Original Article

Baseline morphological characteristics as predictors of final visual acuity in patients with branch retinal vein occlusions: MARVEL report no. 3

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Purpose: To determine the predictive values of baseline optical coherence tomography (OCT) abnormalities on 12-month visual acuity changes in eyes with macular edema (ME) caused by branch retinal vein occlusions (BRVO). **Methods:** We performed a *post hoc* analysis of data from 75 participants in the 12-month MARVEL trial. OCT abnormalities at baseline, including ganglion cell layer cystoid spaces (GCL), intraretinal hyper-reflective dots, and central subfield thickness (CST), were correlated with improvements in visual acuity and the number of anti-vascular endothelial growth factor injections required using a multivariate regression model. **Results:** Eyes with baseline CST > 500 µm had greater visual gains compared to those with CST <500 µm (+21.09 vs +16.08 letters, $P = 0.04$). Eyes with hyper-reflective dots (+13.97 vs +19.93 letters, $P = 0.02$), and GCL cysts (+9.8 vs +18.9, $P = 0.003$) had inferior gains in visual acuity. Neurosensory macular detachments at the baseline did not affect gains in visual acuity. Ninety percent of the gain in visual acuity was recorded after two injections and was maintained until month 12. **Conclusion:** Baseline OCT of <500 µm, hyper-reflective dots, and GCL cystoid spaces are associated with poorer gains in visual acuity. Most of the visual gain occurs after two injections.

Key words: Bevacizumab, branch retinal vein occlusion, disorganization of retinal inner layers, ganglion cell layer cystoid spaces, hyper-reflective spots, macular edema, optical coherence tomography, ranibizumab

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Branch retinal vein occlusion (BRVO) affects 0.6%–1.1% of individuals over the age of 50 years, thereby constituting the second most common retinal vascular disorder.[1,2] Data from pivotal phase III registration trials showed that monthly intravitreal injections of ranibizumab (Lucentis®, Genentech, S. San Francisco, CA/Roche, Basel, Switzerland) and aflibercept (Eylea®, Regeneron, Tarrytown, NY) into eyes with macular edema caused by BRVO improves macular edema and visual acuity (VA) better than sham/photocoagulation.[3-5]

In the MARVEL Report No. 1,[6] we reported that monthly/PRN injections of either bevacizumab (Avastin®, Genentech, S. San Francisco, CA/Roche, Basel, Switzerland) or ranibizumab significantly improves the mean best corrected visual acuity (BCVA) at 6 months by +15.6 and +18.1 letters, respectively. In the MARVEL Report No. 2,[7] we reported that, when the surveillance frequency after the first 6 months was decreased to every 2 months and PRN injections of vascular endothelial growth factor (VEGF) inhibitors were combined with criteria that allowed performance of grid laser photocoagulation in eyes that had macular edema without loss of BCVA, patients maintained BCVA through 12 months.

Baseline optical coherence tomography (OCT) findings in eyes with BRVO have not yet been correlated with either improvements in BCVA or the number of anti-VEGF injections required to control edema. Identifying patients who are likely to respond completely or only partially to long-term anti-VEGF therapy would enable physicians to help patients set realistic expectations for improvements with therapy. Significant correlations between baseline functional and OCT features and 1-year outcomes might even persuade physicians to select treatment regimens to optimize the risk: benefit ratios of therapy.

To address these unresolved issues, we have correlated both the baseline OCT characteristics and the 3-month visual acuity responses after anti-VEGF therapy for edema caused by BRVO with the 1-year visual acuities and the number of required injections.

Methods

The prospective, randomized MARVEL trial was approved by the Institutional Review Board (LEC-11-097). The trial protocol adhered to the tenets of the Declaration of Helsinki, and all participants gave written informed consent before enrolment.

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Patient eligibility

A detailed description of the MARVEL trial methodology was included in reports 1 and 2.[6,7] Briefly, key eligibility criteria included (1) center-involving macular edema caused by BRVO of less than 9 months duration; (2) minimum central retinal thickness (CRT) of >250 μm on spectral domain optical coherence tomography (SD-OCT); (3) best-corrected Early Treatment of Diabetic Retinopathy Study (ETDRS) visual acuity (BCVA) of 24 to 73 letters (20/40 to 20/320) in the study eye.

The key exclusion criteria were: (1) previous macular laser photocoagulation in the study eye; (2) use of intraocular or periocular corticosteroids in the study eye within the previous 3 months; (3) previous treatment with anti-VEGF drugs in the study eye.

