Clinical Trials

Predictors of Short-Term Visual Outcome after Anti-VEGF Therapy of Macular Edema due to Central Retinal Vein Occlusion

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Purpose. The purpose of this study was to analyze predictive factors for best-corrected visual acuity (BCVA) after anti-VEGF treatment in patients with macular edema (ME) secondary to central retinal vein occlusion (CRVO).

Methods. This prospective study enrolled treatment-naive patients with ME secondary to CRVO. BCVA, ophthalmoscopy, fundus photography, and spectral domain optical coherence tomography (SD-OCT) imaging were performed. SD-OCT was analyzed for integrity of the external limiting membrane (ELM), photoreceptor inner segments (IS), and outer segments (OS). Patients were treated with intravitreal bevacizumab (1.25 mg) or ranibizumab (0.5 mg). BCVA outcome was analyzed 4 weeks after the first injection.

Results. Sixty-two eyes of 62 patients (39 men, 23 women; mean age: 67 ±16 years) were included. In 55%, the ELM was intact. These eyes also showed intact photoreceptor IS/OS in horizontal and vertical single scans. Disturbed ELM was seen in 45% and was accompanied by focal disintegration of IS/OS. Four weeks after injection, 58% showed clinically relevant increases of BCVA (≥5 letters). Mean BCVA ranged from 20 to 86 letters. The mean BCVA increase was 18 ± 12 letters in eyes with intact ELM compared with 4 ± 10 letters with disturbed ELM ($P < 0.001$).

Conclusions. Depending on the integrity of the outer retinal layers, the authors observed rapid and clinically relevant improvement in BCVA after the first anti-VEGF injection. In the development of an optimal treatment regime, the indication for treatment and re-treatment should be based on functional and morphologic findings, such as the deterioration of outer retinal layers. Intact ELM in SD-OCT imaging is associated with better visual outcomes after intravitreal anti-VEGF treatment in patients with ME secondary to CRVO. (ClinicalTrials.gov number, NCT00564291.) (*Invest Ophthalmol Vis Sci.* 2011;52:3334–3337) DOI:10.1167/iovs.10-6097

Central retinal vein occlusion (CRVO) is a retinal vascular disease and a common cause of vision loss.[1,2] Vision loss results from macular edema (ME) because of the reduced blood perfusion and subsequent retinal hypoxia.[3] The ME may also lead to an additional reduction in visual acuity that often exceeds the primary ischemic damage and thus represents an important target for therapeutic intervention. Treatment strategies for ME consist of focal laser photocoagulation,[4–6] intravitreal steroids,[7] surgical procedures,[8] and, most recently, injection of anti–vascular endothelial-derived growth factor protein (VEGF) compounds.[9,10] There is now increasing evidence for a reduction of ME after intravitreal injection of anti-VEGF compounds such as ranibizumab (Lucentis; Genentech, South San Francisco, CA) and bevacizumab (Avastin; Genentech).[7,10,11] However, treatment success is highly variable and often only temporary. This leads to important questions: Are there predictive factors for visual outcome? For how long should patients be treated?

Development of new imaging modalities such as spectral domain optical coherence tomography (SD-OCT) offers new insight into retinal structures and their alterations in retinal diseases. The aim of our study was to analyze whether preserved outer retinal layers, especially the integrity of the external limiting membrane (ELM), visualized in SD-OCT images have a predictive value for favorable short-term visual outcome 4 weeks after anti-VEGF treatment for ME secondary to CRVO.

Methods

Treatment-naive patients with ME secondary to CRVO were included in this prospective study. If both eyes qualified equally for the study, one eye was randomly chosen. Before the start of any study procedures, informed written consent was obtained from each patient with an explanation of the nature and possible risks of the study and with special note of the off-label use of bevacizumab or ranibizumab. The research followed the tenets of the Declaration of Helsinki and was approved by the institutional review board.

Exclusion criteria were any history of previous laser coagulation, intravitreal injection, retinal surgery, or other retinal diseases in the study eye (including diabetic retinopathy, age-related macular degeneration, and hereditary retinal dystrophies).

