Association of Inflammatory Factors With Macular Edema in Branch Retinal Vein Occlusion

Hidetaka Noma, MD; Tatsuya Mimura, MD; Shuichiro Eguchi, MD

Objective: To evaluate the association between vitreous fluid levels of inflammatory factors and macular edema in patients with branch retinal vein occlusion (BRVO).

Methods: In 39 patients with BRVO and macular edema and 21 individuals with idiopathic macular hole (MH) serving as controls, vitreous fluid samples were obtained during vitrectomy surgery, and the levels of vascular endothelial growth factor (VEGF), soluble VEGF receptor 2 (sVEGFR-2), soluble intercellular adhesion molecule 1 (sICAM-1), interleukin 6 (IL-6), monocyte chemotactic protein 1 (MCP-1), pentraxin 3 (PTX3), and pigment epithelium-derived factor (PEDF) were measured by enzyme-linked immunosorbent assay. Macular edema was examined by optical coherence tomography.

Results: Vitreous fluid levels of sVEGFR-2, VEGF, sICAM-1, IL-6, MCP-1, and PTX3 were significantly higher in the patients with BRVO than in those with MH; however, the PEDF level was significantly lower in the BRVO group. Vitreous fluid levels of all 7 factors were significantly correlated with the retinal thickness at the central fovea. There were also significant correlations of sVEGFR-2 with sICAM-1, IL-6, MCP-1, and PTX3 but no correlation with VEGF. However, there were significant correlations of VEGF with sICAM-1, IL-6, MCP-1, and PEDF in the BRVO group.

Conclusions: Vitreous fluid levels of sVEGFR-2, VEGF, sICAM-1, IL-6, MCP-1, PTX3, and PEDF are strongly correlated with retinal vascular permeability and the severity of macular edema in patients with BRVO. These findings may be useful for understanding macular edema and developing new treatments for BRVO.

3-month mortality after acute myocardial events.\textsuperscript{13} Long pentraxin 3 is an acute-phase protein that is involved in innate immunity and inflammation. Pentraxins are a family of acute response proteins comprising 3 members—C-reactive protein, serum amyloid P, and PTX3—and these proteins are classic acute-phase reactants that closely reflect the level of inflammatory activity.\textsuperscript{14,15} Long pentraxin 3 is induced by cytokines and is produced mainly by vascular endothelial cells, fibroblasts, and cells in some other extrahepatic tissues.\textsuperscript{14,16-20} Unlike the other 2 family members that are synthesized primarily in the liver,\textsuperscript{21,22} long PTX3 is expressed in various extrahepatic tissues, including PTX3 (range, 3-11 months). Clinical and laboratory characteristics were obtained from the 39 patients enrolled. The indications for PPV were (1) clinically detectable diffuse macular edema or cystoid macular edema in patients with BRVO and macular edema. Seventy-two consecutive patients with BRVO (19 men and 20 women) was 69.2 (9.6) years, and the control group (9 men and 12 women) was aged 68.8 (8.4) years. \textsuperscript{.88} 

Table 1. Clinical and Laboratory Characteristics of the BRVO and MH Groups

<table>
<thead>
<tr>
<th>Variable</th>
<th>BRVO Group</th>
<th>MH Group</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of participants\textsuperscript{a}</td>
<td>39</td>
<td>21</td>
<td>.66</td>
</tr>
<tr>
<td>Sex, No.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>20</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>19</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>Age, mean (SD), y</td>
<td>69.2 (9.6)</td>
<td>68.8 (8.4)</td>
<td>.88</td>
</tr>
<tr>
<td>Blood pressure, mean (SD), mm Hg</td>
<td>134 (14)</td>
<td>121 (11)</td>
<td>.001</td>
</tr>
<tr>
<td>Systolic</td>
<td>78 (8)</td>
<td>74 (8)</td>
<td>.07</td>
</tr>
<tr>
<td>Diastolic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension, No.</td>
<td>22</td>
<td>3</td>
<td>.002</td>
</tr>
<tr>
<td>Hyperlipidemia, No.</td>
<td>12</td>
<td>4</td>
<td>.33</td>
</tr>
<tr>
<td>Duration of BRVO, mean (SD), mo</td>
<td>5.1 (2.4)</td>
<td>. . . . .</td>
<td></td>
</tr>
</tbody>
</table>
| BRVO, branch retinal vein occlusion; ellipsis, not applicable; MH, macular hole. \textsuperscript{a}Number of participants with data.

