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EARLY CRT MONITORING USING TIME-DOMAIN OPTICAL COHERENCE TOMOGRAPHY DOES NOT ADD TO VISUAL ACUITY FOR PREDICTING VISUAL LOSS IN PATIENTS WITH CENTRAL RETINAL VEIN OCCLUSION TREATED WITH INTRAVITREAL RANIBIZUMAB

A Secondary Analysis of Trial Data

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Purpose: Our primary purpose was to assess the clinical (predictive) validity of central retinal thickness (CRT) and best corrected visual acuity (BCVA) at 1 week and 1 month after starting treatment with ranibizumab for central retinal vein occlusion. The authors also assessed detectability of response to treatment.

Methods: The authors used data from 325 participants in the CRUISE study, which included measurement of time-domain CRT and BCVA at baseline, 1 week, 1 month, and 6 months postrandomization. Analysis of covariance models were fitted to assess clinical validity, and distributions of change were constructed to assess detectability of response.

Results: There was no evidence that 1-week CRT, and very strong evidence that 1-week BCVA were associated with baseline-adjusted BCVA at 6 months ($P = 0.17$ and $P < 0.001$, respectively). There was strong evidence that both 1-month CRT and 1-month BCVA were associated with baseline-adjusted 6-month BCVA ($P = 0.005$ and $P < 0.001$, respectively), but simultaneous adjustment found evidence of independent association only for BCVA ($P = 0.71$ and $P < 0.001$ for CRT and BCVA, respectively). Detectability of response tended to be higher for CRT than BCVA at 1 week and 1 month but by 6 months these were equivalent for CRT and BCVA.

Conclusion: In this study, BCVA monitoring of treated central retinal vein occlusion patients seemed more informative than time-domain optical coherence tomography monitoring.

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Treatment of central retinal vein occlusion with intravitreal vascular endothelial growth factor inhibitors such as ranibizumab has been shown to improve clinically relevant outcomes, including visual acuity, visual functioning, and reading speed.[1–3] Optical coherence tomography (OCT) has emerged in recent years as a way to measure anatomical changes in the retina and other eye tissues.[4,5] Central retinal thickness (CRT) measured after retinal vein occlusion is used to estimate the extent of macular edema to judge initial prognosis and need for retreatment. Central retinal thickness is also used to monitor the response to treatment, but the value of this practice is not known.

The best monitoring test may be chosen on the basis of technical factors[6]; the two criteria relevant to central retinal vein occlusion are 1) clinical (predictive) validity, that is, how well the test predicts visual acuity and other patient-centered outcomes; and 2) detectability of

response, that is, how clearly and rapidly the test changes after starting therapy ("signal") relative to background within-patient variability ("noise"). Clinical validity is the most important, and it is usually not worth using a monitoring test without this.[6]

Morphological changes detected by OCT, such as CRT, hypothetically occur before changes in visual acuity are detected. However, the graphical depiction of changes in both best corrected visual acuity (BCVA) and CRT seen in the CRUISE randomized controlled trial suggest that there is no difference in the onset of treatment effects observed at 1 week after treatment, although the maximal effect on BCVA (approximately 5 months) may lag behind the maximal effect on CRT (approximately 7 days).[1] Best corrected visual acuity (or at least presenting VA), is routinely measured at follow-up clinics and may itself be used to monitor patients on treatment. For CRT to be useful as a monitoring test, it needs to have an incremental benefit above and beyond BCVA. That is, for OCT to be useful for making decisions about treatment and prognosis, it needs to provide information which is additional to that already available to the clinician, which includes information on the patient's visual acuity.

Our primary aim was to assess the clinical validity of CRT measured at 1 week and 1 month after starting treatment, and whether there was incremental benefit beyond measuring BCVA, in patients treated with ranibizumab for central retinal vein occlusion. We also evaluated the responsiveness of CRT and BCVA to treatment.

Methods

Study Design and Sample

The study design and population of CRUISE has been described previously.[1,7] In brief, in CRUISE, participants provided informed consent and were randomized to 0.3 mg, 0.5 mg ranibizumab, or sham intraocular injection monthly for 6 months, with an additional 6 months of follow-up (total 12 months), where all study arms received ranibizumab if they met prespecified criteria. The current analysis is limited to the first 6 months. Study participants were adults with foveal center–involved macular edema secondary to central retinal vein occlusion (CRVO) diagnosed within 12 months before study initiation, BCVA 20/40 to 20/320 Snellen equivalent using the Early Treatment Diabetic Retinopathy Study (ETDRS) charts, mean CRT $\geq$250 μm from 2 OCT measurements (at screening and randomization). One eye per participant was chosen as the study eye. Only the study eye was treated with either ranibizumab injection or sham injection and is included in this analysis.