We performed a comprehensive ocular examination with best-corrected visual acuity (BCVA) using Early Treatment Diabetic Retinopathy Study (ETDRS) charts, dilated binocular ophthalmoscopy, color fundus photography (FF 450^{plus}; Carl Zeiss Meditec, Jena, Germany). All patients underwent fluorescein angiography (Heidelberg Retina Angiograph [HRA2]; Heidelberg Engineering, Heidelberg, Germany) to confirm the diagnosis of CRVO. In addition, we performed SD-OCT imaging (Spectralis HRA+OCT; Heidelberg Engineering) at baseline.

We obtained in each study eye two SD-OCT scans 6 mm in cross-hair fashion centered on the fovea (horizontal and vertical) and a volume scan using 49 single scans for measurement of central retinal thickness (CRT) within a 1-mm-diameter circle centered on the fovea. For horizontal and vertical SD-OCT scans, the ART function (averaging of scans) was activated and 25 SD-OCT scans were averaged. For

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TABLE 1. Demographic Characteristics of All Patients at Baseline ($n = 62$)

Age in years, mean ± SD (range)	67.1 ± 15.6 (18.5–89.4)
Gender, *n* (%)	
Men	39 (63)
Women	23 (37)
Days between diagnoses and injection, median ± SD (range)	22 ± 18 (1–72)
Letter score, mean ± SD (range)	41 ± 16 (0–69)
LogMar	−0.9
Subretinal fluid, *n* (%)	10 patients (16)
Intraretinal cysts, *n* (%)	59 patients (95)
Visible vitreoretinal traction, *n* (%)	5 patients (8)
Visible epiretinal gliosis, *n* (%)	10 patients (16)
CRT in μm, mean ± SD (range)	413 ± 168 (218–838)

volume scans, the ART function was activated and 9 SD-OCT scan were averaged.

The SD-OCT images were graded as follows: First, the integrity of the retinal layers was analyzed in the horizontal and vertical scans centered on the fovea. In particular, the presence and integrity of the ELM was analyzed. ELM was graded as "disturbed" if we were unable to follow the hyperreflective band of the ELM in an area measuring 200 μm or more, regardless of whether it was in the horizontal or vertical SD-OCT scan. Second, the integrity of the photoreceptor inner segments (IS), outer segments (OS), and retinal pigment epithelium (RPE) was assessed. Third, the volume scan was evaluated for the presence of subretinal and intraretinal fluid accumulation in all 49 single scans. Fourth, CRT was analyzed from the volume scan using Heidelberg software (Eye Explorer, version 1.6.2.0.).

All grading was performed in a masked fashion by two independent graders from the Bern Photographic Reading Center. In case of discrepancies between the two observers, the differences were discussed and a third observer was asked to arbitrate.

All patients were treated with intravitreal anti-VEGF. After topical anesthesia, application of a sterile speculum, and rinsing the eye with microbicide (Betadine; Purdue Pharma, Stamford, CT), 1.25 mg bevacizumab or 0.5 mg ranibizumab was injected through the pars plana 3 using a 30-gauge needle. The outcome in BCVA was analyzed 4 weeks after the first intravitreal injection, in correlation with the OCT findings.

RESULTS

Sixty-two patients (39 men, 23 women) ranging in age from 19 to 89 years (mean, 67 ± 16 years) were included in the study (Table 1). Time from diagnosis to the first injection ranged between 1 and 72 days (mean, 22 ± 18 days). BCVA at baseline ranged from counting fingers (0 ETDRS letters) to 69 ETDRS letters (mean, 41 ± 16 letters). Ranibizumab was injected into 36 (58%) eyes, whereas bevacizumab was used in 26 (42%) eyes. Severe ocular or systemic side effects during the study period were not observed.

Four weeks after the first anti-VEGF injection, mean BCVA ranged from 20 to 86 letters (mean, 53 ± 17 letters). In total, 36 (58%) patients showed a clinically relevant increase of BCVA (≥5 ETDRS letter increase) 4 weeks after the first injection (Table 2). No differences in the visual acuity response with respect to the different anti-VEGF drugs (bevacizumab, 11 ± 12 letters; ranibizumab, 13 ± 15 letters) were observed.

