Antivascular Endothelial Growth Factor Dosing Frequency and Visual Outcomes in Macular Edema Following Central Retinal Vein Occlusion

Yasha S. Modi, MD1, Lediana Goduni, MD1, Hadi Moini, PhD2, Andrea Gibson, PhD2, Nick Boucher, BS3, Genevieve Lucas, BComm3, and Dilsher S. Dhoot, MD4

Abstract

**Purpose:** We evaluated the relationship between dosing frequency of intravitreal antivascular endothelial growth factor (anti-VEGF) agents and visual acuity (VA) outcomes over 2 years in eyes with macular edema (ME) secondary to central retinal vein occlusion (CRVO) in the US routine clinical practice setting. **Methods:** This retrospective analysis assessed electronic medical records of eyes with ME secondary to CRVO that received their first anti-VEGF injection January 1, 2012, to May 31, 2016, and were followed for 1 year or more in the US-based Vestrum Health Treatment and Outcomes database. Eyes were divided into 2 injection frequency subcohorts (≤6 or ≥7 injections/year). **Results:** Overall, 851 (34.6%) of 2458 eyes with ME secondary to CRVO received 6 or fewer injections, and 1607 (65.4%) received 7 or more injections through 1 year. The mean number of injections in patients receiving 6 or fewer injections and 7 or more injections was 4.7 and 8.8, respectively, and baseline mean VA was 35 and 37 letters, respectively. At year 1, mean letter gain from baseline was less in eyes receiving 6 or fewer injections vs in those receiving 7 or more injections (7.0 vs 12.2, \(P < .001\)). Mean VA at year 2 was 50 letters in eyes receiving 6 or fewer injections (n = 50) and 55 letters in eyes receiving 7 or more injections (n = 157). **Conclusions:** In routine clinical practice, more frequent dosing with anti-VEGF agents was associated with greater visual benefits in eyes with ME secondary to CRVO.

Keywords

antivascular endothelial growth factor, bevacizumab, central retinal vein occlusion, intravitreal aflibercept, ranibizumab, real-world outcomes, treatment frequency, visual acuity

Introduction

The treatment of macular edema (ME) secondary to central retinal vein occlusion (CRVO) was revolutionized by the advent of antivascular endothelial growth factor (anti-VEGF) therapy. The standard of care for treatment outcomes was established in the phase 3 pivotal trials of intravitreal ranibizumab (CRUISE)\(^1\) and aflibercept (COPERNICUS and GALILEO).\(^2,3\) Patients were initially treated with monthly anti-VEGF injections for 6 months followed by as-needed dosing with monthly monitoring for an additional 6 months. These landmark studies demonstrated significant visual gains at 6 months (14.9, 17.3, and 18.0 Early Treatment Diabetic Retinopathy Study [ETDRS] letters) and 12 months (13.9, 16.2, and 16.9 letters), respectively, in CRUISE, COPERNICUS, and GALILEO.\(^1-3\)

Treatment paradigms established in the pivotal phase 3 trials came at a cost of frequent monitoring and treatment burden. In these trials, after the initial monthly dosing through month 6, patients were monitored monthly and received 3.3, 2.7, and 2.5 anti-VEGF injections from month 6 to month 12 in CRUISE, COPERNICUS, and GALILEO, respectively.\(^4-6\) Starting from month 12, patients were monitored less than monthly (every 2 or 3 months) and received 3.5 and 3.3 injections over 12 months in HORIZON and COPERNICUS, respectively.\(^4,7\) Less frequent monitoring and injections, however, came at the expense of visual gains, with patients losing a mean of 4.1 and 3.2 letters from the gains at 12 months, respectively.\(^4,7\) These findings suggest that less stringent follow-up intervals with

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**1** New York University Langone Health, New York, NY, USA

**2** Regeneron Pharmaceuticals Inc, Tarrytown, NY, USA

**3** Vestrum Health, Naperville, IL, USA

**4** California Retina Consultants/Retina Consultants of America, Santa Barbara, CA, USA

**Corresponding Author:**

Dilsher S. Dhoot, MD, California Retina Consultants/Retina Consultants of America, 525 E Micheltorena St, Santa Barbara, CA, 93103, USA.

