Multivariate Analyses of Inflammatory Cytokines in Eyes with Branch Retinal Vein Occlusion: Relationships to Bevacizumab Treatment

Shuzo Kaneda, Dai Miyazaki, Sbin-ichi Sasaki, Keiko Yakura, Yuki Terasaka, Ken-ichiro Miyake, Yoshifumi Ikeda, Taisaku Funakoshi, Takashi Baba, Atsushi Yamasaki, and Yoshitsugu Inoue

PURPOSE. To characterize the differential expression of intraocular inflammatory cytokines in eyes with branch retinal vein occlusion (BRVO) and to assess their roles as prognostic determinants of BRVO.

METHODS. A prospective cohort study of 38 eyes with BRVO. Aqueous humor samples were collected just before the intravitreal injection of bevacizumab and were assessed for 18 cytokines, chemokines, and growth factors. For control, aqueous humor was collected from 28 eyes before cataract surgery.

RESULTS. In the aqueous of eyes with BRVO, the IL-23, IL-8, IL-6, IL-15, IL-12, and IL-17 levels were significantly higher than that in control eyes. Pretreatment visual acuity was significantly correlated with the concentrations of IL-8, IL-10, IL-2, IL-1β, IL-5, IL-6, IL-23, IL-4, MCP-1, IL-1α, IL-12, IL-13, IFN-γ, and IL-15. The pretreatment nonperfused area (NPA) was significantly correlated with the concentrations of IL-8, IL-2, MCP-1, and IL-6. Logistic regression analyses revealed significant associations between the BRVO and the concentrations of IL-8, IL-23, IL-12, IL-15, IL-10, IL-1β, and IL-13. IL-8 had the highest odds ratio (OR) and was significantly associated with NPA, central retinal thickness (CRT), and visual acuity. Bevacizumab treatment significantly improved visual acuity and CRT after 1 month. Refractoriness to bevacizumab (defined as CRT recovery 1 month after treatment by <90%) was significantly associated with the IL-12 level.

CONCLUSIONS. Of the induced cytokines in eyes with BRVO, IL-8 was the most significantly associated with the disease parameters of BRVO. IL-12 is the most likely a factor that blocks the effect of bevacizumab treatment. (www.umin.ac.jp/ctr number, UMIN000003854.) (Invest Ophtalmol Vis Sci. 2011; 52:2982–2988) DOI:10.1167/iovs.10-6299

In eyes with diabetic retinopathy and other retinal disorders including central retinal vein occlusions (CRVOs), the level of vascular endothelial growth factor (VEGF) in the vitreous and aqueous humor is significantly increased. Generally, anti-VEGF therapy is effective in treating ischemic eye diseases and age-related macular diseases.

Atherosclerotic vascular disorders are known to involve ischemic, inflammatory, vascular remodeling, and regenerative cascades. Each of these cascades is directed by inflammatory cytokines, chemokines, and growth factors that orchestrate the lymphocytes, macrophages, and bone marrow-derived endothelial progenitors. Retinal vein occlusion (RVO) is a vascular obstruction associated with atherosclerotic mechanisms. The disease process is considered to be caused by a combination of mechanical, ischemic, and inflammatory reactions. Thus, the pathogenesis and progression of RVO may be dictated or controlled by intraocular mediators of angiogenic and inflammatory processes.

However, our understanding of the relationship between these retinal disorders and the concentrations of the intraocular cytokines, including VEGF, remains limited. Relevant to this study, the results of earlier studies have suggested that the intravitreal concentrations of different cytokines are good indicators of these retinal diseases. A recent analysis of the cytokines in eyes with CRVO detected an elevation in the levels of VEGF, IL-6, IL-8, IL-10, IL-1β, and MCP-1, and platelet-derived growth factor (PDGF)-AA. However, the contribution of each cytokine to the disease parameters was not determined.

Branch retinal vein occlusion (BRVO) is a milder form of RVO, but prolonged retinal edema or nonperfusion of the retina after BRVO can significantly impair the visual prognosis. Earlier, the involvement of VEGF, IL-1α, IL-6, IL-8, and MCP-1 in BRVO was reported in different studies. Although evaluations of the cytokine milieu will greatly help our understanding of the pathogenesis of BRVO, current knowledge on the association of cytokines with BRVO is insufficient in view of the inflammatory milieu of BRVO.