It has also been reported\textsuperscript{9,20} that PPV contributes to an increase in oxygen tension in the inner retina. If retinal oxygen tension increases after PPV, macular edema would be lessened for several reasons. First, an increase in oxygen tension would reduce VEGF production and thus decrease vascular permeability. Second, an increase in oxygen tension would alleviate autoregulatory arteriolar vasodilation and thus reduce the hydrostatic pressure in the retinal capillaries and venules. This would decrease water flux from the vascular compartment to the tissue compartment and reduce edema according to the Starling law. Finally, PPV reduces the intraocular levels of various other inflammatory factors in addition to VEGF,\textsuperscript{10} and this may be another mechanism by which it alleviates macular edema in patients with BRVO. In fact, it has been reported\textsuperscript{29,30} that PPV improves both functional and tomographic outcomes in patients with BRVO and macular edema. Accordingly, we performed PPV in patients with clinically detectable diffuse macular edema or cystoid macular edema more than 3 months after the onset of BRVO.

Thirty-three of the 72 patients were excluded because of preoperative ocular surgery or intravitreal injection of anti-VEGF agents or triamcinolone acetonide in 23 patients, diabetic retinopathy in 2 patients, previous retinal photocoagulation in 7 patients, and a history of ocular inflammation or vitreoretinal disease in 1 patient. Patients with intravitreal injection of anti-VEGF agents or triamcinolone acetonide were excluded because such treatment could influence vitreous fluid levels of inflammatory factors. Vitreous fluid samples were also obtained from 21 patients with nonischemic ocular diseases as a control group (MH group). None of the patients in the MH group had proliferative vitreoretinopathy. The mean (SD) age of the BRVO group (19 men and 20 women) was 69.2 (9.6) years, and the control group (9 men and 12 women) was aged 68.8 (8.4) years. The mean duration of BRVO was 5.1 (2.4) months (range, 3-11 months). Clinical and laboratory characteristics of the BRVO and MH groups are shown in Table 1.

FUNDUS FINDINGS

Both preoperative and operative fundus findings were recorded for each participant. A masked grader (H.N.) independently assessed ischemic retinal vascular occlusion by examining fluorescein angiograms. The ischemic region of the retina was measured with the public domain Scion Image program (Scion Corp), as reported previously.\textsuperscript{6,10} On digital fundus photo-
longer isoforms are cell associated. Each assay was performed
to detect 2 of the 4 VEGF isoforms (VEGF121 and VEGF165), prob-
ably because these 2 shorter isoforms are secreted and the 2
longer isoforms are cell associated. Each assay was performed
according to the manufacturer’s instructions.

tographs, the disc area was outlined with a cursor and then mea-
sured, and the same was done for the nonperfused area.
The severity of retinal ischemia was assessed as the nonperfused area
divided by the disc area.

Optical coherence tomography was performed in each par-
ticipant within 1 week before PPV (Zeiss-Humphrey Ophthal-
mic Systems). The thickness of the central fovea was defined
as the distance between the inner limiting membrane and the
retinal pigment epithelium (including any serous retinal de-
tachment) and was automatically measured by computer soft-
ware. The thickness of the central fovea was defined
as the distance between the inner and outer neurosensory retinal surfaces,26 and the se-
tivity of macular edema was graded from the measured retinal
thickness.

SAMPLE COLLECTION

Samples of undiluted vitreous fluid (0.5-1.0 mL) were col-
clected at the start of PPV by aspiration into a 1-mL syringe
attached to the vitreous cutter before the intravitreal infusion of
balanced salt solution was begun. The vitreous samples were
collected at the start of PPV by aspiration into a 1-mL syringe af-
fter which aliquots were stored at

Vitreous fluid levels of VEGF, sICAM-1, IL-6, MCP-1, and
PTX3 were measured in vitreous samples from the same eye
immediately transferred into sterile tubes and were rapidly fro-
messed, and the same was done for the nonperfused area. The