Email: ddhoot@yahoo.com
significantly fewer injections were associated with a decline in visual acuity (VA). Collectively, these level 1 data demonstrated the importance of regular long-term follow-up and the need for frequent retreatment to maintain vision in patients with ME secondary to CRVO.

Although these clinical studies demonstrated the success of monthly and as-needed treatment with monthly follow-up, there remains a paucity of “real-world” outcome data in patients with ME secondary to CRVO in the United States.\textsuperscript{8,9} Most currently available real-world data from routine clinical practice in the United States and Europe indicate that, compared with clinical trials, injection frequency is low and outcomes are suboptimal in ME secondary to CRVO following anti-VEGF therapy.\textsuperscript{10-14} However, there is no study specifically evaluating the relationship between injection frequency and VA outcomes. To address some of these shortcomings, the authors used a large database of real-world data from patients with ME secondary to CRVO in the United States to evaluate the relationships between vision, anatomic outcomes, and treatment frequency.

Methods

Data Source

The authors used deidentified electronic medical records of patients with ME secondary to CRVO in the Vestrum Health Treatment and Outcomes database (Vestrum Health, Naperville, Illinois, USA), which were obtained from 251 retina specialists at 54 private clinics in the United States. The records included information about demographics, procedures, diagnoses, medications, and treatment outcomes including visual and anatomic measurements. For patients who received laser treatments, “laser” referred to either panretinal photocoagulation or focal/grid laser photocoagulation. Data were extracted from the database using structured query language queries. Institutional review board approval was not sought because it is not generally required for studies such as this in which data collection is in the form of historic, deidentified patient electronic health records, which does not affect or influence patient treatment.

Study Population

The study population consisted of patients who were diagnosed with ME secondary to CRVO and were administered their first (index) anti-VEGF injection (bevacizumab, ranibizumab, or aflibercept) between January 1, 2012, and May 31, 2016. Eyes were included in the study if they had a VA reading on the index date, at month 12, and at least once during each quarter of the study period. Eyes were excluded if there was a break in treatment duration for more than 11 months at any point in the 24 months following the index date and, as such, were considered to have discontinued anti-VEGF therapy. Eyes were also excluded if sex information was not on record. To ensure comparable results, all Snellen VA measurements for an individual patient were required to use the same methodology; these were calculated using the following formula: approximate ETDRS letters = 85 + 50 × log(Snellens fraction).\textsuperscript{15}

Observation Period

All patients were observed for a period of 12 to 24 months from baseline. The observation period began on January 1, 2012, and ended on May 31, 2018, inclusive of all eyes.

Cohorts

For data analysis, eyes were divided into 2 cohorts: year 1 cohort (eyes that were treated for 1 year) and year 2 cohort (eyes that were treated for 2 years). Each of these cohorts was further divided into 2 subcohorts based on whether 6 or fewer injections (≤6-injection subcohort) or 7 or more injections (≥7-injection subcohort) were administered per year. The 2 subcohorts (≤6 or ≥7 injections) were identified based on the initial analysis of injection frequency in the total patient population included in the first year of treatment. That analysis showed a normal distribution with a mean of 7.4 injections and a median of 7 injections. Hence, outcomes were evaluated in 2 subcohorts that received either less-than-average or average-or-greater number of injections. Injection frequencies refer to exclusively anti-VEGF injections.

Statistical Methods

Descriptive statistics were calculated for the year 1 and year 2 cohorts to identify changes in injection frequency and ETDRS letters over time. Paired $t$ tests were used to determine whether the changes in injection frequency and ETDRS letters over time were significant. Independent $t$ tests assuming unequal variance were used to determine whether the differences in injection frequency and ETDRS letters change between cohorts were significant. $Z$ score tests were used to determine whether the difference in the proportion of patients who received steroid or laser treatment between the 2 subcohorts of injection frequency in year 1 was significant. Calculations were performed using Microsoft Excel, and $P$ less than .05 was considered statistically significant.