Measurement of Predictor and Outcome Tests

Best corrected visual acuity was measured by the masked investigating physician at individual study sites using the ETDRS chart.[8] Best corrected visual acuity in the study eye was based on the ETDRS visual acuity chart and assessed at a starting test distance of 4 meters. Central retinal thickness was measured on OCT by masked graders at the University of Wisconsin Fundus Photograph Reading Center (UWFPRC; Madison, WI), using Zeiss Stratus 3 software with the FastMac protocol (Carl Zeiss Meditec, Inc., Dublin, CA). Central retinal thickness was recorded as the center point thickness using time-domain Stratus 3 software (Carl Zeiss Meditec, Inc.), unless there was an error in computer recognition of the outer or inner boundaries of the retina or the center point. If that occurred, the grader determined CRT with a caliper.

Statistical Methods

We used the following methods to assess clinical validity of CRT. We included participants with available data on both BCVA and CRT at each of baseline, 1 week, 1 month, and 6 months. As a preliminary step, we constructed scatterplots and calculated correlation coefficients of CRT and BCVA at 1 week or 1 month versus change in BCVA from baseline to 6 months. We

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built linear regression models using analysis of covariance to assess baseline-adjusted BCVA at 6 months.[9] The dependent variable in these models was 6 months BCVA, and baseline BCVA was included as a covariate, along with treatment and age. We used these models to estimate associations between baseline-adjusted 6 months BCVA and each of the following potential monitoring variables: CRT, CRT change from baseline, BCVA, and BCVA change from baseline, each measured at 1 week or 1 month. For significant CRT or BCVA monitoring variables, we also estimated associations after adjustment for the other monitoring variable at the same time point. These models allowed us to assess incremental benefit—how much information one monitoring variable (CRT or BCVA) was adding to that already provided by the other. Likelihood ratio tests were used to assess statistical significance.

Finally, we also assessed detectability of response for changes in OCT and BCVA from baseline to 1 week, 1 month, and 6 months, using a method that directly compares change distributions in active and placebo arms of the trial.[10] The detectability of response is the ratio of signal (true treatment effects) to noise (random variation). The true mean response to treatment was estimated from the difference in mean changes between treated and placebo groups; the true between-person variation in treatment effects was estimated from the difference in variances of change in treated and placebo groups. Background within-person variation was estimated from the variance of change in the placebo group. We used the estimates of signal (true mean change or true between-person variation) and noise (background within-person variation) to estimate signal:noise ratios, which indicated the detectability of response.

Ethics Committee approval was not required for this secondary analysis of de-identified data.

Results

We included 325 of the 392 participants in the trial, who had data available on both BCVA and CRT at each of baseline, 1 week, 1 month, and 6 months. Summary characteristics of these participants are presented in Table 1. The low-dose ranibizumab group had more participants with the necessary data available on BCVA and CRT than either the sham group or the high-dose group, but the three groups were otherwise broadly similar.

Clinical Validity

The correlation between CRT and BCVA measured at 1 week and 1 month with change in BCVA from baseline to 6 months is shown in **Supplemental Digital Content 1** (see **level of CRT or BCVA at 1 week and 1 month**, http://links.lww.com/IAE/A502 and http://links.lww.com/IAE/A503) and **Supplemental Digital Content 2** (see **change in CRT from baseline to 1 week and to 1 month**, http://links.lww.com/IAE/A500 and http://links.lww.com/IAE/A501). These plots suggest that the association of each potential monitoring test with change in visual acuity at 6 months is at most modest.

These potential associations were then analyzed in the analysis of covariance models, with adjustment for baseline BCVA, age, and treatment. There was no evidence that CRT measured at 1 week was associated with baseline-adjusted BCVA at 6 months ($P = 0.17$ for level and 0.79 for change from baseline), and this was not explored further. In contrast, there was very strong evidence that BCVA measured at 1 week was associated with baseline-adjusted BCVA at 6 months ($P < 0.001$).

