RELATIONSHIP BETWEEN RETINAL THICKNESS AND VISUAL ACUITY IN EYES WITH RETINAL VEIN OCCLUSION TREATED WITH DEXAMETHASONE IMPLANT

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Purpose: To evaluate the relationship between changes in best-corrected visual acuity (BCVA) and central retinal thickness (CRT) in eyes from two clinical trials of dexamethasone intravitreal implant 0.7 mg for macular edema after branch or central retinal vein occlusion.

Methods: Patients with vision loss as a result of macular edema (≥6-week duration) after branch retinal vein occlusion or central retinal vein occlusion were treated with a single dexamethasone intravitreal implant or sham. Prospectively defined outcomes included BCVA and CRT (as assessed by optical coherence tomography).

Results: There was a modest but statistically significant negative linear correlation between changes in CRT and changes in BCVA in both treatment groups at Days 90 and 180 (correlation coefficient: −0.23 to −0.34; $P < 0.001$). Improvements in BCVA at Day 180 were significantly greater ($P < 0.001$) in eyes that achieved and maintained CRT ≤250 μm from Day 90 to 180 (mean BCVA improvement: 14 letters; 49% of eyes with ≥15-letter gain) than in eyes that never achieved CRT ≤250 μm (mean BCVA improvement: 2 letters; 13% of eyes with ≥15-letter gain).

Conclusion: The greatest improvements in BCVA were seen in eyes that achieved and maintained the greatest improvements in CRT.

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Macular edema (ME) is a common complication of both branch and central retinal vein occlusion (BRVO and CRVO) and is a common cause of vision loss in both of these conditions.[1–3] The underlying events that manifest with ME and that may contribute to vision loss include upregulation of soluble growth factors (such as vascular endothelial growth factor), activation of cytokines (such as interleukins), and expression of mediators of cellular inflammation (such as intercellular adhesion molecule 1).[4] Retinal ischemia also compromises retina function. Our ability to evaluate many of these processes in vivo is limited, but retinal thickness from ME can be reliably assessed by optical coherence tomography (OCT). Although the relationship between visual acuity and central subfield retinal thickness (CRT) as measured by OCT has received some attention in the literature, the data investigating the relationship between changes in CRT and changes in vision are sparse for BRVO and CRVO.

In the treatment of ME, reductions in CRT often accompany improvements in best-corrected visual acuity (BCVA) and are considered to be an important measure of treatment efficacy.[5–9] In the *G*lobal *E*valuation of impla*N*table d*E*xamethasone in retinal *V*ein occlusion with macular edem*A* (GENEVA) trials, treatment with dexamethasone intravitreal implant 0.7 mg (DEX implant 0.7 mg; OZURDEX, Allergan plc, Irvine, CA) for ME after BRVO or CRVO produced significantly greater improvements in BCVA and CRT than did sham treatment.[5,10] A post hoc analysis found that these clinical improvements were accompanied by significant changes in a resolution of intraretinal hemorrhage (as measured by color fundus photographs) and less progression of neovascularization in eyes treated with the DEX implant 0.7 mg than

in eyes treated with sham.[11] The relationship between these various anatomic changes and improvements in BCVA is not clear.

In this report, we present a post hoc analysis of the relationship between the changes in CRT and BCVA in the GENEVA trials.

Methods

These analyses were based on data collected from two identical, prospective, multicenter phase 3 clinical trials of the safety and efficacy of DEX implant in the treatment of ME associated with BRVO or CRVO (GENEVA trials). Each trial enrolled patients with BRVO or CRVO. Each trial consisted of a 6-month, randomized, sham-controlled, parallel-group, double-masked phase followed by a 6-month, open-label extension. Both trials were conducted in compliance with regulatory obligations, the Declaration of Helsinki, and the institutional review board and informed consent regulations at each investigational site. The protocol for these studies has been described in detail previously[5,10] and is summarized briefly below.

These studies enrolled adult patients who had decreased visual acuity as a result of clinically detectable ME associated with BRVO or CRVO. Disease duration was required to be between 6 weeks and 12 months in patients with BRVO and between 6 weeks and 9 months in patients with CRVO. Baseline BCVA was required to be between 34 letters (20/200) and 68 letters (20/50) in the study eye. Retinal thickness in the central 1-mm macula subfield (as measured by time-domain OCT [OCT1 or OCT3 Systems, Carl Zeiss Meditec, Dublin, CA]) was required to be $\geq$300 μm in the study eye. Most (97.8%) of the patients were evaluated using OCT3 ("Stratus OCT"), and each patient was followed using the same OCT machine at each study visit.