<table>
<thead>
<tr>
<th>Variable</th>
<th>Median (Interquartile Range)</th>
<th>BRVO Group</th>
<th>MH Group</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>sVEGFR-2</td>
<td>pg/mL</td>
<td>1500 (1083-2035)</td>
<td>1020 (721-1343)</td>
<td>.002</td>
</tr>
<tr>
<td>VEGF</td>
<td>pg/mL</td>
<td>229 (33.9-153)</td>
<td>15.6 (15.6-31.2)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>sICAM-1</td>
<td>ng/mL</td>
<td>8.20 (5.33-15.6)</td>
<td>4.50 (3.60-6.55)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>IL-6</td>
<td>pg/mL</td>
<td>10.7 (5.53-29.0)</td>
<td>1.00 (0.50-1.18)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>MCP-1</td>
<td>pg/L</td>
<td>1190 (747-1993)</td>
<td>458 (375-636)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>PTX3</td>
<td>ng/mL</td>
<td>0.86 (0.50-1.62)</td>
<td>0.50 (0.50-0.81)</td>
<td>.01</td>
</tr>
<tr>
<td>PEDF</td>
<td>ng/mL</td>
<td>25.6 (8.14-40.7)</td>
<td>59.9 (25.0-101)</td>
<td>.005</td>
</tr>
</tbody>
</table>

Abbreviations: BRVO, branch retinal vein occlusion; IL-6, interleukin 6; MCP-1, monocyte chemotactic protein 1; MH, macular hole; PEDF, pigment
epithelium-derived factor; PTX3, pentraxin 3; sICAM-1, soluble intercellular
adhesion molecule 1; sVEGFR-2, soluble vascular endothelial growth factor
(VEGF) receptor 2.

Table 3. Correlation of Vitreous Factors
With the Nonperfused Area and Retinal Thickness

<table>
<thead>
<tr>
<th>Variable</th>
<th>Nonperfused Area</th>
<th>Retinal Thickness</th>
</tr>
</thead>
<tbody>
<tr>
<td>sVEGFR-2</td>
<td>r</td>
<td>P Value</td>
</tr>
<tr>
<td>VEGF</td>
<td>0.77</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>sICAM-1</td>
<td>0.36</td>
<td>.02</td>
</tr>
<tr>
<td>IL-6</td>
<td>0.46</td>
<td>.004</td>
</tr>
<tr>
<td>MCP-1</td>
<td>0.52</td>
<td>.001</td>
</tr>
<tr>
<td>PTX3</td>
<td>0.37</td>
<td>.02</td>
</tr>
<tr>
<td>PEDF</td>
<td>-0.39</td>
<td>.02</td>
</tr>
</tbody>
</table>

Abbreviations: See Table 2; r, correlation coefficient.

STATISTICAL ANALYSIS

Analyses were performed with commercial software (SAS, ver-
sion 9.1; SAS Institute Inc). A t test was used to compare nor-
mally distributed unpaired continuous variables between the
2 groups, and the Mann-Whitney test was used for variables
with a skewed distribution. The y2 test or Fisher exact test
was used to compare discrete variables. Differences between the
median plasma and vitreous levels were assessed with the Wil-
coxon single rank test. To examine relationships among the vari-
ables, Spearman rank order correlation coefficients or Pearson
correlation coefficients were calculated. Statistical signifi-
cance was set at P < .05, with 2-tailed values.

The vitreous fluid concentration of sVEGFR-2 (median [in-
terquartile range]) was significantly higher in the BRVO
group (1500 pg/mL [1083-2035]) than in the MH group
(1020 pg/mL [721-1343]; P = .002) (Table 2). The vitreous fluid concentration of VEGF was significantly higher in the BRVO group (229 pg/mL [33.9-1353]) compared with the MH group (15.6 pg/mL [15.6-31.2]; P < .001) (Table 2). Likewise, vitreous sICAM-1 levels were significantly higher in the BRVO group (8.20 ng/mL [5.33-15.6]) than in the MH group (4.50 ng/mL [3.60-5.65]; P < .001) (Table 2). Furthermore, the vitreous level of IL-6 was significantly higher in the BRVO group (10.7 pg/mL [5.53-29.0]) than in the MH group (1.00 pg/mL [0.50-1.18]; P < .001), as was the vitreous level of MCP-1 (1190 pg/mL [747-1993] vs 458 pg/mL [375-636]; P < .001) and the vitreous level of PTX3 (0.86 ng/mL [0.50-1.62] vs 0.50 ng/mL [0.50-0.81]; P = .01) (Table 2). In contrast, the vitreous fluid level of PEDF was significantly lower in the BRVO group (25.6 ng/mL [8.14-40.7]) than in the MH group (59.9 ng/mL [25.0-101]; P = .005) (Table 2).