Results

Patients

A total of 37,099 patients with ME secondary to CRVO were assessed for eligibility (Figure 1). Of these, 7,857 received their first anti-VEGF injection between January 1, 2012, and May 31, 2016, and had a VA reading the same day as the index injection. After excluding patients without all required quarterly VA readings, sex identification, and those with treatment breaks longer than 11 months during follow-up, 2,458 and 1,239 patients were included in the year 1 and year 2 cohorts, respectively. In total, 50% (n = 1,239) of patients in the year 1 cohort qualified for inclusion in the year 2 cohort.
Overall, 7% (n = 179) of patients in the year 1 cohort did not have any visits in year 2 and therefore were excluded from the year 2 cohort.

Patients in the year 1 cohort received a mean of 7.4 (median = 7.0) injections in year 1. Patients in this cohort were divided into 2 subcohorts: those who received fewer than average (≤6) injections and those who received average or greater (≥7) injections. Of the 2458 eyes in the year 1 cohort, 851 (34.6%) received 6 or fewer injections and 1607 (65.4%) received 7 or more injections through 1 year. Baseline characteristics were balanced between the ≤6-injection and ≥7-injection subcohorts (Table 1). However, significantly greater proportions of eyes in the ≤6-injection subcohort received steroid and laser treatments concomitant to anti-VEGF treatment in year 1: 9.0% (77 of 851) of eyes in the ≤6-injection subcohort received a mean of 1.7 (range, 0-4) steroid injections compared with 5.0% (80 of 1607) of eyes in the ≥7-injection subcohort that received a mean of 1.4 (range, 0-5) steroid injections (P < .001). During year 1, 14.0% (119 of 851) of eyes in the ≤6-injection subcohort also received laser treatment, with a mean of 1.5 (range, 0-5) laser treatments; the corresponding values in the ≥7-injection subcohort were 7.0% (112 of 1607) and 1.2 (range, 0-4) (P < .0001).

### Year 1 Outcomes

For eyes that were treated for 1 year or more, those in the ≤6-injection subcohort received a mean of 4.7 (range, 2-6) injections in the first year, and eyes in the ≥7-injection subcohort received a mean of 8.8 (range, 7-14) injections in the first year. In the ≤6-injection subcohort, mean VA increased from 35 letters at baseline to 42 letters after 1 year of treatment (Figure 2). In the ≥7-injection subcohort, mean VA increased from 37 letters at baseline to 49 letters after 1 year of treatment. Mean VA gain from baseline was significantly less in the ≤6-injection subcohort compared with the ≥7-injection subcohort at year 1 (+7.0 vs +12.2 letters, respectively; P < .001).

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**Table 1.** Demographic and Baseline Characteristics of Patients with ME Secondary to Central Retinal Vein Occlusion in the Year 1 Cohort by Injection Frequency During Year 1.a

| Injection subcohort | Total (n = 2458) | ≤6 injections (n = 851) | ≥7 injections (n = 1607) |
|---------------------|-----------------|------------------------|------------------------|
| Age, mean, y        | 73              | 74                     | 72                     |
| Female, n (%)       | 1276 (52)       | 450 (53)               | 826 (51)               |
| VA, letters         |                 |                        |                        |
| Mean                | 51              | 50                     | 52                     |
| Median              | 65              | 64                     | 65                     |
| VA subgroups, n (%) |                 |                        |                        |
| ≥20/40              | 252 (10)        | 108 (13)               | 144 (9)                |
| <20/40-20/100       | 978 (40)        | 315 (37)               | 663 (41)               |
| <20/100-20/200      | 449 (18)        | 151 (18)               | 298 (19)               |
| <20/200             | 779 (32)        | 277 (33)               | 502 (31)               |

Abbreviations: ME, macular edema; VA, visual acuity.

aVA is reported in approximate Early Treatment in Diabetic Retinopathy Study letters.
To better assess the relationship between the frequency of treatment and VA outcomes, eyes were stratified into 4 subcohorts based on injection frequency: 1 to 3, 4 to 6, 7 to 9, and 10 or more injections over year 1. Across the 4 subcohorts, mean VA ranged from 33 to 38 letters at baseline and improved to 37 to 50 letters at year 1 (Figure 3). Overall, letters gained appeared to increase with injection frequency. In the subset of eyes in the 4 subcohorts with both VA and central retinal thickness (CRT) measurements at baseline and all quarters of year 1, there appeared to be a slight trend toward improved vision and CRT with increasing injection frequency (Supplemental Figure 1).