At baseline, study eyes (1 per patient) were randomized to either a sham procedure or treatment with DEX implant 0.7 mg or 0.35 mg. All patients who completed this 6-month, double-masked, sham-controlled phase were eligible for treatment with DEX implant 0.7 mg at the start of the open-label phase if BCVA was $<$84 letters (20/20) or CRT was $>$250 μm in the central 1-mm macula subfield and if, in the investigator's opinion, the procedure would not put the patient at significant risk. Patients receiving sham treatment were prepared in exactly the same manner as those receiving a DEX implant, but a needleless applicator was used to simulate injection and pressure on the sclera.

The analyses in the present report included all patients randomized to either the DEX implant 0.7-mg group or the sham group during the 6-month, double-masked phase (6-month intent-to-treat population). Data from patients in the DEX implant 0.35-mg treatment group were not included in this analysis because this formulation is not commercially available, and the results would therefore not be clinically relevant.

Outcome measures for both GENEVA trials included BCVA and CRT in the study eye. The CRT was obtained using OCT on each patient at baseline, Day 90, and Day 180 in the randomized treatment phase. Fast macular volume scans and high-resolution cross-hair scans were obtained by certified technicians and submitted to the reading center as paper printouts. At the reading center, scans were checked for centration and boundary line errors. If the CRT from the OCT analysis software was considered incorrect by the graders, then a manual caliper measurement of the center of the macula was obtained from the Fast Mac scan that the grader believed gave the best view of the fovea, and this value was substituted for the machine-reported CRT for analysis purposes. Approximately 30% of scans required manual grading. Less than 2% of scans were considered ungradable because of low signal strength or severe artifacts.

In this study, the statistical analyses for the evaluation of the relationship between CRT and BCVA were based on the observed data collected during the 6-month, double-masked, and randomized phase. The relationship between changes in CRT and BCVA was

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examined by Pearson correlation coefficient and multiple linear regression analyses. The regression models included the treatment group (DEX implant 0.7 mg or sham), duration of disease (in 2-month intervals), baseline BCVA, baseline CRT, age, and RVO diagnosis (BRVO vs. CRVO) as the independent variables. Treatment by covariate interactions was evaluated by adding the interaction term to the regression model. Stepwise regression analysis was performed to select independent predictors for BCVA change. The R-square statistic (R^2) from the linear regression analysis is reported as a measure of the proportion of variability in BCVA change that was explained by the variables included in the model. The relationship between change in CRT and the percentage of patients achieving at least a 15-letter improvement in BCVA was evaluated using logistic regression models, which included the same independent variables as used in the multiple linear regression analysis. The primary objective of these analyses was to evaluate the predictive effect of baseline CRT and changes from baseline CRT on change from baseline in BCVA.

For the analysis of baseline characteristics, group comparisons were performed using the chi-square test for categorical variables and the 2-sample *t*-test for continuous variables.

All statistical tests were 2-sided and performed at the $\alpha = 0.05$ significance level. Statistical analyses were completed using the SAS commercial software (version 9.2; SAS Institute Inc, Cary, NC).

Results

Study Population

Patients were recruited into the GENEVA trials between November 2004 and March 2008. At baseline, a total of 1,267 eyes were randomized to treatment (6-month study population) with either DEX implant 0.7 mg (n = 427), DEX implant 0.35 mg (n = 414), or a sham procedure (n = 426). Of these, approximately 94% (1,196) completed Day 180 of the study (initial treatment phase): 403 from the DEX implant 0.7-mg group, 395 from the DEX implant 0.35-mg group, and 398 from the sham group. This study will focus on only those eyes treated with DEX implant 0.7 mg or sham at baseline. Retinal thickness measurements at both baseline and Day 180 were available for 420/427 eyes in the DEX implant 0.7-mg group and 420/426 eyes in the sham group.

The baseline characteristics for the subset of the study population for which retinal thickness measurements were available are summarized in Table 1. In both treatment groups, the mean age was approximately 64 years and most patients enrolled were white. Approximately twice as many patients with BRVO as CRVO were enrolled in this study. Patients with BRVO had slightly higher mean visual acuity and markedly thinner retinas at baseline than did patients with CRVO, but there were no statistically significant differences between the DEX implant group and the sham group for any demographic or baseline characteristic (Table 1).