Retreatment criteria for PRN dosing during the first 6 months

Subjects received additional injections of the study drug during the first 6 months if any of the following retreatment criteria was satisfied: (1) >50 μm increase in CRT compared to the thinnest previous measurement; (2) new or persistent cystoid retinal edema or subretinal fluid on SD-OCT; (3) loss of ≥5 letters from the best previous BCVA measurement together with any increase in CRT; (4) increase of ≥5 letters from the most recent BCVA measurement.

Retreatment criteria for PRN dosing during the second 6 months

Subjects received additional injections of the study drug from months 6 through 12 if the BCVA decreased by at least 5 letters together with cystoid edema or subretinal fluid on SD-OCT.

Rescue laser criteria

Subjects in both treatment arms were eligible to receive modified macular grid laser photocoagulation if the following pre-specified criteria were met: (1) >50 μm increase in CRT compared to the previous measurement and (2) persistent, diffuse edema with CRT ≥250 μm.

Optical coherence tomography measures

SD-OCT (Cirrus®, Carl Zeiss Meditec, Dublin, CA) was performed at each patient visit. Raster scans and macular cube scans were analyzed for the following parameters at the baseline and month 12: vitreoretinal interface abnormalities, central retinal thickness and volume, subretinal fluid [Fig. 1], macular edema in the temporal and nasal subfields, inner segment/outer segment (IS-OS) line continuity, external limiting membrane (ELM) continuity, cystoid fluid in the outer and inner nuclear layers, highly reflective dots in the inner and outer plexiform layers, disintegration of inner retinal layers (DRIL) [Fig. 2], and cystoid fluid in the ganglion cell layer (GCL) [Fig. 3]. Each of these findings was correlated with BCVA acuity at the baseline and 12 months, gains in BCVA, and number of injections.

Statistical analysis

Mean and standard deviations (SD) of continuous variable parameters were calculated. Both Wilcoxon rank sum test and two sample *t*-test were used to analyze continuous variables, and Fisher's exact Chi-square test was used to analyze categorical variables. Probability values and confidence intervals (CI) were based on two-sided distributions, and

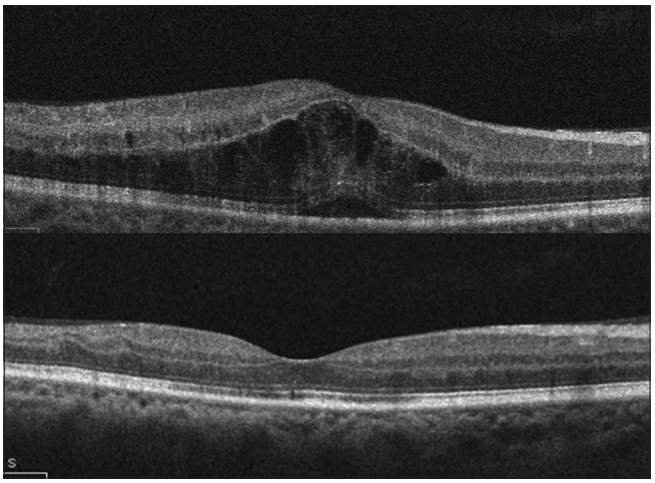

Figure 1: Spectral domain optical coherence tomography scan shows a neurosensory macular detachment together with significant macular edema at the baseline (top), both of which resolved at 12 months (bottom), with a gain of 15 letters

P values of <0.05 were considered significant. A univariate and multivariate linear regression was used to assess the effect of preoperative characteristics on predicting visual acuity change at 12 months. Data were analysed using R software version 3.1.2 (R Development core team, R Foundation for Statistical Computing, Vienna, Austria).

Results

Seventy-five patients were enrolled in the MARVEL trial. There were no significant differences in demographic or ocular characteristics between the study groups at the baseline.[6]

Anatomic outcomes at month 12

The mean reductions in CRT at month 6 (ranibizumab: −177.1 μm; bevacizumab: −201.7 μm) were maintained at month 12 (ranibizumab: −165.7 μm; bevacizumab: −184.8 μm). In a multivariate regression model, eyes with baseline CRT >500 μm had better gains in BCVA than those with CRT <500 μm [+21.1 vs +16.1 letters, $P = 0.04$; Table 1]. Eyes with hyper-reflective dots (+14.0 vs +19.9 letters, $P = 0.02$) and GCL cystoid edema (+9.8 vs +18.9, $P = 0.003$) had smaller gains in BCVA [Table 2]. A neurosensory macular detachment at the baseline did not affect the gain in BCVA. Integrity of the outer retinal structures correlated positively with absolute BCVA ($P = 0.03$), but not with the gain in visual acuity. Eyes with outer retinal disintegration could still have significant gain in BCVA if there was edema or SRF at the baseline. DRIL correlated with the number of injections ($P = 0.04$). OCT findings were similar in both the ranibizumab and bevacizumab treatment groups.