The purpose of this study was to identify and evaluate the levels of different inflammatory cytokines, chemokines, and growth factors to the pathogenicity and prognosis of BRVO. Intravitreal injection of bevacizumab suppressed VEGF-related events in the diseased eyes. We reasoned that analyses of patients undergoing bevacizumab treatment would reveal the VEGF-related molecular signatures and relationships to the prognosis of the disease. To determine the complex relationship of cytokines and other parameters, we used multivariate logistic regression analyses to show a significant association of some of these factors with the disease parameters and determined their contributions to this disease and their processes. We shall show significant increases in the concentrations of IL-23, IL-8, IL-6, IL-15, IL-12, and IL-17 in eyes with BRVO. IL-8 had the highest significant odds ratio (OR) for BRVO and was significantly correlated with visual acuity, central retinal thick-
ness (CRT), and nonperfused area (NPA) size. Analysis of cases refractory to the bevacizumab treatment showed that IL-12 had a significant relative risk against a resolution of the retinal edema.

**METHODS**

**Subjects: Eligibility Criteria and Diagnosis**

This was a prospective study performed in the Division of Ophthalmology and Visual Science at Tottori University. The study protocol was approved by the Ethics Committee of the Tottori University, and the procedures used conformed to the tenets of the Declaration of Helsinki. Informed consent was obtained from all the participants.

Thirty-eight eyes with BRVO that were scheduled to undergo intravitreal injection of 1.25 mg bevacizumab (Genentech and Hoffmann-La Roche, Basel, Switzerland) were studied. Aqueous humor was collected just before the injection of bevacizumab. Criteria for the intravitreal injection of bevacizumab were macular edema involving the fovea, visual acuity (VA) >0.22 logarithm of minimum angle of resolution (logMAR) units, and persistent edema after laser coagulation. Exclusion criteria included neovascularization on the disc or elsewhere, rubecosis iridis, laser coagulation during the preceding 2 months, and intraocular surgery including cataract surgery in the study eye within 6 months of the planned injection of bevacizumab. Mean duration of the disease from the onset was 7.6 ± 2.0 months. Percentages of patients with a history of hypertension, diabetes mellitus, and laser photocoagulation were 44.7%, 13.2%, and 31.6%, respectively.

**Evaluation of Nonperfused Area**

Ophthalmoscopy and fluorescein angiography (FA) were performed to evaluate the degree of vascular leakage, NPA size, and neovascular complications. All diagnostic procedures followed a standardized protocol.

Fundus photographs were taken with a digital fundus camera (Topcon, Tokyo, Japan), and the NPA size and disc area were analyzed in the photographs with image editing software (Photoshop CS4; Adobe Systems Inc., San Jose, CA). To assess the degree of retinal ischemia, NPA size was divided by the disc area as performed in an earlier report.4

**Evaluation of Retinal Edema**

CRT was measured by spectral domain optical coherence tomography (3D-OCT-1000 MARK II; Topcon) before and 1 month after bevacizumab treatment to assess responsiveness of the edema to the bevacizumab treatment. The recovery rate was calculated by the following formula: Recovery = (pretreatment CRT − posttreatment CRT)/(pretreatment CRT − mean CRT of control group) × 100. Patients whose recovery rate was <90% were defined as refractory to treatment.

**Control Group**

Control aqueous samples were collected from 28 patients undergoing routine cataract surgery by limbal paracentesis, and the samples were stored frozen. Exclusion criteria were any type of retinal disease, uveitis, previous intraocular surgery, diabetes mellitus, use of immuno-suppressive drugs, and malignant tumor.

**Measurement of Cytokines and Growth Factors**

Samples were analyzed using chemiluminescence based-ELISA for high-sensitivity detection. A human cytokine-screen (Q-Plex; Quansys Biosciences, West Logan, UT) was used to measure concentrations of IL-1α, IL-1β, IL-2, IL-4, IL-5, IL-6, IL-8, IL-10, IL-12, IL-13, IL-15, IL-17, IL-23, tumor necrotizing factor (TNF)-α, lymphotoxin-α, and IFN-γ. MCP-1 and VEGF levels were measured with ELISA kits according to the manufacturers’ instructions (PeproTech, Rocky Hill, NJ; R&D Systems, Minneapolis, MN, respectively).