Mean CRT was 413 ± 168 μm at baseline. Analysis of the SD-OCT scans revealed the following morphologic abnormalities: subretinal fluid was detected in 10 eyes, intraretinal cysts in 59 eyes, epiretinal membranes in 10 eyes, and vitreoretinal tractions in 5 eyes. In 34 (55%) eyes, the ELM was intact (Fig. 1), whereas in 28 (45%) eyes the ELM was disturbed (Fig. 2).

All eyes with intact ELM also had intact photoreceptor IS and OS in the horizontal and vertical SD-OCT scans. However, when analyzing all 49 scans from the volume scans of eyes with intact ELM, we found an elevation of the photoreceptor IS with separation from the photoreceptor segment interface in 23 (68%) of eyes. RPE was intact and regular in 24 (70%) eyes with intact ELM and irregular in 10 (30%) eyes with intact ELM.

In all 28 eyes with disturbed ELM, a focal disintegration of the photoreceptor IS and OS was noted. The RPE was intact and regular in 8 (28%) eyes with disturbed ELM, whereas 20 (71%) of these eyes showed irregularities or disruption of the RPE.

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The mean increase in letter score after anti-VEGF therapy in eyes with intact ELM was 18 ± 12 ETDRS letters, whereas eyes with disturbed ELM showed only a mean increase of 4 ± 10 ETDRS letters ($P < 0.001$; Table 2). Differences in letter score between baseline and 4 weeks after the first anti-VEGF treatment in all 62 patients, depending on ELM status, are shown in Figure 3.

Comparing the demographics of patients with intact ELM (group 1) and those with disturbed ELM (group 2), no significant differences regarding mean age (group 1, 66.4 ± 15.6 years; group 2, 67.9 ± 15.8 years), gender, time between diagnosis and injection, and BCVA at baseline (group 1, 42 ± 14 letters; group 2, 40 ± 18 letters) could be observed.

In addition, OCT baseline characteristics, including the presence of subretinal fluid or cysts, vitreoretinal traction, epiretinal membranes, and CRT values, showed no significant differences between the groups or influence on the visual acuity outcome.

DISCUSSION

Off-label injection of anti-VEGF compounds has become an effective and important therapeutic option in ME secondary to CRVO, but not all patients experience a visual gain after this

TABLE 2. Differences in Mean BCVA and Letter Score between Baseline and 4 Weeks after First Anti-VEGF Treatment

	All Patients ($n = 62$)	Intact ELM ($n = 34$)	Disturbed ELM ($n = 28$)
Mean BCVA 4 weeks after first injection*	53 ± 17 (0–82)	61 ± 13 (18–82)	44 ± 18 (0–71)
LogMar	−0.6	−0.4	−0.8
Mean difference in letter score*	12 ± 13 (−13–52)	18 ± 12 letters (0–52)	4 ± 10 (−13–46)

* Data are shown as mean letters ± SD (range).