The vitreous fluid levels of VEGF, sICAM-1, IL-6, MCP-1, and
PTX3 were significantly correlated with the nonperfused
area of the retina in the BRVO group (r = 0.77, P < .001; r = 0.36, P = .02; r = 0.46, P = .004; r = 0.52, P = .001; and r = 0.37, P = .02, respectively) (Table 3). Conversely, the vitreous fluid level of PEDF showed a significant negative correlation with the nonperfused area in the BRVO group (r = −0.39, P = .02) (Table 3). However, the vitreous fluid level of sVEGFR-2 was not significantly correlated with the nonperfused area in this
group (r = 0.19, P = .25) (Table 3).

RESULTS

MEASUREMENT OF INFLAMMATORY
AND ANTI-INFLAMMATORY FACTORS

The levels of VEGF, sVEGFR-2, sICAM-1, IL-6, MCP-1, and
PTX3 were measured in vitreous samples from the same eye
and in plasma samples by enzyme-linked immunosorbent as-
say, using kits for human VEGF, sVEGFR-2, IL-6, MCP-1, and
PTX3 (R&D Systems); sICAM-1 (Bender Med Systems); and
PTX3 (Perseus Proteomics Inc).8,10,33 Similarly, levels of anti-
flammatory PEDF were measured in vitreous samples with a
human PEDF sandwich enzyme-linked immunosorbent as-
say kit (Chemicon International).9 The VEGF kit was able to
detect 2 of the 4 VEGF isoforms (VEGF121 and VEGF165), prob-
ably because these 2 shorter isoforms are secreted and the 2
longer isoforms are cell associated. Each assay was performed
according to the manufacturer’s instructions.

Vitreous fluid levels of VEGF, sICAM-1, IL-6, MCP-1, and
PTX3 were significantly correlated with the nonperfused
area of the retina in the BRVO group (r = .77, P < .001; r = .38, P = .02; r = .46, P = .005; r = .52, P = .001; and r = .37, P = .02, respectively) (Table 3). Conversely, the vitreous fluid level of PEDF showed a significant negative correlation with the nonperfused area in the BRVO group (r = −.39, P = .02) (Table 3). However, the vitreous fluid level of sVEGFR-2 was not significantly correlated with the nonperfused area in this group (r = 0.19, P = .25) (Table 3).
Vitreous fluid levels of sVEGFR-2, VEGF, sICAM-1, IL-6, MCP-1, PTX3, and PEDF were significantly correlated with the retinal thickness at the central fovea according to simple linear regression analysis \( (r = 0.36, P = .02; r = 0.47, P = .003; r = 0.56, P < .001; r = 0.41, P = .01; r = 0.63, P < .001; r = 0.39, P = .02; \) and \( r = -0.36, P = .02 \)) (Table 3).

In the BRVO group, there were significant correlations between the vitreous fluid level of sVEGFR-2 and the levels of sICAM-1, IL-6, MCP-1, and PTX3 \( (r = 0.76, P < .001; r = 0.63, P < .001; r = 0.69, P < .001; \) and \( r = 0.66, P < .001 \)) (Table 4). There were also significant correlations between the vitreous fluid level of VEGF and the levels of sICAM-1, IL-6, MCP-1, and PEDF in the BRVO group \( (r = 0.34, P = .03; r = 0.41, P = .01; r = 0.46, P = .004; \) and \( r = -0.33, P = .04 \)); and \( r = 0.66, P < .001 \) (respectively) (Table 4). Furthermore, there was a significant correlation between the vitreous fluid level of sICAM-1 and the levels of IL-6, MCP-1, and PTX3 \( (r = 0.63, P < .001; r = 0.66, P < .001; \) and \( r = 0.64, P < .001 \)) (respectively) (Table 4). Moreover, there was a significant correlation between the vitreous fluid level of VEGF and the levels of sICAM-1, IL-6, MCP-1, and PTX3 (Table 3); and \( r = 0.12, P = .44; r = 0.03, P = .87; r = -0.10, P = .52; \) and \( r = 0.04, P = .82 \) (respectively) (Table 4), as well as a significant correlation between MCP-1 and PTX3 or PEDF \( (r = 0.53, P < .001; \) and \( r = -0.39, P = .02 \)) (respectively) (Table 4). In contrast, there was no significant correlation between the vitreous levels of sVEGFR-2 and VEGF \( (r = 0.14, P = .38) \) or between the vitreous levels of VEGF and PTX3 in the BRVO group \( (r = 0.23, P = .19) \) (Table 4). There were also no significant correlations between the vitreous fluid level of PEDF and the levels of sVEGFR-2, sICAM-1, IL-6, and PTX3 in the BRVO group \( (r = -0.12, P = .44; r = 0.03, P = .87; r = -0.10, P = .52; \) and \( r = 0.04, P = .82 \)) (respectively) (Table 4).