**Statistical Analysis**

Data are presented as the mean ± SEM. ANOVAs were used to evaluate statistical differences between groups. Spearman correlation analyses were used to determine the correlation between factors. Logistic regression analyses were carried out to compute the ORs and 95% confidence intervals.
Results

Thirty-eight eyes of 38 patients with BRVO who were scheduled for intravitreal injection of bevacizumab because of macular edema were studied. Twenty-eight eyes of 28 patients who were undergoing routine cataract surgery were studied as controls.

The mean age of the patients with BRVO was 67.1 ± 1.8 years, and it was 71.4 ± 1.8 years in the control patients (P > 0.05). The mean CRT of the eyes with BRVO was 561 ± 41 µm, which was significantly thicker than that of the control (166 ± 8 µm, P < 0.0001). VA in the eyes with BRVO was 0.62 ± 0.06 logMAR units before injection, which was significantly lower than that of the controls at 0.37 ± 0.07 logMAR units (P < 0.01).

Our analyses of the aqueous cytokine levels showed significantly higher concentrations of IL-23, IL-8, IL-6, IL-15, IL-12, and IL-17 in eyes with BRVO than in control eyes in a descending order (Fig. 1, Table 1).

Spearman correlation analyses showed that visual acuity was significantly correlated with the CRT before bevacizumab treatment (P < 0.005; r = 0.43, Spearman correlation analysis). When the relationship between the cytokine levels and visual acuity before bevacizumab treatment was assessed for eyes with BRVO, significant correlations were found between the levels of IL-8, IL-10, IL-1β, IL-5, IL-6, IL-4, MCP-1, IL-1α, IL-23, IL-12, IL-13, IFN-γ, and IL-15 and the visual acuity (P < 0.05 for all), with r = 0.45, 0.44, 0.39, 0.39, 0.37, 0.33, 0.33, 0.30, 0.29, 0.28, 0.25, and 0.23, respectively (Table 2).

Next, the relationship between cytokine level and CRT before bevacizumab treatment was assessed. Significant correlations were found between the levels of IL-8, IL-2, IL-6, and IL-1α and the CRT (P < 0.05), with r = 0.38, 0.35, 0.35, and 0.33, respectively (Table 2).

To understand the relationships among NPA size, CRT, and visual acuity in eyes with BRVO, we determined their correlations. Visual acuity and CRT before bevacizumab treatment were significantly correlated with NPA size, with r = 0.54 and 0.38 (P < 0.05, Spearman correlation analysis). When the relationships between cytokine levels and NPA size were assessed, significant correlations were found between IL-8, IL-2, MCP-1, and IL-6 levels and NPA size (P < 0.05), with r = 0.54, 0.48, 0.39, and 0.37, respectively (Table 2). Collectively, visual acuity, CRT, and NPA were reciprocally correlated, and the IL-8 level consistently had the highest correlation coefficient in these representative parameters in the eyes with BRVO.

We also assessed the relationship between each cytokine level and possible confounding factors: history of hypertension, diabetes mellitus, laser photocoagulation, and disease duration. When each cytokine level was compared with the presence or absence of hypertension, diabetes mellitus, or laser photocoagulation, none of the cytokine levels were significantly associated. Moreover, none of the cytokine levels were significantly correlated with disease duration (Spearman correlation analysis).

To further assess the contribution of each cytokine to BRVO, logistic regression analysis was used to differentiate eyes with BRVO from control eyes. ORs were calculated for the highest quartile of distribution of each variate, and ratios were compared with those in the lowest quartile group. Our analyses showed significantly higher ORs for IL-8, IL-23, IL-12, IL-15, IL-10, IL-1β, and IL-13 after adjusting for age, indicating these...
cytokine levels are good discriminators for BRVO (Table 3). Of these, IL-8 had the highest significant likelihood ratio as a discriminator (OR, 96.7; \( P < 0.0001 \)). The second-ranked cytokine was IL-23, a Th17-inducing cytokine, with an OR of 47.5 (\( P < 0.005 \)), and the third highest was IL-12, a Th1-type cytokine with an OR of 9.1 (\( P < 0.005 \)). Additionally, a regulatory cytokine, IL-10, and a canonical Th2-type cytokine, IL-13, also had significant ORs.

Intravitreal bevacizumab therapy significantly improved visual acuity and decreased CRT 1 month after injection (Figs. 2A, 2B). This clearly confirmed reports that VEGF contributes significantly to the pathophysiology of BRVO. When the effects of the cytokine levels were compared with those of VEGF, the IL-8 level had the highest correlation with VEGF (\( r < 0.0005; r = 0.40 \), Spearman correlation analysis).