Relationship Between CRT and BCVA

A univariate analysis found that there was a modest but statistically significant negative relationship between changes in CRT and BCVA at both Day 90 and Day 180 in both the DEX implant group (Day 90 Pearson correlation coefficient: −0.23 and $P < 0.001$; Day 180 correlation coefficient: −0.34 and $P < 0.001$) and the sham treatment group (Day 90 correlation coefficient: −0.25 and $P < 0.001$; Day 180 correlation coefficient: −0.27 and $P < 0.001$). Note that the correlation coefficients were similar regardless of the treatment group or the study visit. Similar results were obtained using the Spearman correlation coefficient (not shown).

A multiple linear regression analysis confirmed that CRT decrease was a significant predictor of mean BCVA improvement at Days 90 and 180 after adjusting for the confounding effect of treatment, duration of disease, baseline BCVA, baseline CRT, age, and RVO diagnosis (Table 2). Note that at Day 90, the parameter estimate for CRT decrease versus mean BCVA increase (in letters) was approximately 2.7 letters/100 μm (95% CI = 2.3–3.2; $P < 0.001$). This parameter estimate was similar at Day 180 (3.3 letters/100 μm; 95% CI = 2.9–3.8; $P < 0.001$). A separate analysis found that CRT decrease was also a significant predictor of the likelihood of achieving $\geq$15 letters of improvement in BCVA (Table 2). The R^2 from the multiple regression analysis was 30% at Day 90 and 35% at Day 180. Similar results were obtained when the analysis was repeated using log-transformed baseline CRT data (not shown).

Several other baseline characteristics, including age, baseline BCVA, baseline CRT, and type of RVO, were also significantly associated with improvements in BCVA. Stepwise regression indicated that reduction in OCT was the first significant predictor of mean improvement in BCVA, followed by baseline CRT, baseline BCVA, age, treatment group, and then RVO type. A similar relationship between CRT and BCVA was found when the data were analyzed for each

Table 1. Key Baseline Characteristics of the Study Population

Characteristic	DEX Implant 0.7 mg (n = 420)	Sham (n = 420)	*P**
Age (years)			0.259
Mean (range)	64.8 (33–90)	63.9 (31–91)	
Sex, n (%)			0.128
Male	214 (51.0)	236 (56.2)	
Female	206 (49.0)	184 (43.8)	
Race, n (%)			0.937†
White	315 (75.0)	314 (74.8)	
Black	15 (3.6)	20 (4.8)	
Asian	38 (9.1)	44 (10.4)	
Hispanic	36 (8.6)	24 (5.7)	
Other	16 (3.8)	18 (4.3)	
Diagnosis in study eye, n (%)			0.379
BRVO	287 (68.3)	275 (65.5)	
CRVO	133 (31.7)	145 (34.5)	
Duration of ME			
Mean duration, days	157.2 (19–374)	156.2 (19–374)	0.850
<90 days, n (%)	70 (16.7)	63 (15.0)	
≥90 days, n (%)	350 (83.3)	357 (85.0)	
Mean baseline visual acuity, letters ± SD (Snellen equivalent)	54.3 ± 9.90 (20/80)	54.8 ± 9.77 (20/80)	0.466
BRVO	55.1 ± 9.50	55.5 ± 9.18	0.576
CRVO	52.7 ± 10.58	53.5 ± 10.71	0.534
Mean baseline retinal thickness (μm ± SD)	562 ± 187.6	539 ± 186.3	0.071
BRVO	522 ± 161.3	496 ± 175.8	0.064
CRVO	648 ± 210.9	620 ± 178.9	0.236

Only included patients with baseline retinal thickness data.

*P values were based on a t-test for continuous variables (age, duration of ME, baseline BCVA, and baseline retinal thickness) and the Pearson χ^2 test for categorical variables (sex, race, and diagnosis). P value >0.05 was not statistically significant.

