examination, and treatment data were extracted from clinical charts and tabulated for analysis. For functional outcomes, Snellen visual acuity (VA) measurements were collected from individuals using their most up-to-date distance correction or best pinhole correction. Patients' VA scores were then converted into logarithm of the minimum angle of resolution (logMAR) score for subsequent statistical analysis. Visual acuity measurements were additionally converted into approximate Early Treatment Diabetic Retinopathy Study (approxETDRS) scores to determine the mean gain in letters during the first 12 months of treatment, as well as the proportion of eyes gaining/losing ≥15 letters in VA.[19]

For anatomic outcomes, SDOCT scans were reviewed at the time of diagnosis and after approximately 3, 6, and 12 months of therapy to document the presence or absence of intraretinal/subretinal fluid and record the automated central retinal thickness (CRT) measurements. The mean maximum period of successful treatment extension and the mean number of total injections received after 12 months were also calculated. Ability to extend a subject's treatment interval to at least 8 weeks was defined as successful extension.

Categorical variables were reported as proportions. Data for continuous variables were recorded as mean ± standard deviation (SD). Pearson chi-square tests were used to compare dichotomous baseline characteristics between successfully extended eyes and those unable to be extended. Two-tailed *t* tests were used to compare continuous baseline characteristics between these groups. Paired 2-tailed *t* test analysis with significance set at $P < 0.05$ was used to compare mean outcome data at baseline with months 3, 6, and 12 of follow-up. A multivariable logistic regression model was created to further explore factors associated with successful extension. Analyses were carried out using GraphPad software (GraphPad, La Jolla, CA) and Stata Statistical Software: Release 14 (StataCorp LP, College Station, TX).

Table 1. Baseline Patient Demographics

Baseline Characteristics	TER (N = 58 Patients, 60 Eyes)
Age (yrs)	
Mean ± SD	72.8±14.3
Median (min, max)	74 (21, 94)
Gender (N = 58)	
Male	24 (41.4%)
Female	34 (58.6%)
Hypertension (N = 58)	
Yes	42 (72.4%)
No	16 (27.6%)
Diabetes mellitus (N = 58)	
Yes	7 (12.1%)
No	51 (87.9%)
Eye (N = 60)	
Right	33 (55.0%)
Left	27 (45.0%)
Lens status (N = 60)	
Phakic	44 (73.3%)
Pseudophakic	16 (26.7%)
logMAR VA	
Mean ± SD	1.18±0.71
Median	1.0
CRT (μm)	
Mean ± SD	564.7±219.3
Median	514.9

CRT = central retinal thickness; Max = maximum; Min = minimum; SD = standard deviation; TER = treat-and-extend regimen; VA = visual acuity.