Reading Speed Improvements in Retinal Vein Occlusion After Ranibizumab Treatment

Ivan J. Suñer, MD; Neil M. Bressler, MD; Rohit Varma, MD; Paul Lee, MD; Chantal M. Dolan, PhD; James Ward, PhD; Shoshana Colman, PhD; Roman G. Rubio, MD

**IMPORTANCE** Treatment of macular edema secondary to retinal vein occlusion with ranibizumab has been shown to improve visual acuity compared with macular laser or observation. It is important to determine whether these visual acuity improvements translate into measurable improvements in visual function.

**OBJECTIVE** To examine the benefit of ranibizumab (Lucentis) on measured reading speed, a direct performance assessment, through 6 months in eyes of patients with macular edema after retinal vein occlusion (RVO).

**DESIGN** Two multicenter, double-masked, phase 3 trials in which participants with macular edema after branch RVO or central RVO were randomized 1:1:1 to monthly sham, ranibizumab, 0.3 mg, or ranibizumab, 0.5 mg, for 6 months.

**SETTING** Community- and academic-based ophthalmology practices specializing in retinal diseases.

**PARTICIPANTS** Seven hundred eighty-nine eyes of 789 participants who were at least aged 18 years with macular edema secondary to retinal vein occlusion in the branch vein occlusion (BRAVO) and central vein occlusion (CRUISE) trials.

**INTERVENTIONS** Eyes were randomized 1:1:1 to 1 of 3 groups for monthly injections for 6 months: sham (132 in BRAVO and 130 in CRUISE), intravitreal ranibizumab, 0.3 mg (134 in BRAVO and 132 in CRUISE), and intravitreal ranibizumab, 0.5 mg (131 in BRAVO and 130 in CRUISE). Patients were able to receive macular laser after 3 months if they met prespecified criteria.

**MAIN OUTCOMES AND MEASURES** Reading speed in the study eye was measured with enlarged text (letter size equivalent to approximately 20/1500 at the test distance) at baseline and 1, 3, and 6 months. The number of correctly read words per minute (wpm) was reported. The reading speed test requires a sixth-grade reading level and does not account for literacy or cognitive state.

**RESULTS** In patients with branch RVO, the mean gain for the 0.5-mg group was 31.3 wpm compared with 15.0 wpm in sham-treated eyes (difference, 16.3 wpm; \( P = .007 \)) at 6 months. In patients with central RVO, the mean gain for the 0.5-mg group was 20.5 wpm compared with 8.1 wpm in sham-treated eyes (difference, 12.4 wpm; \( P = .01 \)) at 6 months. A gain of 15 or more letters of best-corrected visual acuity letter score corresponded to an increase in reading speed of 12.3 wpm and 15.8 wpm in patients with branch and central RVO, respectively.

**CONCLUSIONS AND RELEVANCE** These results suggest that patients with macular edema after RVO treated monthly with ranibizumab are more likely to have improvements in reading speed of the affected eyes through 6 months compared with sham treatment. These results demonstrate the relevance of the treatment benefit to functional visual gain.

**TRIAL REGISTRATION** clinicaltrials.gov Identifier: NCT00486018 and NCT00485836

Published online May 9, 2013.

Author Affiliations: Retina Associates of Florida, Tampa (Suñer); Wilmer Eye Institute, The Johns Hopkins University School of Medicine, Baltimore, Maryland (Bressler); Doheny Eye Institute, University of Southern California, Los Angeles (Varma); Duke Eye Center, Duke University School of Medicine, Durham, North Carolina (Lee); Genentech, Inc, South San Francisco, California (Dolan, Ward, Colman, Rubio).

Corresponding Author: Ivan J. Suñer, MD, Retina Associates of Florida, P.A. 602 South MacDill Ave, Tampa, FL 33609 (ivansuner@gmail.com).
Retinal vein occlusion (RVO), involving a branch retinal vein or the central retinal vein, is the second most common retinal vascular disease and may result in moderate to severe loss of visual acuity (VA). The most common cause of vision loss in RVO is macular edema. The Ranibizumab for the Treatment of Macular Edema following Branch Retinal Vein Occlusion: Evaluation of Efficacy and Safety (BRAVO) and the Ranibizumab for the Treatment of Macular Edema after Central Retinal Vein Occlusion: Evaluation of Efficacy and Safety (CRUISE) trials demonstrated the benefits of anti–vascular endothelial growth factor treatment with ranibizumab on VA and retinal thickness in patients with branch and central retinal vein occlusion.