†White versus non-white patient.

treatment group (DEX implant or sham) separately (data not shown). The lack of an effect of treatment on the relationship between BCVA and CRT suggests that similar increases in BCVA would be expected with a given CRT reduction regardless of whether the reduction in CRT was due to treatment or spontaneous improvement. It should be noted, however, that when the regression analysis was performed without CRT reduction in the model, the effect of treatment on the change from baseline BCVA was highly significant ($P < 0.001$) at both Day 90 and Day 180. The observed CRT reduction was a direct result of treatment; therefore, treatment was a stronger predictor of BCVA improvement than the extent of reduction in retina thickness. However, the treatment effect (DEX implant vs. sham) was largely reflected in the CRT decrease when this variable was included in the model.

A subgroup analysis for those eyes that achieved anatomic treatment success (defined as a CRT of ≤250 μm) was also performed (Figure 1; see **Table, Supplemental Digital Content 1**, http://links.lww.com/IAE/A405). In this analysis, improvements in BCVA at Days 90 and 180 were evaluated for eyes that achieved a CRT ≤250 μm at Day 90 that was maintained through Day 180 (persistent CRT responders), eyes that achieved a CRT ≤250 μm at Day 90 that was not maintained through Day 180 (early CRT responders), eyes that only achieved CRT ≤250 μm at Day 180 (delayed CRT responders), and eyes that never achieved CRT ≤250 μm (CRT nonresponders). As can be seen in Figure 1, the greatest and most sustained improvements in BCVA (across both treatment groups) occurred in the persistent CRT responders (mean improvement of 14 letters at Day 180; 49% with a 15-letter gain), followed closely by the delayed CRT responders (12-letter gain at Day 180; 43% with a 15-letter gain). Visual improvement was transient in those eyes with an early and transient CRT improvement and very poor in the CRT nonresponders (2-letter gain at Day 180; 13% with a 15-letter gain). It should be noted that the percentage of eyes achieving a BCVA improvement of ≥15 letters was nearly as great among delayed CRT responders as in persistent CRT responders, even though the delayed CRT responders did not achieve CRT ≤250 μm until after Day 90.

Discussion

Although improvements in BCVA are often accompanied by improvements in CRT,[5–10] the relationship between changes in BCVA and CRT is poorly

Table 2. Effect of Various Parameters on Visual Outcomes at Day 90 and Day 180

Variable	Mean Change in BCVA (Letters)		Patients Achieving ≥15-Letter Gain (%)	
	Parameter Estimate (95% CI)	*P*	Odds Ratio (95% CI)	*P*
Day 90				
Reduction in CRT (per 100 μm)	2.74 (2.29 to 3.18)	<0.001	1.63 (1.38 to 1.92)	<0.001
Treatment effect (DEX implant 0.7 mg vs. sham)	1.12 (–0.32 to 2.56)	0.130	1.35 (0.88 to 2.07)	0.171
Duration of ME (per 60 days)	–0.23 (–0.79 to 0.32)	0.414	0.89 (0.75 to 1.05)	0.157
Age (per year)	–0.22 (–0.28 to –0.15)	<0.001	0.95 (0.93 to 0.97)	<0.001
Baseline BCVA (per letter)	–0.19 (–0.26 to –0.11)	<0.001	0.95 (0.93 to 0.97)	<0.001
Baseline CRT (per 100 μm)	–2.77 (–3.25 to –2.29)	<0.001	0.61 (0.51 to 0.73)	<0.001
Type of RVO (BRVO vs. CRVO)	2.88 (1.38 to 4.38)	<0.001	1.48 (0.92 to 2.38)	0.109
Day 180				
Reduction in CRT (per 100 μm)	3.34 (2.88 to 3.80)	<0.001	1.84 (1.57 to 2.15)	<0.001
Treatment effect (DEX implant 0.7 mg vs. sham)	3.31 (1.81 to 4.80)	<0.001	1.55 (1.04 to 2.30)	0.032
Duration of ME (per 60 days)	–0.53 (–1.13 to 0.07)	0.085	0.85 (0.72 to 1.01)	0.059
Age (per year)	–0.22 (–0.29 to –0.15)	<0.001	0.96 (0.94 to 0.98)	<0.001
Baseline BCVA (per letter)	–0.27 (–0.35 to –0.19)	<0.001	0.93 (0.91 to 0.95)	<0.001
Baseline CRT (per 100 μm)	–3.75 (–4.27 to –3.24)	<0.001	0.55 (0.47 to 0.65)	<0.001
Type of RVO (BRVO vs. CRVO)	1.95 (0.24 to 3.65)	0.025	0.93 (0.59 to 1.48)	0.769