Fewer injections were given to eyes with CRT <500 μm compared to eyes with CRT > 500 μm (2.9 vs 3.4), though the difference was not statistically significant. Twenty-three out of 48 (47.9%) eyes in the less than 500 microns group and 14 out of 27 (51.8%) in the more than 500 microns group achieved a final vision of 20/40 or better.

Ninety percent of the total gain in BCVA (+20.85 out of the final +22.5 letters) occurred at 1 month of the second injection. Though patients required additional injections for recurrent

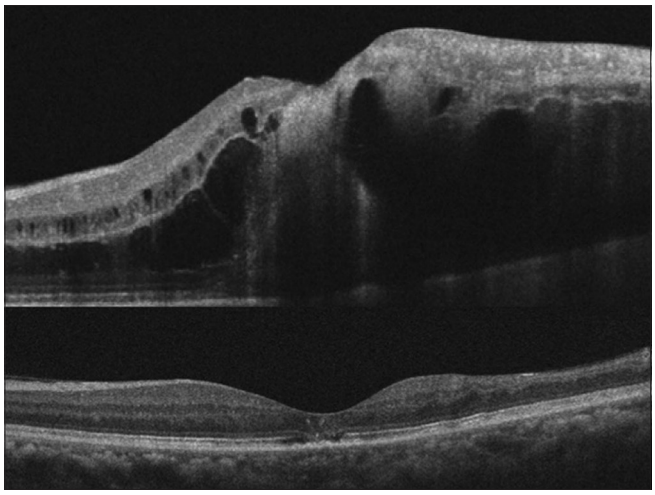

Figure 2: Baseline spectral domain optical coherence tomography scan shows significant disintegration of inner retinal layers that is sufficient to cast "shadows" on the outer retina and pigment epithelium (top). With resolution of the macular edema (bottom), the hyper-reflectivity diminished

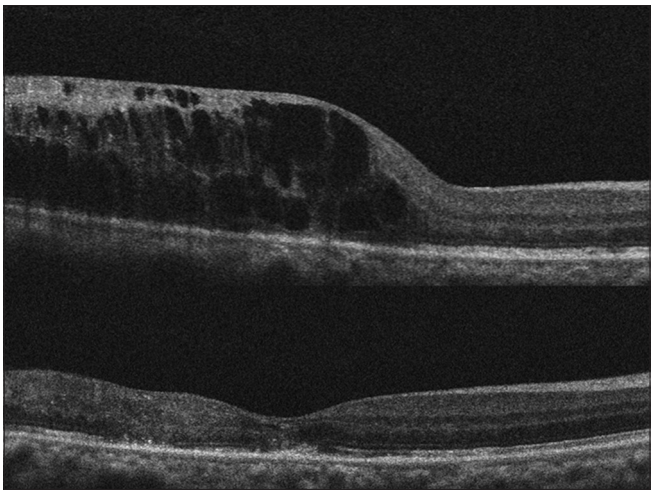

Figure 3: Baseline spectral domain optical coherence tomography scan shows large cystoid spaces in the ganglion cell layer (top). With successful treatment, the macular edema has resolved, as have the cystoid spaces (bottom). This patient gained only one letter at the final visit

Table 1: Effect of baseline central subfield thickness (central retinal thickness) on the visual acuity gain, central retinal thickness reduction, and the number of injections

Characteristic	Mean±SD		*P* Student *t*-test
	CRT <500 microns (48 eyes)	CRT >500 microns (27 eyes)	
Baseline BCVA (letters)	56.76±10.94	51.37±13.37	0.04
Final VA 12 m (letters)	72.04±16.72	71.77±16.80	0.91
Gain in VA 6 m (letters)	15.16±11.47	19.7±14.32	0.06
Gain in VA at 12 m (letters)	16.08±10.83	21.19±15.62	0.04
CRT reduction (microns)	131.5±27.60	292.7±45.51	0.0001
Number of injections	2.91±1.33	3.4±1.55	0.14

CRT: Central retinal thickness, SD: Standard deviation, VA: Visual acuity, BCVA: Best corrected visual acuity

edema, the BCVA after the second injection was similar to the BCVA at month 12.