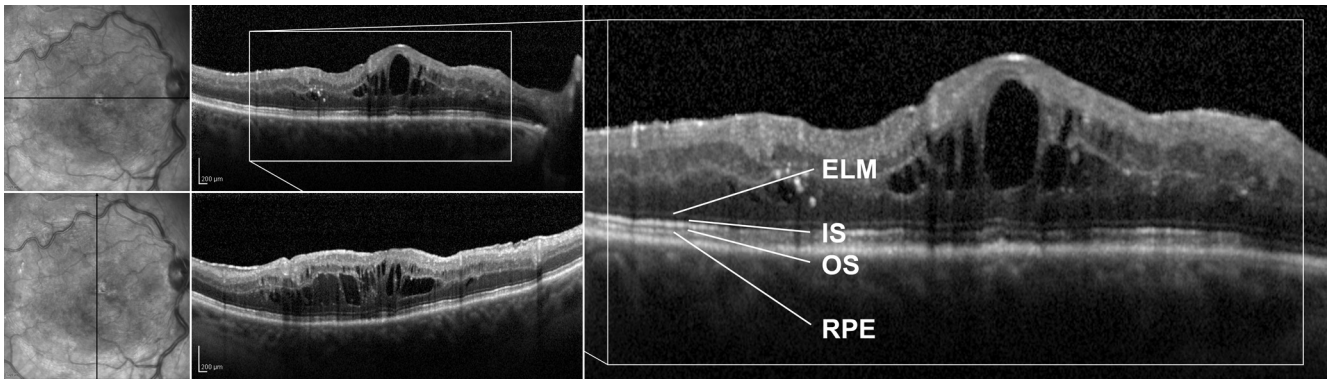

FIGURE 1. Female patient (TK, 69 years old). Right eye with cystoid edema from CRVO. BCVA was 33 letters at baseline. SD-OCT images show intact ELM, intact photoreceptor IS and OS, and intact RPE in the horizontal and vertical scan. This patient was included in group 1 because of the intact outer retina complex.

treatment.[10–13] Therefore, it is important to identify predictive factors for visual gain after anti-VEGF therapy. The aim of our study was to analyze whether preserved outer retinal layers, especially the integrity of the ELM, visualized in SD-OCT images have a predictive value for favorable short-term visual outcome 4 weeks after anti-VEGF treatment for ME secondary to CRVO. We observed rapid and clinically relevant improvement of BCVA after the first anti-VEGF injection, depending on the integrity of the outer retinal layers.

The prognostic value of other factors such as age, BCVA at baseline, and gender in patients with ME caused by CRVO was analyzed in several other studies. These studies[14,15] identified young age and good BCVA at baseline as favorable prognostic signs. Age has proved to be a risk factor for CRVO[3,16] but also a prognostic factor for response to anti-VEGF therapy in CRVO patients. The duration of retinal vessel occlusion might be an additional factor for visual outcome. The integrity of the outer retinal layers may correlate with the duration of macular edema. However, since the exact duration of the disease is difficult to determine, we have not included this factor in our analysis.

Some studies report initial CRT as a predictive factor for the short- and long-term response to anti-VEGF treatment.[13] In our study, we found no correlation between initial CRT and visual outcome, possibly because CRT is not related to the integrity of the retinal layers. Even after the complete resolution of ME, visual outcome can be poor if the integrity of the retinal layer was disturbed.

It will be important to look into details of persistent ME secondary to CRVO. Some studies evaluated the role of VEGF level and the severity and persistence of ME.[16–19] Several authors have postulated a positive correlation between VEGF level and severity of ME.[17–19] Another explanation for persistent macular edema could be the upregulation of VEGF receptors.[19] A rebound phenomenon was reported by Matsumoto et al.[20] in some patients, with worsening of ME after treatment with bevacizumab. Randomized clinical trials are needed for further evaluation of this.

Limiting factors of our study included the small number of patients, the short follow-up, the missing differentiation between ischemic and nonischemic CRVO, and the lack of analysis of a correlation between the extent and location of the disturbed outer retinal layers and the visual acuity response. Ischemia grade might also have an impact on visual outcome, but it is often difficult to analyze because of extensive bleeding at baseline[21] and because later the conversion of nonischemic vein occlusion to ischemic occlusion may occur.[14]

Despite an increasing body of evidence for the efficacy of anti-VEGF treatment for ME secondary to CRVO, an optimal treatment regime is yet to be determined. Indications for treatment should not only be based on deterioration of BCVA and CRT but also on morphologic changes in the retina. In the present study, visual acuity in patients with disturbed ELM did not increase after a single anti-VEGF injection. This does not exclude that some patients may be late responders, with visual acuity increasing after repeated anti-VEGF injections. Therefore, even in patients with disturbed outer retinal layers, anti-VEGF therapy should be considered.

Future studies should investigate the correlation of visual outcome between the extent and location of the disturbances