All factors listed were included in the multiple regression model.

understood. The multifactorial nature of increased retinal thickness in ME results in a generally weak correlation between visual acuity and retinal thickness (regardless of the underlying disease etiology).[12–14] Nevertheless, CRT as measured by OCT is the most readily available parameter for exploring some of the structure/function interrelationships in clinical trials of ME. This analysis of data from the GENEVA trials demonstrated that the greatest improvements in BCVA were seen in those eyes that achieved and maintained the greatest improvements in CRT. Importantly, the relationship between changes in CRT and BCVA appeared to be similar regardless of whether the changes occurred as a result of treatment or the result of spontaneous improvement.

The correlation between absolute changes in CRT and BCVA was found to be statistically significant, but only moderate in strength. The Pearson correlation coefficient was only –0.34 for the DEX implant group and –0.27 for the sham group. In addition, the R^2 from the multiple regression analysis was 30% at Day 90 and 35% at Day 180. This suggests that changes in CRT (adjusted for the effect of treatment, duration of disease, baseline BCVA, baseline CRT, age, and RVO diagnosis) can only explain approximately one third of the variation seen in the improvement in BCVA. Other factors were also found to affect improvements in BCVA, but the most significant predictor of BCVA improvement was the change in CRT. The other significant predictors of improvements in BCVA (in order

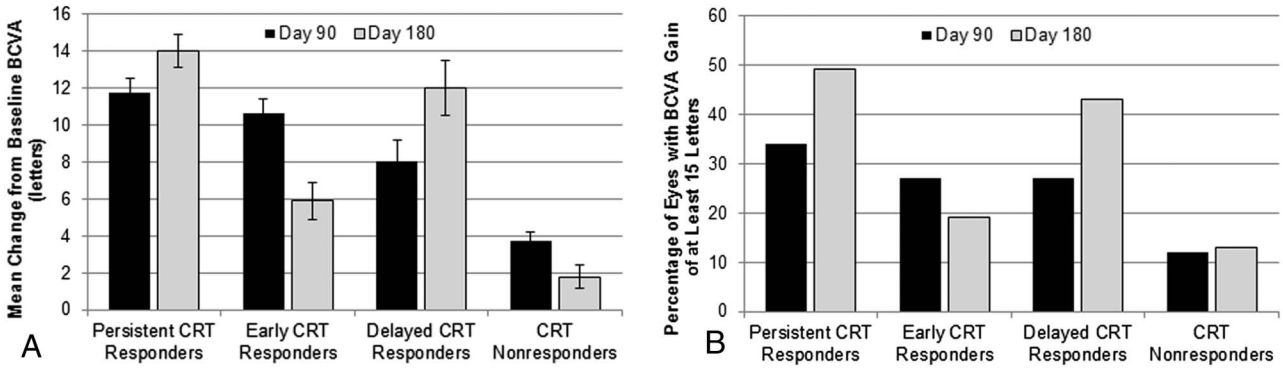

Fig. 1. Relationship between anatomic success and improvements in BCVA in both treatment groups combined. Anatomic success was defined as CRT ≤250 μm. **A.** Mean change from baseline BCVA (error bars are the standard errors of the means). $P < 0.001$ for persistent responders versus nonresponders at Days 90 and 180. **B.** Percentage of eyes with BCVA gain of at least 15 letters. $P < 0.001$ for persistent responders versus nonresponders at Days 90 and 180.

of decreasing significance) were baseline CRT, baseline BCVA, age, treatment group, and then RVO type. The possible contribution of retinal perfusion status was not evaluated in this study. Fluorescein angiography was obtained as part of normal standard of care in the GENEVA trials and not as a study assessment,[11] and therefore was available only in a subset of subjects. This made the results unsuitable for inclusion in the regression analyses performed for this study. It is possible that inclusion of variables from fluorescein angiography, such as the area of ischemia or fluorescein leakage, might strengthen the anatomic associations with vision.