| Injection frequency | Mean number of injections (range) by quarter |
|---------------------|---------------------------------------------|
| ≤6 injections per year (n = 851) | 2.3 (1–4) | 1.0 (0–3) | 0.8 (0–3) | 0.6 (0–3) |
| ≥7 injections per year (n = 1607) | 2.9 (1–7) | 2.1 (0–6) | 1.9 (0–6) | 1.9 (0–7) |

**Figure 2.** Mean Early Treatment in Diabetic Retinopathy Study (ETDRS) letters through year 1 in eyes with ME secondary to central retinal vein occlusion in the ≤6-injection and ≥7-injection subcohorts. *P* < .001 for the change in mean ETDRS gain from baseline in the ≤6-injection vs ≥7-injection subcohort. BSL indicates baseline; ME, macular edema; Q, quarter.

| Cohort | No. of eyes | BSL | Q1 | Q2 | Q3 | Q4 | ETDRS Δ from BSL |
|--------|-------------|-----|----|----|----|----|-----------------|
| 1–3    | 167         | 33  | 42 | 38 | 40 | 37 | 4               |
| 4–6    | 684         | 35  | 47 | 46 | 45 | 43 | 8               |
| 7–9    | 1117        | 36  | 51 | 50 | 50 | 48 | 12              |
| ≥10    | 490         | 38  | 50 | 51 | 50 | 50 | 12              |

**Figure 3.** Mean Early Treatment in Diabetic Retinopathy Study (ETDRS) letters change through year 1 by injection frequency in eyes with ME secondary to central retinal vein occlusion. BSL indicates baseline; ME, macular edema; Q, quarter.

**Year 2 Outcomes**

Eyes that received 6 or fewer injections in year 1 and continued to receive 6 or fewer injections in year 2 (n = 187) received a mean of 5.1 and 4.0 injections in years 1 and 2, respectively. These eyes started year 2 with a mean VA of 51 letters and ended year 2 with a mean of 46 letters, losing an average of 5 letters (Figure 4). Eyes that received 6 or fewer injections in year 1 but 7 or more injections in year 2 (n = 35) were administered a mean of 5.4 and 7.6 injections in years 1 and 2, respectively. These eyes started year 2 with 54 letters and ended year 2 with a mean of 52 letters, losing an average of 2 letters.
Eyes that received 7 or more injections in year 1 but 6 or fewer injections in year 2 (n = 514) received a mean of 7.4 and 4.8 injections in years 1 and 2, respectively. These eyes started year 2 with a mean of 51 letters and ended year 2 with a mean of 48 letters, losing an average of 3 letters (see Figure 4). Eyes that received 7 or more injections in year 1 and continued to receive 7 or more injections in year 2 received a mean of 9.7 and 8.5 injections in years 1 and 2, respectively. These eyes started and ended year 2 with a mean of 56 letters. The change in mean VA between the start and end of year 2 in the subcohort of eyes that received 7 or more injections in year 1 and 6 or fewer injections in year 2 differed significantly from the subcohort of eyes that received 7 or more injections in both years 1 and 2 (–3 vs 0 letters, \( P < .004 \)).

In the subset of eyes that were in the \( \leq 6 \)-injection or \( \geq 7 \)-injection subcohorts for both years 1 and 2 and had both mean VA and mean foveal thickness measurements at baseline and all 8 quarters through year 2, there was a trend toward increased letters and decreased foveal thickness with increased injection frequency (Figure 5).

**Figure 4.** Mean Early Treatment in Diabetic Retinopathy Study (ETDRS) letters at the start and end of year 2 by injection frequency in years 1 and 2 in eyes with ME secondary to central retinal vein occlusion. \*\( P < .004 \) compared with the change in the \( \geq 7/\geq 7 \)-injection subcohort. ME indicates macular edema.

**Figure 5.** Mean Early Treatment in Diabetic Retinopathy Study (ETDRS) letters and mean foveal thickness through year 2 by injection frequency over years 1 and 2 in eyes with ME secondary to central retinal vein occlusion in the \( \leq 6 \)-injection and \( \geq 7 \)-injection subcohorts. Analysis included eyes with ETDRS and foveal thickness measurements at baseline and all 8 quarters through year 2. BSL indicates baseline; ME, macular edema; Q, quarter.