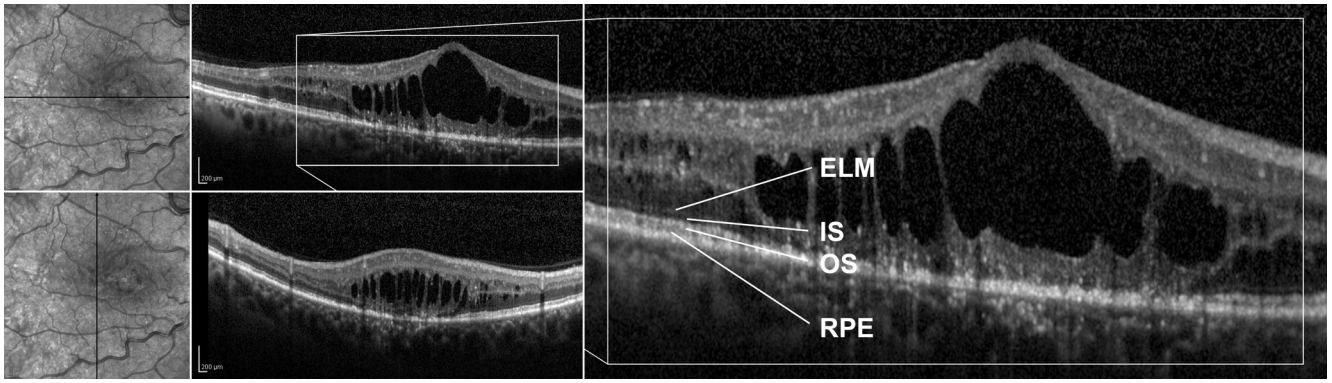

FIGURE 2. Female patient (JP, 59 years). Right eye with hard exudates and cystoid edema from CRVO. BCVA was 22 letters at baseline. SD-OCT images show cystoid edema, disturbances in the outer retina complex with involvement of ELM, IS/OS, and irregular RPE in the horizontal and vertical scan. This patient was included in group 2 because of disturbances in the outer retina complex.

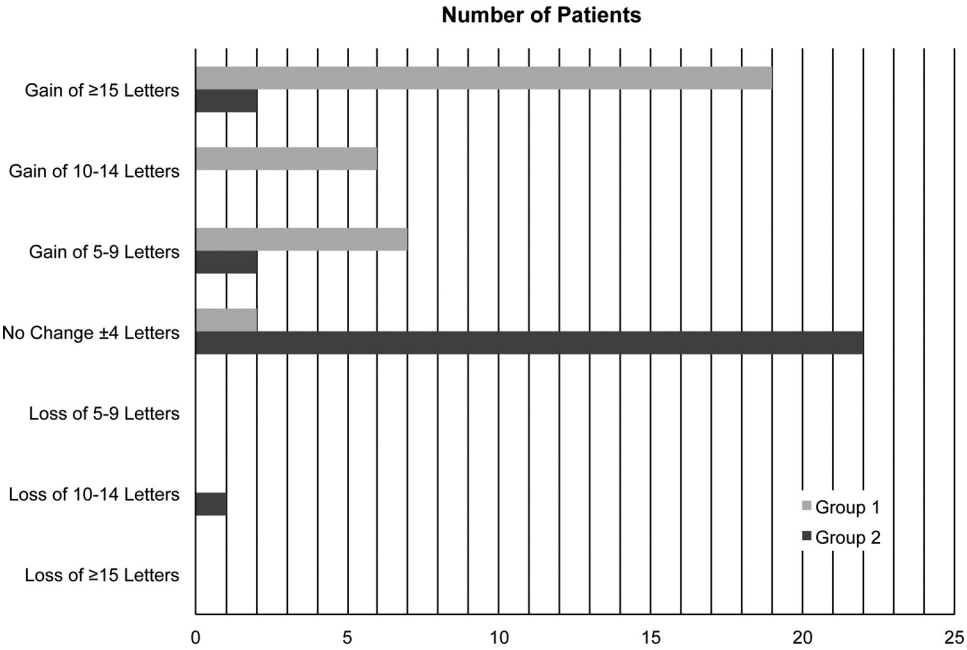

FIGURE 3. Comparing the changes in mean letter score between baseline and 4 weeks after treatment significant differences regarding the visual outcome, depending from the status of ELM, were found. Group 1, patients with intact ELM ($n = 34$). Group 2, patients with disturbances in the ELM ($n = 28$).

of the outer retinal layers and the influence of repeated anti-VEGF injections on visual acuity in patients with disturbed outer retinal layers.

Patients with ME in whom SD-OCT images demonstrate an intact outer limiting membrane have better outcomes after intravitreal anti-VEGF therapy than do patients with severely compromised outer retinal structures.

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