The associations of the measurement of CRT or BCVA at 1 month with baseline-adjusted BCVA at 6 months are summarized in the first row of Table 2 (baseline-adjusted BCVA at 6 months is equivalent to 6 months change in BCVA from baseline). There was strong evidence that 1 month CRT level had an association, but not CRT change from baseline ($P = 0.005$ and $P = 0.09$, respectively). For each SD increase in CRT level, there was a decrease in baseline-adjusted BCVA at 6 months by 0.13 letters (95% CI: decrease by 0.046–0.21 letters). However, after adjusting for 1 month BCVA, there was no longer evidence of an association ($P = 0.71$). This indicates that 1 month CRT had no incremental benefit in predicting baseline-adjusted BCVA at 6 months. There

Table 1. Baseline Characteristics of 325 Included Participants

Characteristic	Sham (n = 101)	Ranibizumab	
		0.3 mg (n = 117)	0.5 mg (n = 107)
Age, years, mean (SD)	64.8 (13.2)	70.2 (11.2)	68.6 (11.6)
Male, n (%)	57 (56)	64 (55)	65 (61)
White ethnicity, n (%)	89 (88)	97 (83)	89 (84)
BCVA (mean ETDRS letter score, SD)	49.7 (14.5)	47.8 (14.4)	49.1 (14.0)
Approximate Snellen equivalent	20/100	20/100	20/100
CRT, μm, mean (SD)	595.7 (149.4)	591.4 (163.2)	600.0 (157.3)

Table 2. Association Between CRT and BCVA Measured at 1 Month, and Change in BCVA: Overall and by Treatment Group

Monitoring Variable			Unadjusted for Other Monitoring Variable		Adjusted for Other Monitoring Variable	
Treatment	N		Estimate (Change in ETDRS Letter Score)*	P†	Estimate (Change in ETDRS Letter Score)*	P†
All participants	325	CRT 1 month	−0.13 (−0.21 to −0.046)	0.005	−0.039 (−0.12 to 0.044)	0.71
		BCVA 1 month	0.25 (0.17–0.33)	<0.001	0.23 (0.15–0.32)	<0.001
Sham	101	CRT 1 month	−0.30 (−0.47 to −0.13)	<0.001	−0.24 (−0.41 to −0.07)	0.03
		BCVA 1 month	0.24 (0.10–0.38)	<0.001	0.19 (0.04–0.33)	<0.001
0.3 mg	117	CRT 1 month	−0.13 (−0.32 to 0.06)	0.10	−0.003 (−0.21 to 0.20)	0.06
		BCVA 1 month	0.24 (0.10–0.39)	<0.001	0.24 (0.08–0.40)	<0.001
0.5 mg	107	CRT 1 month	−0.16 (−0.32 to −0.006)	0.05	−0.07 (−0.22 to 0.09)	0.45
		BCVA 1 month	0.30 (0.18–0.42)	<0.001	0.29 (0.16–0.41)	<0.001

*Estimated changes in BCVA (ETDRS letter score) at 6 months per SD in the monitoring variable are from models where effects of baseline BCVA, age, and treatment are fixed.
†*P* value is based on likelihood ratio test.

was very strong evidence that 1 month BCVA level was associated with baseline-adjusted BCVA at 6 months, which remained after adjusting for 1 month CRT level ($P < 0.001$ before and after adjusting for CRT). For each SD increase in BCVA at 1 month, there was an increase in baseline-adjusted BCVA at 6 months of 0.25 letters (95% CI: 0.17–0.33 letters).

The results within the different treatment groups are presented in Table 2 (lower rows). There was less evidence for associations between 1 month CRT and baseline-adjusted BCVA at 6 months in both of the treatment groups than for the population as a whole presented above. However, in the sham-treated group, there was very strong evidence of an association ($P < 0.001$), and this remained significant after adjusting for 1 month BCVA ($P = 0.03$). This indicates that 1 month CRT may have incremental benefit in predicting baseline-adjusted BCVA at 6 months for patients not on active treatment.

Sensitivity analyses using log transformed data gave similar results.

Detectability of Response to Treatment

The detectability of CRT and BCVA responses to treatment were estimated from data presented in Figure 1 and **Supplemental Digital Content 3** (see **Appendix Table**, http://links.lww.com/IAE/A504). These show the distributions of change in CRT and BCVA from baseline to 1 week, 1 month, and 6 months, stratified by treatment group. The differences in means for treated groups and sham-treated group at each time point reflects the true mean treatment effect (or the expected effect). The differences in the variances of the distributions reflects the true between-person variation in treatment effects (distributions are wider in treated groups than sham-treated group). The variance of the distribution in the sham-treated group reflects random within-person variation (noise). Detection of response to treatment at 1 week and 1 month appeared more likely with CRT than BCVA (signal:noise ratios were higher for CRT than BCVA for both detection of the expected ranibizumab effect and detection of true between-person differences). However, by 6 months, there appeared to be no difference in the detectability of response.

