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

Ute E. K. Wolf-Schnurrbusch, Ramzi Ghanem, Simon P. Rothenbuehler, Volker Enzmann, Carsten Framme, and Sebastian Wolf

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-naïve 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. Vision loss results from macular edema (ME) because of the reduced blood perfusion and subsequent retinal hypoxia. 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, intravitreal steroids, surgical procedures, and, most recently, injection of anti-vascular endothelial-derived growth factor (VEGF) compounds. 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). 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-naïve 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 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; 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...
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.

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

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Mean ± SD (Range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years</td>
<td>67.1 ± 15.6 (18.5-89.4)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>39 (63)</td>
</tr>
<tr>
<td>Women</td>
<td>23 (37)</td>
</tr>
<tr>
<td>Days between diagnoses and injection, median ± SD (range)</td>
<td>22 ± 18 (1-72)</td>
</tr>
<tr>
<td>Letter score, mean ± SD (range)</td>
<td>41 ± 16 (0-69)</td>
</tr>
<tr>
<td>LogMar</td>
<td>-0.9</td>
</tr>
<tr>
<td>Subretinal fluid, n (%)</td>
<td>10 patients (16)</td>
</tr>
<tr>
<td>Intraretinal cysts, n (%)</td>
<td>59 patients (95)</td>
</tr>
<tr>
<td>Visible vitreoretinal traction, n (%)</td>
<td>5 patients (8)</td>
</tr>
<tr>
<td>Visible epiretinal gliosis, n (%)</td>
<td>10 patients (16)</td>
</tr>
<tr>
<td>CRT in μm, mean ± SD (range)</td>
<td>413 ± 168 (218-838)</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All Patients (n = 62)</th>
<th>Intact ELM (n = 54)</th>
<th>Disturbed ELM (n = 28)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean BCVA 4 weeks after first injection*</td>
<td>53 ± 17 (0-82)</td>
<td>61 ± 13 (18-82)</td>
<td>44 ± 18 (0-71)</td>
</tr>
<tr>
<td>LogMar</td>
<td>-0.6</td>
<td>-0.4</td>
<td>-0.8</td>
</tr>
<tr>
<td>Mean difference in letter score*</td>
<td>12 ± 13 (-13-52)</td>
<td>18 ± 12 letters (0-52)</td>
<td>4 ± 10 (-13-46)</td>
</tr>
</tbody>
</table>

* Data are shown as mean letters ± SD (range).
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 identified young age and good BCVA at baseline as favorable prognostic signs. Age has proved to be a risk factor for CRVO 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. 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. Several authors have postulated a positive correlation between VEGF level and severity of ME. Another explanation for persistent macular edema could be the upregulation of VEGF receptors. A rebound phenomenon was reported by Matsumoto et al. 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 and because later the conversion of nonischemic vein occlusion to ischemic occlusion may occur.

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.
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.

Acknowledgments

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References