Intravitreal Plasmin Without Vitrectomy for Macular Edema Secondary to Branch Retinal Vein Occlusion

Patricia Udaondo, MD; Manuel Diaz-Llopis, MD, PhD; Salvador Garcia-Delpech, MD, PhD; David Salom, MD; Francisco J. Romero, MD, PhD

Objectives: To evaluate the effects and safety of intravitreal injections of autologous plasmin enzyme (APE), without vitrectomy, as a treatment for macular edema secondary to branch retinal vein occlusion.

Design: Prospective, comparative, interventional case series.

Methods: Patients were recruited and enrolled consecutively from February 1 through October 31, 2008, at the Retina Unit of the Hospital General Universitario, Valencia, Spain. An eye from 8 patients diagnosed as having macular edema due to branch retinal vein occlusion received an injection, after having received topical anesthesia, of 0.2 mL of APE, which had been obtained using a simplified method. Best-corrected visual acuity and central macular thickness measured by optical coherence tomography constitute the main outcome measures of the study.

Results: The mean (SD) central macular thickness decreased from 494.875 (68.82) to 226.375 (28.67) μm 1 month after APE injection and to 228.570 (21.53) μm after 6 months (P < .001). The best-corrected visual acuity (logarithm of the minimal angle of resolution) improved from a preoperative value of 0.552 (0.17) to 0.217 (0.087) (mean, 20/80-20/32, Snellen equivalent) at the end of follow-up (P < .01). No secondary effects were observed during 6 months of follow-up.

Conclusion: This pilot study suggests that intravitreal injection of APE as a treatment for macular edema secondary to branch retinal vein occlusion improves central macular thickness and best-corrected visual acuity and may be a safe and effective alternative therapy for this condition if confirmed in controlled trials compared with standard care with longer follow-up.


ACULAR EDEMA (ME) IS the most common eye complication and a major cause of loss of visual acuity in patients with branch retinal vein occlusion (BRVO).

Because of deterioration of vision caused by ME secondary to BRVO, different medical and surgical therapies have been tested and the results reported. Laser photocoagulation was superior to no treatment by 6 months after treatment in selected case individuals evaluated in the Branch Vein Occlusion Study. Intravitreal injections of triamcinolone acetate and bevacizumab as a treatment for ME due to BRVO currently are being evaluated.

Surgical options, including cannulation of branch retinal veins, pars plana vitrectomy with or without adjunctive sheathotomy of the retinal vein adventitia, and pars plana vitrectomy with or without removal of internal limiting membrane, have not been shown definitively to yield more favorable results than standard care (grid photocoagulation in cases of BRVO). The incidence of ME has been suggested to be lower in cases of spontaneous posterior vitreous detachment, and traction of the vitreous cortex at the macula can play a role in exacerbating ME. In the presence of posterior vitreous detachment, intravitreal treatments using triamcinolone or antivascular endothelial growth factors theoretically could be less effective.

It has been hypothesized that pharmacologic vitreolysis by intravitreal injection of autologous plasmin enzyme (APE) may allow better results to be obtained with vitreous surgery in cases in which a macular hole or diabetic ME is present. Recently, APE injection without associated vitrectomy was shown to be associated with decreased edema and improved visual acuity, at least for a few months, in the treatment of diabetic ME involving the center of the macula. This prospective controlled study, which has an interventional case series design, aimed to evaluate the effects and safety of APE intravitreal injections in the absence of an associated vitrectomy as a treatment for ME secondary to BRVO, using optical coherence tomography (OCT) to evaluate anatomical results.

Methods

Patients were recruited and enrolled consecutively from February 1 through October 31,
2008, at the Retina Unit of the Hospital General Universitario, Valencia, Spain. The protocol was approved by the institutional review board of the hospital. An eye from 8 patients with ME due to BRVO was studied.

All patients were diagnosed by means of fluorescein angiography as having ME secondary to BRVO. Central macular thickness (CMT) was measured using OCT (Stratus OCT-3; Carl Zeiss Meditec AG, Jena, Germany). Treatment with intravitreal APE was offered to those who showed poor outcomes in visual acuity or macular thickness after grid laser, triamcinolone, or bevacizumab therapy or a combination of these treatments. Inclusion criteria consisted of the following: ME (perfused or nonperfused) secondary to BRVO, defined as fluorescein leakage as measured by fluorescein angiography and macular thickness greater than 300 µm as measured by OCT; patients with ME who had proven to be unresponsive to laser photocoagulation or other intravitreal treatments (<20% reduction and persistence of macular thickness >300 µm); and best-corrected visual acuity (BCVA) converted into logarithm of the minimal angle of resolution (logMAR) of 1.0 or greater (20/200). Exclusion criteria consisted of the following: uncontrolled blood pressure (systolic and diastolic blood pressure greater than 150 and 90 mm Hg, respectively), renal insufficiency, intraocular surgery or any intravitreal treatment during the previous 3 months, and history of ocular hypertension and/or glaucoma. The nature of off-label use of autologous plasmin and its potential adverse effects, including endophthalmitis, retinal detachment, and uveitis, were discussed in depth with patients before obtaining their consent to participate in the study.