Although our findings showed that intravitreal bevacizumab therapy was effective for retinal edema, we found a subpopulation of BRVO patients who were refractory to treatment. There were 11 of 35 eyes (31%) that were refractory, as defined as <90% recovery to the normal thickness at 1 month after bevacizumab treatment. Therefore, we sought to identify the exacerbating cytokine or cytokines by comparing the improved and refractory groups. Before bevacizumab treatment, there was no significant difference in CRT and NPA size between the improved and refractory groups (Figs. 2C, 2D).

We then compared the pretreatment cytokine levels of both groups (Fig. 2E). In the refractory group, the levels of IL-12 and IFN-\( \gamma \) were significantly higher than in the improved group (Fig. 2; \( P < 0.05 \)). VEGF levels were elevated in the refractory group, but the level was not significantly elevated.

### Table 2. Correlation of Cytokines and Clinical Parameters of BRVO by Spearman Correlation Analysis

<table>
<thead>
<tr>
<th>Cytokine</th>
<th>Correlation Coefficients</th>
<th>( P )</th>
<th>Central Retinal Thickness</th>
<th>Correlation Coefficients</th>
<th>( P )</th>
<th>Nonperfused Area/Disc</th>
<th>Correlation Coefficients</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-1( \alpha )</td>
<td>0.31</td>
<td>0.0044</td>
<td>0.33</td>
<td>0.0453</td>
<td>0.39</td>
<td>0.0035</td>
<td>0.58</td>
<td>0.0017</td>
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<tr>
<td>IL-1( \beta )</td>
<td>0.39</td>
<td>0.0035</td>
<td>0.35</td>
<td>0.0359</td>
<td>0.48</td>
<td>0.0037</td>
<td>0.62</td>
<td>0.0017</td>
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<tr>
<td>IL-2</td>
<td>0.43</td>
<td>&lt;0.0001</td>
<td>0.35</td>
<td>0.0035</td>
<td>0.48</td>
<td>0.0037</td>
<td>0.62</td>
<td>0.0017</td>
</tr>
<tr>
<td>IL-4</td>
<td>0.33</td>
<td>0.0028</td>
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<td></td>
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<td></td>
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<tr>
<td>IL-5</td>
<td>0.39</td>
<td>0.0004</td>
<td></td>
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<tr>
<td>IL-6</td>
<td>0.37</td>
<td>0.0006</td>
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<tr>
<td>IL-8</td>
<td>0.45</td>
<td>&lt;0.0001</td>
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<tr>
<td>IL-10</td>
<td>0.44</td>
<td>&lt;0.0001</td>
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<tr>
<td>IL-12</td>
<td>0.29</td>
<td>0.0086</td>
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<tr>
<td>IL-13</td>
<td>0.28</td>
<td>0.01</td>
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<tr>
<td>IL-15</td>
<td>0.23</td>
<td>0.0357</td>
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<tr>
<td>IL-23</td>
<td>0.30</td>
<td>0.0268</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>IFN-( \gamma )</td>
<td>0.25</td>
<td>0.0202</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>MCP-1</td>
<td>0.33</td>
<td>0.0028</td>
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</table>

Using this cohort of 11 eyes whose CRT recovery was incomplete, we determined whether IL-12 and IFN-\( \gamma \) were significantly associated with refractoriness by logistic regression analyses (Table 4). IL-12 had a significant association OR of 44.5 (95% CI, 1.5–1356.2; \( P < 0.05 \), after adjustments for age and IL-2) after the variables were statistically selected by stepwise regression for the highest quartile compared with the lowest quartile as reference. In contrast, IFN-\( \gamma \) did not demonstrate statistically significant OR by stepwise regression.

### Discussion

Our results provided strong evidence that elevated levels of different cytokines and growth factors are significantly associated with the development of BRVO. In addition, our results provided evidence about how these cytokines might modulate BRVO and affect the prognoses of eyes with BRVO.

Our ANOVAs of the levels of the different cytokines provided information on the specific cytokines that are involved in BRVO (Fig. 1); however, what specific roles they play in the disease processes remain undetermined. Logistic regression analyses of the induced cytokines provided information on the possible roles of the different cytokines. For example, the levels of IL-23, IL-8, IL-6, IL-15, IL-12, and IL-17 in the BRVO eyes were significantly different from the levels in healthy eyes (Table 2). Each had a different OR for eyes with BRVO (Table 3), irrespective of whether they were disease promoting or protective. We unexpectedly found that IL-8 had the highest OR, which is interesting because IL-8 is known to be a risk factor for age-related macular degeneration, as determined by an analysis of promoter polymorphisms.