Although RVO is typically a unilateral condition, patients report a decrease in their overall quality of life (QoL) and visual function. Patients with RVO also typically report increased difficulty in performing near-activity functions, specifically reading. Several studies have reported that difficulty reading is a frequent complaint of patients with low vision, and reading speed has been shown to be an important indicator of vision-related QoL.

In this article, we describe the effect of ranibizumab treatment on reading speed, a direct performance assessment test. Performance assessment testing is becoming increasingly valuable in evaluating objectively the impact of medical therapies on patient function. Visual acuity is an objective clinical measurement of visual ability, and vision-related QoL measures, such as the National Eye Institute Visual Function Questionnaire–25, are patient-reported outcomes that attempt to capture day-to-day vision-related function. In contrast, reading speed is a direct, measurable assessment of a specific aspect of reading performance or function. In patients with low vision, reading rates are particularly influenced by central-field vision. The loss of central vision that is typical in RVO and is associated with decreased VA also is expected to have a negative impact on reading speed and, thus, reading function.

Reading speed as a performance measure is complementary to clinical measures, such as VA and patient-reported QoL measures, in assessing visual function. To our knowledge, this is the first report of the impact of pharmacologic therapy for RVO on visual performance.

Methods

For both BRAVO and CRUISE, institutional review board approval was obtained prior to patient enrollment, and Health Insurance Portability and Accountability Act compliance was maintained at all participating study sites. All patients provided written informed consent for participation before enrollment and randomization of treatment assignment.

Synopsis of the Protocols

Detailed descriptions of the eligibility requirements for patients and eyes, clinical evaluation procedures, and clinical data collection methods and schedules are described in detail elsewhere. BRAVO and CRUISE were 6-month, multicenter, double-masked, sham-controlled phase 3 trials (treatment period), with an additional 6 months of follow-up for a total study duration of 12 months. During the second 6 months of follow-up, all patients were eligible for treatment with ranibizumab (Lucentis; Genentech, Inc) as needed if they had best-corrected VA of 20/40 or worse or mean central subfield thickness, as measured by time-domain optical coherence tomography, greater than or equal to 250 μm in the study eye.

Patients in the 0.3-mg and 0.5-mg groups continued to receive their assigned dose, and patients in the sham group received ranibizumab, 0.5 mg. Patients with branch retinal vein occlusion also were eligible for laser treatment once during the treatment period, starting at month 3, and once during the second 6 months of follow-up, starting at month 9, if the following criteria were met: best-corrected VA of 20/40 or worse (Snellen equivalent) or a mean central subfield thickness greater than or equal to 250 μm, and a best-corrected VA gain of less than 5 letters or a decrease of less than 50 μm in mean central subfield thickness compared with the visit 3 months prior to the current visit.

Reading Speed Assessment

Reading speed was assessed at baseline and months 1, 3, and 6 using the reading speed test developed for use in the Macular Photocoagulation Study. Patients were asked to read cards containing meaningful paragraphs of approximately 40 words each, including both uppercase and lowercase letters. Patients were given 3 minutes per eye to read the text, which was written at a sixth-grade reading level. Each eye was tested separately while the other eye was occluded. Reading speed score was defined as the number of correctly read words per minute (wpm). Nonfluent reading or low reading speed was defined as 40 wpm, and high fluent or high reading speed was defined as 160 wpm for this test.

Data Analysis and Statistical Methods

In the BRAVO and CRUISE trials, the primary outcome measure was the mean change from baseline in best-corrected VA letter score at month 6. Exploratory efficacy outcomes included mean change from baseline to 6 months in reading speed. All analyses were performed on an intent-to-treat patient population. Missing values were imputed using the last-observation-carried-forward method. Sensitivity analyses based on observed data with no imputations of the missing data were performed and did not change the direction of the primary outcome results of this study.

Mean changes in the reading speed test scores from baseline to follow-up were compared between treatment groups using t tests from analysis of covariance models that adjusted for baseline VA (<55, 54 to 35, ≤34 Early Treatment Diabetic Retinopathy Study letter score) and baseline reading speed. Patients with nonfluent reading speed (40 wpm) or high reading speed (160 wpm) at 6 months were compared using descriptive statistics (percentages and corresponding 95% CIs).