It is possible that the modest linear relationship between changes in CRT and BCVA is a result of a complex relationship between CRT and retinal cellular function; changes in CRT may have little effect on cellular function until a certain threshold is achieved. This hypothesis was explored using a responder analysis in which CRT threshold was set at $\leq$250 μm (based on the clinical experience of the investigators). It was found that the greatest likelihood of achieving a clinically meaningful improvement in vision at Day 180 occurred in those eyes that achieved a CRT $\leq$250 μm by Day 90 and maintained this CRT through Day 180 (persistent CRT responders; 49% with a 15-letter gain). In contrast, the least likelihood of clinically meaningful improvement (13% with a 15-letter gain) was seen in eyes that never achieved a CRT $\leq$250 (CRT nonresponders). The difference in the response between persistent CRT responders and CRT nonresponders was statistically significant for mean BCVA, mean change in BCVA, and the percentage of eyes achieving a 15-letter gain regardless of whether all eyes were analyzed together (Figure 1; $P \leq 0.001$) or each treatment group was analyzed separately (see **Table, Supplemental Digital Content 1**, http://links.lww.com/IAE/A405; $P \leq 0.002$).

Regardless of the type of analysis performed, the relationship between changes in BCVA and changes in CRT was similar in eyes treated with DEX implant or sham, suggesting that similar improvements in vision may occur in association with any given reduction in CRT regardless of the cause of the CRT improvement.

The mechanism by which increases in CRT due to ME may affect vision is unclear. Metabolic dysfunction, toxic cytokines from inflammatory cells, or mechanical distortion of retinal cells could all interfere with photoreceptor function. Noma et al[15] evaluated the relationship between electroretinograms and morphologic findings in eyes with BRVO and ME, and found that both retinal thickness and volume in the temporal region of the retina were significant determinants of electroretinogram findings. The authors suggested that OCT parameters of the temporal region of the retina are associated with postreceptoral cone pathway function in patients with BRVO and ME, but it is not clear how this may relate to the relationship between CRT and BCVA seen in this study.

A limited number of earlier studies have investigated the relationship between visual acuity and CRT, but, as far as we were able to determine, none of these studies investigated the relationship between changes in visual acuity and changes in CRT over time. For example, in the *S*tandard Care vs. *CO*rticosteroid for *RE*tinal Vein Occlusion (SCORE) study (a randomized double-masked comparison of intravitreal triamcinolone with standard of care), baseline retinal thickness was found to be correlated with baseline BCVA (approximately 2 letters BCVA/100 μm retinal thickness in patients with BRVO and approximately 1.5 letters/100 μm in patients with CRVO)[16] and to be predictive of improvements in visual acuity after treatment with either intravitreal triamcinolone or standard of care.[17] A separate study confirmed a correlation between retinal thickness and BCVA in patients with BRVO and ME, but found that retinal thickness was more closely correlated with retinal sensitivity than with BCVA.[12] Neither of these studies, however, analyzed the relationship between changes in BCVA and changes in CRT with time or in response to treatment.

The ability to draw strong conclusions from this study is limited by the post hoc study design and the lack of information about the perfusion status of the study eyes. The strengths of the study include the large study population, the inclusion of both treated and untreated eyes, and the ability to evaluate changes in BCVA and CRT over time. The OCT assessments in this study were obtained from time-domain OCT, which limits the structural information available from the scans. Future studies should examine retinal layer volumes and outer retinal band integrity using more modern OCT instrumentation. This may provide more sensitive indicators of clinically important changes, such as in the retinal vasculature, which might correlate more strongly with visual function than the measurements obtained in this study. It would also be valuable to compare the effect of different therapies (e.g., intravitreal steroids and anti–vascular endothelial growth factor therapies) on signs of retinal and/or retinal vascular damage in an effort to understand the underlying cell biology through a possible differential treatment effect independent of the effect on CRT.

In conclusion, this study demonstrated that there was a significant relationship between changes in CRT and changes in BCVA in eyes with ME after BRVO or CRVO. Although the linear correlation between CRT and BCVA was only modest, the markedly greater

improvements in BCVA in CRT responders (decrease in CRT to 250 μm or below) suggest that there may be an important and complex relationship between these parameters that is worthy of further study. It is also important to note that the relationship between CRT and BCVA was similar in eyes that improved in response to treatment and in those that improved spontaneously. This suggests that changes in CRT are a valuable clinical outcome measure that should continue to be investigated, and that therapies that can markedly reduce CRT may also be likely to produce significant improvements in vision.

Key words: macular edema, optical coherence tomography, retinal thickness, retinal vein occlusion, regression analysis.

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