Discussion

In this study of 325 participants of a randomized controlled trial, we found no evidence overall that CRT measured 1 week or 1 month after starting treatment had incremental benefit in predicting baseline-adjusted 6 months BCVA, for either 0.3 mg or 0.5 mg ranibizumab. At least for these intervals, CRT seems to fail the critical "clinical validity" criterion needed for a monitoring test in that it provides no incremental value beyond information already provided by contemporaneous BCVA measurement. The absence of clinical validity means that, although responses to treatment are more likely to be detected with CRT than BCVA (higher signal:noise ratios), these responses do not have major clinical relevance. In contrast, BCVA measured at 1 week and 1 month after starting treatment strongly predicted baseline-adjusted BCVA at 6 months and may be of potential value for monitoring patients.

The detectability of response to treatment was poorer for BCVA than CRT within the first month, and ratios for signal (treatment effects) to noise (background variation) were ≤1. This indicates that, at best, treatment and chance contributed equally to an observed change in BCVA. However, this is better than many other measures commonly used for clinical monitoring such as blood pressure, cholesterol, and

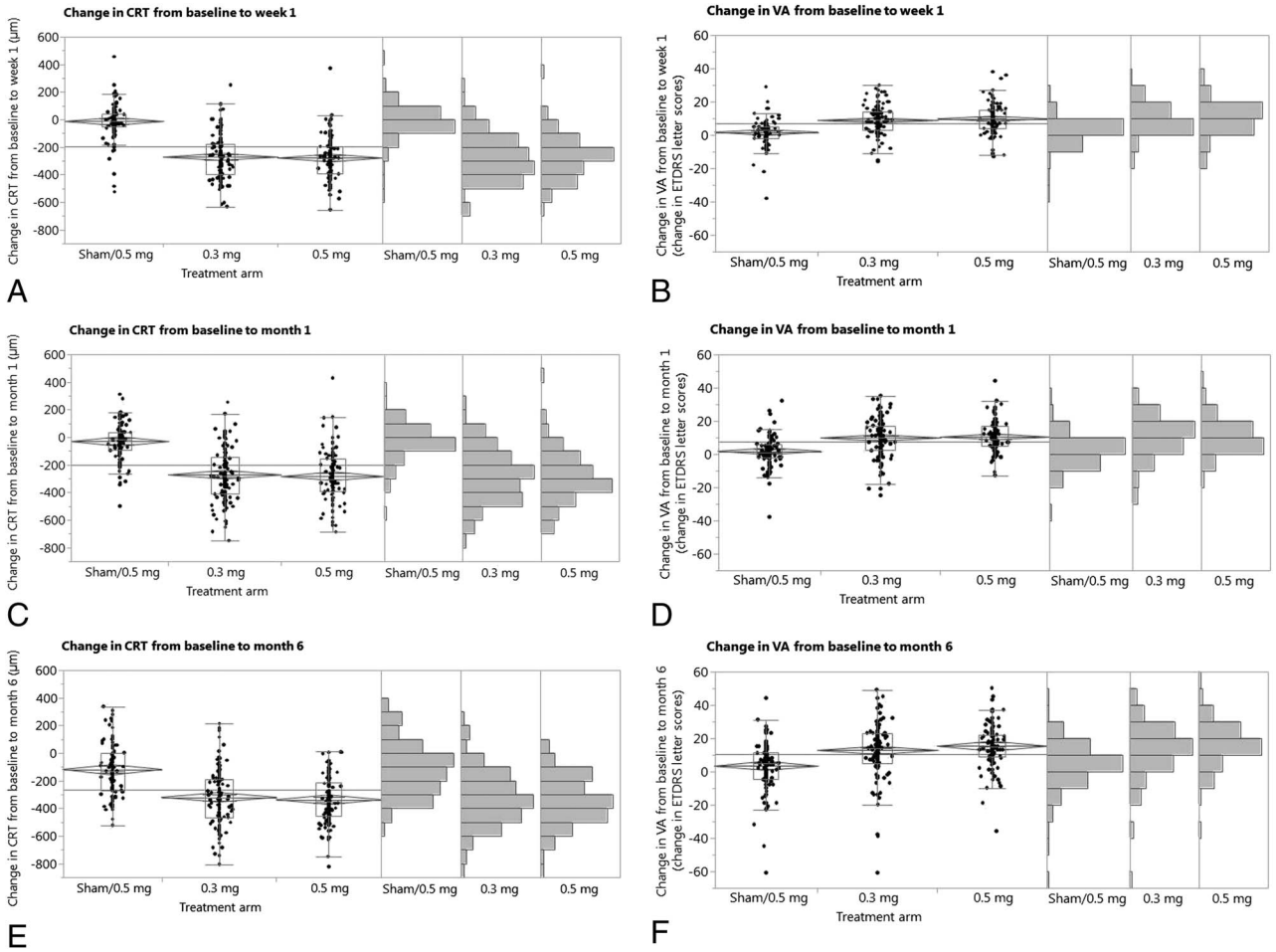

Fig. 1. A. Change in CRT from baseline to Week 1; (**B**) change in BCVA from baseline to Week 1; (**C**) change in CRT from baseline to Month 1; (**D**) change in BCVA from baseline to Month 1; (**E**) change in CRT from baseline to Month 6; (**F**) change in BCVA from baseline to Month 6.

bone mineral density.[10–15] The ability to detect a true response to treatment using BCVA is likely to be improved using repeat measurements.[12,14,16,17]

Central retinal thickness did have incremental benefit (and clinical validity) in the sham-treated group, suggesting that measurements made before starting treatment may usefully add to BCVA measurements in predicting later deterioration in BCVA. We did not directly assess the usefulness of pre-treatment measurements for predicting response to treatment, but this might be investigated by looking at how baseline measurements of CRT and BCVA modify the effect of treatment on BCVA at 6 months.

Strengths of our study are that rigorous statistical methods have been applied to data derived from a large RCT. A limitation of our study is that the assessment of OCT was based on quantitative measures using time-domain (Stratus) technology. Qualitative and quantitative measures using spectral domain technology may be more relevant clinically.[18,19] However, the evidence showing treatment effectiveness is from the same trial data, and using the same type of OCT machines, as we have used here. Furthermore, there is likely to be at least a modest correlation between time and spectral domain machines, and between quantitative and qualitative findings. Our estimates of "noise" are likely to be "best case" scenarios and within-person variation may be larger in clinical practice where there may be larger differences in OCT measurement of an individual at baseline and follow-up, possibly including different instruments.