Regression analyses of reading speed change from baseline at 6 months (wpm, imputing missing values using last ob-
Dichotomous Reading Speed Outcomes

In BRAVO and CRUISE, a large reduction in the number of patients in the ranibizumab groups began in the low reading speed group (<40 wpm). In BRAVO, the number of patients reading at least 40 wpm in the 0.5-mg group dropped from 14.0% (95% CI, 5.4 to 25.8) wpm higher compared with sham-treated patients (P = .001 for 0.3-mg and 0.5-mg ranibizumab-treated patients, respectively). In CRUISE, from baseline to 6 months, mean reading speed in ranibizumab-treated patients was 15.6 (95% CI, 5.4 to 25.8) wpm higher compared with sham-treated patients (P = .001 for 0.3-mg and 0.5-mg ranibizumab-treated patients, respectively).

Table. Patient Baseline Characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>BRAVO</th>
<th>CRUISE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sham (n = 132)</td>
<td>0.3 mg Ranibizum (n = 134)</td>
</tr>
<tr>
<td>Age, mean (SD), y</td>
<td>65.2 (12.7)</td>
<td>66.6 (11.2)</td>
</tr>
<tr>
<td>Female sex, No. (%)</td>
<td>58 (43.9)</td>
<td>67 (50.0)</td>
</tr>
<tr>
<td>White race, No. (%)</td>
<td>108 (81.8)</td>
<td>112 (83.6)</td>
</tr>
<tr>
<td>Median best-corrected VA, approximate Snellen equivalent</td>
<td>20/80</td>
<td>20/80</td>
</tr>
<tr>
<td>Reading speed, mean (SD), wpm*</td>
<td>99.2 (47.4)</td>
<td>108.0 (46.4)</td>
</tr>
</tbody>
</table>

Abbreviations: BRAVO, Ranibizumab for the Treatment of Macular Edema Following Branch Retinal Vein Occlusion: Evaluation of Efficacy and Safety; CRUISE, Ranibizumab for the Treatment of Macular Edema After Central Retinal Vein Occlusion Study: Evaluation of Efficacy and Safety; VA, visual acuity; wpm, words per minute.

* BRAVO: n = 130 (sham), 129 (0.3 mg), and 129 (0.5 mg); CRUISE: n = 124 (sham), 125 (0.3 mg), and 125 (0.5 mg).

Results

Patient Baseline Characteristics

Of the 397 patients enrolled in BRAVO, 132 were randomized to sham injection, 134 were randomized to ranibizumab, 0.3 mg, and 131 were randomized to ranibizumab, 0.5 mg. Of the 392 patients enrolled in CRUISE, 130 were randomized to sham injection, 132 were randomized to ranibizumab, 0.3 mg, and 130 were randomized to ranibizumab, 0.5 mg. Baseline distribution of demographic characteristics and VA was similar in both studies and balanced across the treatment arms (Table). In BRAVO, baseline reading speed was 99.2 wpm in the sham group (n = 130), 108.0 wpm in the 0.3-mg ranibizumab group (n = 129), and 95.0 wpm in the 0.5-mg ranibizumab group (n = 129). In CRUISE, baseline reading speed was 89.4 wpm in the sham group (n = 124), 89.0 wpm in the 0.3-mg ranibizumab group (n = 125), and 91.4 wpm in the 0.5-mg ranibizumab group (n = 125).

Effect of Ranibizumab Treatment on Reading Speed of the Study Eye

In BRAVO and CRUISE, the mean reading speed of the study eye increased in all treatment arms from baseline to 6 months. At 6 months, patients treated with ranibizumab had greater increases in reading speed compared with patients treated with sham (Figure 1). In BRAVO, from baseline to 6 months, change in mean reading speed in the ranibizumab-treated groups was 6.8 (95% CI, −3.9 to 17.6) wpm higher and 16.3 (95% CI, 4.9 to 27.8) wpm higher compared with sham-treated patients (P = .04 and P = .007 for 0.3-mg and 0.5-mg ranibizumab-treated patients, respectively). In CRUISE, from baseline to 6 months, mean reading speed in ranibizumab-treated patients was 15.6 (95% CI, 5.4 to 25.8) wpm higher and 12.4 (95% CI, 1.8 to 23.0) wpm higher compared with sham-treated patients (P = .001 and P = .01 for 0.3-mg and 0.5-mg ranibizumab-treated patients, respectively).

P values are from tests of treatment differences using analysis of covariance t tests (stratified) with end-point baseline value as a covariate and baseline visual acuity letter score (≥55, 54 to 35, ≤34) as the stratification variable. Error bars represent 95% CI. Last-observation-carried-forward method was used to impute missing values. BRAVO indicates Ranibizumab for the Treatment of Macular Edema Following Branch Retinal Vein Occlusion: Evaluation of Efficacy and Safety; CRUISE, Ranibizumab for the Treatment of Macular Edema After Central Retinal Vein Occlusion Study: Evaluation of Efficacy and Safety; and VA, visual acuity; wpm, words per minute.
at baseline to 2.3% at 6 months. In the control group, there was a small change from 9.2% at baseline to 6.9% at 6 months. In CRUISE, patients in the 0.5-mg ranibizumab group went from 14.4% to 7.9%, while there was a minimal change in the control group, from 19.4% to 18.5% (Figure 2).