Eyes that received 7 or more injections in year 1 but 6 or fewer injections in year 2 (n = 514) received a mean of 7.4 and 4.8 injections in years 1 and 2, respectively. These eyes started year 2 with a mean of 51 letters and ended year 2 with a mean of 48 letters, losing an average of 3 letters (see Figure 4). Eyes that received 7 or more injections in year 1 and continued to receive 7 or more injections in year 2 received a mean of 9.7 and 8.5 injections in years 1 and 2, respectively. These eyes started and ended year 2 with a mean of 56 letters. The change in mean VA between the start and end of year 2 in the subcohort of eyes that received 7 or more injections in year 1 and 6 or fewer injections in year 2 differed significantly from the subcohort of eyes that received 7 or more injections in both years 1 and 2 (–3 vs 0 letters, \( P = .0004 \)).

In the subset of eyes that were in the \( \leq 6 \)-injection or \( \geq 7 \)-injection subcohorts for both years 1 and 2 and had both mean VA and mean foveal thickness measurements at baseline and all 8 quarters through year 2, there was a trend toward increased letters and decreased foveal thickness with increased injection frequency (Figure 5).

**Annual Trend in Treatment Frequency During Year 1**

The mean number of anti-VEGF injections received during year 1 was constant over calendar years 2012 to 2016 in both the \( \leq 6 \)-injection subcohort (4.5-4.8 injections) and the \( \geq 7 \)-injection subcohort (8.3-8.9 injections; Supplemental Figure 2). However, numerically greater proportions of eyes received 7 or more injections during year 1 over 2013 to 2016 (60%-70%) than in 2012 (51%; see Supplemental Figure 2).
Conclusions

This outcome-based study of patients with ME secondary to CRVO treated with anti-VEGF agents demonstrated a strong association between injection frequency and long-term visual gains over 2 years in routine clinical practice in the United States. Patients receiving 7 or more injections per year demonstrated greater VA gains than those receiving 6 or fewer injections, and both groups had similar baseline VAs. Correspondingly, the mean reduction in CRT was consistent with the VA gains over 2 years. When further stratified by injection frequency (1-3, 4-6, or 7-9 injections) in year 1, visual gains further increased with increasing frequency of injections. This suggests that undertreatment, on average, is associated with suboptimal visual gains. Additionally, a ceiling effect was observed in which 7 or more injections (7-9 and 10+ injections) did not demonstrate an incremental VA or anatomic benefit for patients. Thus, through year 1, 7 or more injections in this cohort of patients appeared to approximate the optimal anti-VEGF treatment frequency.

Our findings in patients receiving 6 or fewer injections per year (mean of 4.7 injections and 7.0-letter gain at year 1) are consistent with those reported for a US population of patients with CRVO by Wai et al\textsuperscript{11} (mean of 6.0 injections and 9.1-letter gain at year 1) as well as the Portuguese populations of patients with CRVO by Farinha et al\textsuperscript{14} (mean of 4.1 injections and 6.7-letter gain at year 1) and Vaz-Pereira et al\textsuperscript{13} (median of 4 injections and approximately 6-letter gain at year 1). However, patients who received 7 or more injections in the present study (mean of 8.8 injections and 12.2-letter gain at year 1) had better visual gains than patients in those real-world studies as well as largely similar, albeit still inferior, gains as patients in CRUISE, COPERNICUS, and GALILEO.\textsuperscript{1-3,5,6} It is important to note that clinical trials typically mandate visit schedules and strict inclusion and exclusion criteria. Real-world studies, however, include patients who might otherwise have been excluded from clinical trials. This may account for some of the differences observed in visual outcomes. However, injection frequency remains one of the key variables that can be modified by the treating clinicians to close the gap between real-world outcomes and clinical trial outcomes.

Caution must be exercised when interpreting the results of the present study because there are some intrinsic limitations in the study analysis. These data evaluated only injection frequency and not visit frequency. Thus, it is difficult to decipher whether increased injection frequency alone accounts for improved outcomes or if injection frequency is a surrogate for closer follow-up. The COPERNICUS study showed that VA gains after monthly injections for 6 months were maintained after moving to an as-needed treatment strategy (fewer injections than the first 6 months) but with monthly follow-up.\textsuperscript{4} However, when the evaluation window was extended beyond monthly evaluations in year 2, there was a decline in visual gain.\textsuperscript{4} This argues that frequent evaluation may be as important as treatment frequency, and delays in treatment of ME may account for diminished visual gains.