Consistent with the earlier reports, we detected an increase in VEGF levels in BRVO eyes, but the increase was not significant. In contrast, eyes with CRVO had a significant increase of VEGF (unpublished observation, 2010), possibly because BRVO is a milder inducer of VEGF in patients with vascular occlusion. Importantly, our bevacizumab treatment significantly decreased the NPA and CRT and improved the visual acuity. Indeed, VEGF is a strong mediator of increasing vascular leakage leading to macular edema. Although the exact mechanism for the effectiveness of anti-VEGF treatment remains undetermined, our findings clearly indicate that VEGF is an important mediator of the pathogenesis of BRVO.

Previous studies of the cytokine in eyes with BRVO reported the induction of VEGF, IL-1\( \alpha \), IL-6, IL-8, and MCP-1, depending on reports. Although the sample size for the Yoshimura et al. study was smaller than ours, it also detected
elevated levels of IL-6, IL-8, and MCP-1. In contrast, we detected significant increases in IL-23, IL-8, IL-6, IL-15, IL-12, and IL-17 levels. Because the detected cytokines appeared limited to relatively abundant cytokine species in the earlier studies, the differences in the cytokine profiles might be attributed to the relatively lower sensitivity of their assay systems. Importantly, in BRVO, an unexpectedly greater impact on the inflammatory milieu appears to have occurred.
Retinal ischemia, vascular remodeling, and atherosclerotic diseases have been reported to activate inflammatory components. In the context of VEGF induction, IL-6 and IL-17 are strong stimuli for angiogenesis involving VEGF. IL-6 is the master inflammatory cytokine, and it induces numerous inflammatory cytokines directly or indirectly, which may explain the induction of the large number of cytokines in our analyses.

Earlier examinations on cytokines profile in eyes with BRVO were largely restricted to the elevation of each cytokine. However, we do not know whether the elevated cytokines may be therapeutically targeted based on the elevation. Thus, an important finding of our study was the comprehensive view of the associations of inflammatory cytokines with BRVO. We found that the IL-8 elevation had the highest OR and that it may thus serve as a useful discriminator of BRVO. Furthermore, IL-8 was significantly correlated with NPA size, CRT, visual acuity, and VEGF level. These findings suggest that IL-8 probably represented a VEGF-centered pathologic arm. When we estimated the relative risk of cytokine elevation for the refractory eyes, IL-8 was not significantly elevated and was no longer a significant relative risk factor. Treatment by bevacizumab is supposed to counteract the VEGF-dependent arm, supporting the role of IL-8 as a VEGF-related pathologic event. IL-8 is an inflammatory chemokine induced in the acute phase of injury and ischemia. IL-8 exerts its effect through CXCR2 by recruiting neutrophils and activating endothelial cells or macrophages, which serve as direct angiogenic factors. In vascular injury, CXCR2 is expressed on the monocytes that accumulate on the intima, on the regenerating vascular endothelial cells, and on bone marrow-derived endothelial progenitor cells. Moreover, IL-8 directly stimulates VEGF expression and the autocrine activation of VEGFR2 in vascular endothelial cells. This may explain why IL-8 had the highest OR and correlation coefficient with VEGF in eyes with BRVO. Thus, IL-8 appears to be involved in angiogenesis, endothelial cell binding, endothelial cell regeneration, endothelial wound healing, and vascular remodeling, presumably together with VEGF.

Generally, the induction of VEGF by ischemia is transient, and it is cleared from the local environment. In a BRVO model in rats, VEGF induction was transient and limited to the time of disease onset. Additionally, VEGF levels were shown to be lower when the duration of the RVO was longer. Considering different durations of BRVO and its moderate impact on the cytokine milieu, the presumable acute-phase mediator may not serve as a good discriminator or predictor of the development of BRVO, as was shown as a trend in elevation in our analysis and in that of another group.