When comparing the increase in the number of patients in the high reading speed groups (>160 wpm), there were similar increases in the control and study groups for BRAVO and CRUISE. In BRAVO, the baseline numbers of patients reading more than 160 wpm ranged from 7.8% in the 0.5-mg group to 16.3% in the 0.3-mg group, with an intermediate 11.5% in the control group. At 6 months, there were similar numbers across all 3 groups in the range of 21.5% (control group) to 25.4% (0.5 mg group). In CRUISE, the number of patients reading more than 160 wpm at baseline ranged from 7.2% (0.3 mg group) to 9.7% (control group). At 6 months, the 3 groups had similar results with reading more than 160 wpm, ranging from 15.3% in the control group to 18.1% in the 0.3-mg group (Figure 3).

Regression Analyses
Regression analyses assessed the change in reading speed associated with a gain of 15 or more letters in best-corrected VA. In BRAVO and CRUISE, the βs for the regression of change in reading speed on change in VA were 0.82 and 1.05, respectively (R² = 0.24 for BRAVO; R² = 0.33 for CRUISE; P for correlation <.0001 for both comparisons). Correspondingly, a 15-letter improvement in best-corrected VA was associated with a 12.3- and 15.8-wpm improvement in reading speed for BRAVO and CRUISE, respectively.

Discussion
The BRAVO and CRUISE trials demonstrated early and sustained VA gains with pharmacologic treatment with ranibizumab for RVO. The results of this analysis show that those VA gains translated to improvements in reading speed, a direct performance-based measure of visual function. Reading speed improvements in the treatment arms of BRAVO and CRUISE were rapid and similar to VA results. These observations were more apparent in the BRAVO trial.

When analyzing the decrease in the low reading speed groups or the increase in the high reading speed groups in
BRAVO and CRUISE, improvement was evident in the reduction of patients reading less than 40 wpm, but there were no clear differences in increases in patients reading more than 160 wpm. While there was little reduction in the percentage of patients reading less than 40 wpm in the sham arms of the studies, reductions of approximately 12 and 7 percentage points were observed in the 0.5-mg ranibizumab arms of BRAVO and CRUISE, respectively. The results were more difficult to interpret in the patients with baseline reading speed greater than 160 wpm. While there was a greater increase in the percentage of patients reading more than 160 wpm in BRAVO (almost 18 percentage points in the treatment group compared with 10 percentage points in the control group), there was a disparity in the baseline numbers in the 2 groups (only 7.8% in the treatment group began at a reading speed greater than 160 wpm as compared with 11.5% in the control group). As for the CRUISE group, there was not much difference in the absolute number (21.5% vs 25.4%) or percentage points of change (5.6% vs 7.9%) in patients achieving greater than 160 wpm between the sham and ranibizumab groups.

Regression analysis of the reading speed and VA data yielded a close relationship between these 2 measures. The βs for the regression of change of the 2 measures were 0.8 and 1.1 for BRAVO and CRUISE, respectively, with P values less than .0001 for both. Of further interest, improvement of 15 letters (or 3 lines) of VA correlated with clinically meaningful changes of 12- and 16-wpm improvements in reading speed, respectively.

One limitation of this study is that reading speed, much like VA, is a monocular measure.27 Since RVO is largely a unilateral disease, the treated or affected eye is generally the eye with worse visual function. If the affected eye is the eye with better function, improvement in overall binocular visual function—in this case reading speed—may be more dramatic. Furthermore, reading speed itself is just one component of reading ability and vision-related QoL.25 For example, reading speed in patients with low vision does not necessarily correlate with reading comprehension.24 Although the slow reading speeds observed in patients with low vision may reflect rates normally associated with low literacy, it is likely that patients with low vision do not lose comprehension owing to reduced speed alone, although no literacy or reading comprehension tests were conducted in this analysis.

In summary, pharmacologic treatment of RVO with ranibizumab resulted in improvements in reading speed, mirroring improvements observed in best-corrected distance VA. Performance-based assessments of visual function are becoming increasingly important in evaluating the socioeconomic benefit and impact across different therapies as medical costs continue to rise and resources become limited.