Discussion

Several OCT abnormalities in patients with various pathologic macular conditions have been associated with poor visual acuity. Disruption of the outer retina (ELM, IS/OS) in eyes with macular edema or traction maculopathies has often been associated with poor visual acuity.

Macular edema due to retinal vasculopathies such as diabetic macular edema and BRVO is often associated with poor vision. Affected eyes often experience greater improvements in both macular edema and visual acuity after treatment with anti-VEGF therapy.[3,5,8] The MARVEL trial produced similar results as eyes with baseline CRT > 500 μm had greater gains in BCVA compared to those eyes with baseline CRT <500 μm. Eyes with neurosensory macular detachments had similar 1-year gains in BCVA compared to eyes that did not have subretinal fluid at baseline ($P = 0.38$).

Baseline OCT abnormalities of the inner retina that may limit the effectiveness of therapy were also evaluated. Intraretinal hyper-reflective dots have recently been noted in eyes with diabetic macular edema and retinal vein occlusion.[9-12] We found that eyes with intraretinal hyper-reflective dots at the baseline had poorer BCVA improvements compared to eyes that did not have hyper-reflective dots. The presence of hyper-reflective dots suggests extravasation of inflammatory factors or lipoproteins. This could suggest a more severe vascular insult, and a more extensive breach of the inner blood retinal barrier. We also found that disintegration of inner retinal layers correlated with a greater number of intravitreal injections.

Ganglion cell layer cystoid spaces had the highest negative predictive value for visual acuity gains ($P = 0.003$) and we speculate that these spaces may signify permanent damage to the inner retina. Results from the MARVEL trial suggest that baseline changes in inner retinal architecture (ganglion cell layer cystoid spaces and intraretinal hyper-reflective dots) may limit improvements in BCVA more than abnormalities in the outer retina (ELM and IS/OS discontinuity). DRIL may be associated with overall worse visual acuity, but macular edema is more closely associated with gain in vision, irrespective of DRIL. This information has important clinical significance, and eyes with outer retinal abnormality could still gain a good amount of vision if they have macular edema.

Between months 6 and 12 in the MARVEL trial, eyes maintained their visual acuity gains from the first 6 months despite mild increases in CRT (ranibizumab: +16.9 μm; bevacizumab: +11.4 μm). These data suggest that mild increases in macular thickness (<50 μm) may not necessarily decrease

Table 2: Effect of optical coherence tomography biomarkers at baseline on the 12-month visual acuity gain

Characteristic	Present	Absent	*P*
Disintegration of inner retinal layers			
Gain in VA (letters)	+16.45	+17.63	0.83
Hyper-reflective dots			
Gain in VA (letters)	+13.97	+19.93	0.02
GCL cysts			
Gain in VA (letters)	+9.8	+18.9	0.003
Neurosensory detachment			
Gain in VA (letters)	+15.76	+18.02	0.38
IS/OS integrity (100%)			
Gain in VA	+13.72	+13.18	0.9

GCL: Ganglion cell layer, VA: Visual acuity, IS/OS: Inner segment/outer segment

BCVA and may not need to be treated. According to our modified retreatment criteria, 73.3% of eyes did not require injections during the final 6 months of the trial.

BCVA after the second injection closely resembled the 12-month outcome, though several eyes required additional injections for recurrent edema to maintain this acuity. These results resemble those from randomized trials for RVO and DME, in which visual acuity improves for the first 3 to 6 months of treatment, with only minimal additional gains accrued through the next 18 months.[8,13,14] Baseline BCVA is another predictor of the magnitude of visual acuity improvement with anti-VEGF therapy since greater improvements occur in eyes with poorer baseline acuities.

Limitations of this analysis of the MARVEL data include its *post hoc* nature. Imaging features that can be seen in eyes with RVOs such as macular ischemia and other fluorescein angiography findings were not included in this study. Despite these limitations, this study is the first to show that baseline hyper-reflective dots and ganglion cell layer cystoid spaces and early response to anti-VEGF therapy correlate with the 12-month visual acuity outcomes.

Conclusion

This *post hoc* analysis of the MARVEL trial shows that 90% of the visual acuity gains occur by 1 month after the second injection. Patients with damage to the outer retinal structures at the baseline benefited from anti-VEGF treatment but eyes with inner retinal damage at the baseline improved the least. The optimal therapy for eyes with inner retinal abnormalities is unknown, but future studies may consider alternative treatments if satisfactory responses are not seen after 2 injections.

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Conflicts of interest

There are no conflicts of interest.

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