In the BRVO group, the vitreous fluid levels of VEGF, IL-6, and MCP-1 were significantly higher (all \( P < .001 \)) than the plasma levels of these molecules \( (18.1 \text{ pg/mL} [15.6-44.1], 0.59 \text{ pg/mL} [0.35-0.98], \) and \( 142 \text{ pg/mL} [117-167], \) respectively), whereas the vitreous levels of sVEGFR-2, sICAM-1, and PTX3 were significantly lower (all \( P < .001 \)) than their plasma levels \( (6750 \text{ pg/mL} [5895-8245], \) 423 ng/mL [332-508], and 3.66 ng/mL [2.66-5.11], respectively).

<table>
<thead>
<tr>
<th>Variable</th>
<th>sVEGFR-2</th>
<th>VEGF</th>
<th>sICAM-1</th>
<th>IL-6</th>
<th>MCP-1</th>
<th>PTX3</th>
<th>PEDF</th>
</tr>
</thead>
<tbody>
<tr>
<td>sVEGFR-2</td>
<td>( r = 0.14 ), ( P = .38 )</td>
<td>( r = 0.76 ), ( P &lt; .001 )</td>
<td>( r = 0.63 ), ( P &lt; .001 )</td>
<td>( r = 0.69 ), ( P &lt; .001 )</td>
<td>( r = 0.66 ), ( P &lt; .001 )</td>
<td>( r = 0.64 ), ( P &lt; .001 )</td>
<td>( r = 0.12 ), ( P = .44 )</td>
</tr>
<tr>
<td>VEGF</td>
<td>( r = 0.34 ), ( P = .03 )</td>
<td>( r = 0.41 ), ( P = .01 )</td>
<td>( r = 0.46 ), ( P = .004 )</td>
<td>( r = 0.66 ), ( P &lt; .001 )</td>
<td>( r = 0.64 ), ( P &lt; .001 )</td>
<td>( r = 0.65 ), ( P = .01 )</td>
<td>( r = 0.41 ), ( P = .01 )</td>
</tr>
<tr>
<td>sICAM-1</td>
<td>( r = 0.63 ), ( P &lt; .001 )</td>
<td>( r = 0.66 ), ( P &lt; .001 )</td>
<td>( r = 0.66 ), ( P &lt; .001 )</td>
<td>( r = 0.64 ), ( P &lt; .001 )</td>
<td>( r = 0.65 ), ( P = .01 )</td>
<td>( r = 0.64 ), ( P &lt; .001 )</td>
<td>( r = 0.64 ), ( P &lt; .001 )</td>
</tr>
<tr>
<td>IL-6</td>
<td>( r = 0.70 ), ( P &lt; .001 )</td>
<td>( r = 0.66 ), ( P &lt; .001 )</td>
<td>( r = 0.66 ), ( P &lt; .001 )</td>
<td>( r = 0.64 ), ( P &lt; .001 )</td>
<td>( r = 0.65 ), ( P = .01 )</td>
<td>( r = 0.64 ), ( P &lt; .001 )</td>
<td>( r = 0.64 ), ( P &lt; .001 )</td>
</tr>
<tr>
<td>MCP-1</td>
<td>( r = 0.53 ), ( P &lt; .001 )</td>
<td>( r = 0.66 ), ( P &lt; .001 )</td>
<td>( r = 0.66 ), ( P &lt; .001 )</td>
<td>( r = 0.64 ), ( P &lt; .001 )</td>
<td>( r = 0.65 ), ( P = .01 )</td>
<td>( r = 0.64 ), ( P &lt; .001 )</td>
<td>( r = 0.64 ), ( P &lt; .001 )</td>
</tr>
<tr>
<td>PTX3</td>
<td>( r = 0.53 ), ( P &lt; .001 )</td>
<td>( r = 0.66 ), ( P &lt; .001 )</td>
<td>( r = 0.66 ), ( P &lt; .001 )</td>
<td>( r = 0.64 ), ( P &lt; .001 )</td>
<td>( r = 0.65 ), ( P = .01 )</td>
<td>( r = 0.64 ), ( P &lt; .001 )</td>
<td>( r = 0.64 ), ( P &lt; .001 )</td>
</tr>
</tbody>
</table>