Rigorous treat-and-extend (T&E) protocols have been used to balance visit burden with treatment frequency,\textsuperscript{16-21} reporting a mean gain of 14.8 letters with a mean of 8.3 aflibercept injections over 1 year, and a mean gain of 12.8 letters with a mean of 8.1 ranibizumab and/or bevacizumab injections over 1 year in the treatment of ME secondary to CRVO.\textsuperscript{12,13} As such, according to the 2019 Preferences and Trends Survey by the American Society of Retina Specialists,\textsuperscript{22} most physicians in the United States have adopted T&E paradigms, an approach that individualizes visit frequency with treatment rendered at every visit (if the regimen is truly T&E and not a mix of T&E with as-needed treatment), and may converge better with regular injection frequency to improve visual outcomes.

An inherent limitation of the present study was that the treatment paradigm used by the treating physicians was not taken into consideration in the analysis of data because this information was not captured in the Vestrum Health database. Also, in routine clinical practice, patients may start on one treatment paradigm and switch to another based on initial response and physician and patient preferences. This study, however, was not intended to assess the superiority of one treatment paradigm relative to another. It was merely intended to evaluate treatment outcome in relation to treatment frequency in routine clinical practice.

This study was not designed to establish a causative relationship between the injection frequency and visual and anatomic outcomes, as other factors such as macular ischemia, epiretinal membrane formation, and severe glaucoma could also affect both visual outcomes and how aggressively treatment is pursued. Additionally, the study consciously did not evaluate outcomes between different anti-VEGF drugs, because that has already been subject to evaluation in randomized clinical trials, with the SCORE2 (Study of Comparative Treatments for Retinal Vein Occlusion 2)\textsuperscript{23} study demonstrating that bevacizumab was not inferior to aflibercept whereas the LEAVO (Lucentis, Eylea, Avastin in Vein Occlusion)\textsuperscript{24} study concluded that bevacizumab may not be interchangeable with aflibercept or ranibizumab.

This study did not correct for the confounding impact of concomitant therapies, including steroids and laser, on visual outcomes. Less than 15% of patients received steroids or laser, and excluding patients who received steroids or laser would have reduced the size and scope of our real-world study. Our study also did not distinguish between ischemic vs nonischemic CRVO.

Additional limitations of this study included its retrospective design, lack of data on visit frequency, and conversion of Snellen acuity to ETDRS letters. Nonetheless, the attributes of this study included a large patient data set that far exceeded the number of patients in phase 3 clinical trials and other real-world studies. A larger population size may help to better understand the correlation between injection frequency and outcomes in routine clinical settings.

In conclusion, this study affords meaningful real-world information that informs the treating retinal physician on
optimal treatment frequency through 2 years to maximize and maintain visual and anatomic outcomes.

Authors’ Note
The results of this study were presented at the 2019 meeting of the Retina World Congress, March 21-24, 2019, Fort Lauderdale, Florida, USA, and at the Association for Research in Vision and Ophthalmology 2019 Annual Meeting, April 28-May 2, 2019, Vancouver, British Columbia, Canada.

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Ethical Approval
Deidentified electronic medical records of patients with CRVO in the Vestrum Health treatment and outcomes database (Vestrum Health, Naperville, Illinois, USA) constitute a “limited data set” in which all patient identifiers have been completely removed and site and clinician data pseudononymized. On this basis, formal ethics approval is not required, and formal ethics approval was not obtained.

Statement of Informed Consent
Deidentified electronic medical records of patients with CRVO in the Vestrum Health treatment and outcomes database (Vestrum Health, Naperville, Illinois, USA) constitute a “limited data set” in which all patient identifiers have been completely removed and site and clinician data pseudononymized. On this basis, informed consent is not required, and informed consent approval was not obtained from patients.

Declaration of Conflicting Interests
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Supplemental Material
Supplemental material is available online with this article.

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