Our findings build on those of a cross-sectional analysis of baseline data from 262 patients with CRVO who participated in the Standard Care versus Corticosteroid for REtinal Vein Occlusion Study. The authors found only a modest correlation between time-domain CRT and BCVA, both measured before starting the study treatment (correlation coefficient = −0.27; 95% CI: −0.38 to −0.16), and concluded that OCT cannot reliably substitute for visual acuity measurements.[20] This estimate is in keeping with our estimated correlation coefficients (Figure 1), and our

further longitudinal analysis shows that CRT actually has no incremental benefit over BCVA in predicting the baseline-adjusted 6-month BCVA.

A possible explanation of these results is that OCT may fail to detect any underlying ischemic maculopathy which persists despite treatment, and which results in failure of vision to improve. However, an early vision response is likely to indicate underlying health of the macula on treatment and that the vision was able to be preserved with treatment.

The most immediate implication of this report for clinicians and policymakers is that monitoring CRT in patients treated with ranibizumab for CRVO does not add incremental benefit over standard measurements of vision, at least using time-specific OCT. This finding is likely to also apply to CRT monitoring of other treatments for CRVO. This report also more generally demonstrates how published criteria on how to assess monitoring tests[6] may be used to appraise tests used in patients with eye disease or other chronic conditions to inform clinical and funding decisions. Results based on individual patient data such as we have presented here allow for more in-depth exploration of how well each test meets the monitoring criteria and testing of the statistical assumptions that underpin analysis. Where these types of data are not available, appraisal may still be possible using published summary data from trials, particularly if there are sufficient data to enable metaanalysis.

Future research may address the extent to which spectral domain technology differs from time domain and whether there is likely to be incremental benefit to measurements made with these newer instruments over measurements of visual acuity.

Conclusions

There is no evidence to support early CRT monitoring with time-domain OCT after starting ranibizumab to treat CRVO, at least in addition to the information obtained from BCVA.

Key words: evidence-based medicine, intravitreal injections, macular edema, retinal vein occlusion, tomography, optical coherence, visual acuity.

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