| Abbreviations: See Table 2; \( r \), correlation coefficient. |
sine phosphorylation of phospholipase Cγ,37-39 which in turn increases the intracellular levels of inositol 1,4,5-triphosphate and diacylglycerol. Inositol 1,4,5-triphosphate increases the intracellular calcium level by promoting efflux of calcium from the endoplasmic reticulum. This increase in intracellular calcium stimulates sphingosine kinase to produce sphingosine 1-phosphate,40 which then activates protein kinase C (PKC). Activated phospho-factor cylglycerol, and activated PKC is a strong activator of nuclear factor κB (NF-κB).41 There is ample evidence that NF-κB promotes the transcription of inflammatory factors (including ICAM-1, IL-6, and MCP-1).42-47 Nuclear factor-κB is found in almost all cell types and is involved in cellular responses to stimuli such as stress, proinflammatory gene expression (including cytokines, adhesion molecules, and chemokines), free radicals, UV irradiation, and bacterial or viral antigens in addition to its central role in the immune response.48-50 It has also been reported51,52 that VEGF, via the VEGFR-2–PKC axis, induces the production of proinflammatory cytokines (including IL-6 and MCP-1) in endothelial cells. Thus, VEGF promotes the expression of inflammatory factor messenger RNAs (including ICAM-1, IL-6, and MCP-1), mainly through the activation of PKC and NF-κB, indicating that VEGF induces the expression of inflammatory proteins by vascular endothelial cells through binding to VEGFR-2. This is supported by reports53,54 that a specific VEGF-2 antagonist blocks VEGF-induced expression of inflammatory factors (including ICAM-1, IL-6, and MCP-1) and also blocks activation of NF-κB by VEGF. Expression of the PTX3 gene also requires the activation of NF-κB.55 In addition, Souza et al56 reported that NF-κB activation was significantly suppressed in PTX3-deficient mice. Taken together with our results, these reports suggest that the vitreous level of sVEGF-2 influences various inflammatory factors (including ICAM-1, IL-6, MCP-1, and PTX3) in patients with BRVO and macular edema. On the other hand, the vitreous level of sVEGF-2 may be regulated independently of VEGF, although the VEGF–VEGFR-2 signaling pathway is considered essential for controlling vascular permeability.57-59 The VEGF is upregulated by hypoxia through hypoxia-inducible factor 1α,60 which is another transcription factor that regulates genes responding to hypoxia.61 Vascular endothelial growth factor may act via an independent pathway to promote the retinal changes that occur in BRVO; therefore, additional studies are required to identify the mechanism. Differences in the activation of various transcription factors may determine the severity of ocular ischemic and inflammatory changes.

Considering our results, as well as the balance between VEGF and inflammatory cytokines, we should select treatment with anti-VEGF agents (to reduce the level of free VEGF) or triamcinolone acetonide (with a broad spectrum of action, as appropriate). Because the aqueous level of VEGF is significantly correlated with the vitreous level of VEGF,62 measuring the concentrations of various molecules in aqueous humor by enzyme-linked immunosorbent assay or multiplex bead analysis could help with the selection of treatment between anti-VEGF agents, triamcinolone acetonide, or combined therapy. In addition, upregulation of inflammatory factors may be dependent on VEGFR-2 because there were significant correlations between the vitreous fluid level of sVEGFR-2 and the vitreous levels of 4 inflammatory factors (sICAM-1, IL-6, MCP-1, and PTX3) in our patients with BRVO and macular edema. Accordingly, multiple inflammatory factors could be inhibited by an antibody targeting VEGFR-2, so it may be worth also considering anti–VEGFR-2 therapy to treat macular edema in this population. However, a prospective clinical trial would be required to investigate the efficacy of such therapy.

This study also had some other limitations. For example, it is unclear from our data whether elevated vitreous levels of cytokines and chemokines were related to increased retinal vascular permeability or local production in the retina, but the mechanism involved may be revealed by animal studies.

In the present study, the vitreous fluid levels of sVEGFR-2, VEGF, sICAM-1, IL-6, MCP-1, PTX3, and PEDF were strongly correlated with retinal vascular permeability and the severity of macular edema. The sVEGFR-2 level was significantly correlated with the levels of sICAM-1, IL-6, MCP-1, and PTX3 but not with the level of VEGF. These findings suggest the importance of investigating relationships among VEGF and the cytokine network and may contribute to understanding the mechanism of macular edema in patients with BRVO and developing new treatments.