Interestingly, we found significant elevations of IL-12 and IFN-γ in patients who were refractory to bevacizumab. IL-12 was found to be a good discriminator of BRVO, with the third highest OR. Thus, IL-12 may serve as a factor that reduces the effects of bevacizumab treatment. IL-12 is a key inducer of Th1-type cytokines (e.g., IFN-γ). In atherosclerotic plaques, IL-12 and IFN-γ are strongly expressed. Importantly, in atherothrombotic vascular diseases, prolonged inflammation and perturbed clearance of apoptotic cells lead to the development of atherosclerotic lesions and plaques. Prolonged production of IL-12 and IFN-γ would potentiate the Th1-biased chronic inflammatory responses, which involves activation of macrophages and dendritic cells. This leads to tissue and vascular injury. Together with its proinflammatory activity, IL-12 inhibits endothelial cell cycle and adhesion and triggers antiangiogenic pathways. Based on our detection of IL-12 as a significant factor for refractoriness to bevacizumab (Fig. 2), IL-12 appears to play a distinct role against VEGF. IL-12 may interfere with reperfusion and promote inflammatory responses.

NPA and CRT are important changes in the retinas of eyes with BRVO and may reflect the ischemic condition. IL-8, IL-6, and IL-2 levels were found to be correlated with both NPA size and CRT. Correlations for IL-8 and IL-2 were not expected and were new findings. The known functions of IL-8 in angiogenesis may well explain these findings.

IL-2 is a Th helper, lymphocyte-derived cytokine and has been shown to be elevated in ischemia and after an infarction. In myocardial infarctions in patients with angina, a persistent, long-term elevation of IL-2 and IL-10 has been reported. IL-2 is also induced in microglia after hypoxia. IL-6 is a proinflammatory cytokine and induces the expression of VEGF by vascular endothelial cells, and VEGF is a strong stimulator of vascular permeability and angiogenesis. IL-6 is induced in vascular endothelial cells by hypoxia, and it stimulates angiogenesis by circulating blood-derived endothelial progenitor cells.

The fourth most significantly elevated cytokine in eyes with BRVO was IL-15, which has not been reported to be involved in BRVO. The level of IL-15 was significantly correlated with visual acuity, and its association with BRVO had a significant OR (Tables 1, 2). IL-15 can stimulate endothelial cells and promote angiogenesis. IL-15 also induces the expression of VEGF by vascular endothelial cells, and VEGF is a strong stimulator of vascular permeability and angiogenesis. IL-6 is induced in vascular endothelial cells by hypoxia, and it stimulates angiogenesis by circulating blood-derived endothelial progenitor cells.

The Th17 lymphocytes, characterized by IL-17 secretion, have been well recognized to be involved in proinflammatory responses and autoimmunity. IL-23, secreted from antigen-presenting cells, is a Th17 lymphocyte-related cytokine and induces IL-17. We detected significant elevations of IL-17 and IL-23 in BRVO, and IL-23 had a significant OR. IL-17 induces the production of an array of inflammatory cytokines and chemokines including IL-8, MCP-1, and IL-6, which were elevated in our BRVO patients (Fig. 1). IL-17 also enhances the mitogenic activity of VEGF for vascular endothelial cells and may promote angiogenesis and vascular leakage.

MCP-1 level was significantly correlated with NPA size: the highest levels were found in the aqueous humor, with a trend toward elevation in eyes with BRVO (Fig. 1). MCP-1 is a canonical cytokine that recruits and activates monocytes and macrophages. During vascular remodeling, MCP-1 serves in the inflammatory arm and induces monocyte infiltration and stimulates proliferation of smooth muscle cells. In vascular injury, MCP-1 is rapidly upregulated and contributes to neointimal formation, presumably by increased macrophage infiltration. Thus, the probable role of MCP-1 in vascular pathology may involve regeneration.

Results of an earlier study showed significant correlations of cytokine levels in vitreous and aqueous humor. However, cytokine levels in the aqueous are affected by its diffusion rate and its binding to extracellular matrix. We acknowledge that aqueous fluid may not reflect actual findings in the retina. However, its accessibility is an advantage when a larger sample...
size is needed to increase statistical power in more detailed analyses.

In summary, our data showed that many inflammatory- and atherosclerotic-related cytokines are upregulated during the development of BRVO. The levels and kinds of cytokines provide information on the role they play in the prognosis of BRVO. Considering the fact that BRVO has not been associated with a gene polymorphism, changes in the inflammatory cytokine production may likely develop independently of the etiology, or the etiology of BRVO might be related to environmental or lifestyle-related factors. Collectively, better understanding of the disease using the measurements of aqueous cytokines or chemokines may help improve the prognosis for patients with BRVO.

Acknowledgments

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References