Table 1. Baseline Clinical Characteristics of Patients With Macular Edema Due to Branch Retinal Vein Occlusion Before Injection of the Autologous Plasmin Enzyme

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Treated Eyes (N=8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, No. (%)</td>
<td>Male 3 (38)</td>
</tr>
<tr>
<td></td>
<td>Female 5 (62)</td>
</tr>
<tr>
<td>Age, mean (range), y</td>
<td>65 (58-73)</td>
</tr>
<tr>
<td>Eye, No.</td>
<td>Right 5</td>
</tr>
<tr>
<td></td>
<td>Left 3</td>
</tr>
<tr>
<td>Lens, No.</td>
<td>Phakic 7</td>
</tr>
<tr>
<td></td>
<td>Pseudophakic 1</td>
</tr>
<tr>
<td>Systemic disease, No.</td>
<td>Hypertension 6</td>
</tr>
<tr>
<td></td>
<td>Hypercholesterolemia 3</td>
</tr>
<tr>
<td></td>
<td>Diabetes mellitus 1</td>
</tr>
<tr>
<td>Previous treatments</td>
<td>Photoacoagulation and triamcinolone acetate 2</td>
</tr>
<tr>
<td></td>
<td>Photoacoagulation and triamcinolone plus bevacizumab 2</td>
</tr>
<tr>
<td></td>
<td>Bevacizumab 3</td>
</tr>
<tr>
<td></td>
<td>Triamcinolone and bevacizumab 1</td>
</tr>
<tr>
<td>Macular edema in FA</td>
<td>Perfused 5</td>
</tr>
<tr>
<td></td>
<td>Nonperfused 3</td>
</tr>
<tr>
<td>CMT, mean (SD)</td>
<td>494.875 (68.82)</td>
</tr>
<tr>
<td>BCVA, mean (SD)</td>
<td>0.552 (0.17)</td>
</tr>
</tbody>
</table>

Abbreviations: BCVA, best-corrected visual acuity; CMT, central macular thickness; FA, fluorescein angiography.

PREOPERATIVE EXAMINATION

Before receiving an injection of APE, all patients underwent a complete ophthalmologic examination consisting of BCVA measurement converted to logMAR, slitlamp examination, application tonometry, indirect ophthalmoscopy, macular mapping using OCT, fundus photography, and fluorescein angiography. The previous presence of posterior vitreous detachment was excluded by OCT and biomicroscopy in all cases.

PREPARATION OF APE AND INJECTION TECHNIQUE

The APE was prepared in the operating room approximately 45 minutes before injection, as previously described.15 Topical anesthesia was induced by applying 1% tetracaine eye drops on at least 3 occasions. The conjunctiva bulbi and fornices were rinsed repeatedly with povidone-iodine solution. An anterior chamber paracentesis was performed in all cases before injection. Patients then received a unilateral intravitreal injection of 0.2 mL of APE, sterilized through a 0.22-µm pore filter, via a 30-gauge needle. After the injection, intraocular pressure and retinal artery perfusion were assessed. Antibiotic eye drops (ofloxacin) and topical prednisone were applied 4 times a day for 10 days.

OUTCOME MEASURES AND STATISTICAL ANALYSIS

After the injection, BCVA measurement converted to logMAR and OCT were performed on each patient before treatment.
and at 1 and 6 months after treatment. Demographic characteristics of the patients were summarized with descriptive statistics via SPSS statistical software, version 13.0 for Windows (SPSS Inc, Chicago, Illinois). The Wilcoxon signed rank test for paired samples was used to compare the BCVA and CMT between baseline and at 1 and 6 months. 
P < .05 was accepted as significant.

RESULTS
Of the 8 patients (8 eyes) with ME associated with BRVO, 5 were women and 3 were men. Six had a history of hypertension (requiring treatment) or hypercholesterolemia. Mean age was 65 years (age range, 58-73 years). All showed a limited or nonexistent response to previous treatment with laser photocoagulation, intravitreal triamcinolone, bevacizumab injections, or a combination of those treatments, which had resulted in a less than 20% reduction of macular thickness. Patients 1, 2, and 7 showed nonperfused edema (ischemic area involving the macula) in the angiographic image before the plasmin treatment. Patients had received no treatment for 3 months before the APE injection. Pretreatment characteristics of the patients are summarized in Table 1. Patients were observed during a mean of 6 months of follow-up. Major adverse effects, such as uveitis, endophthalmitis, ocular toxicity, glaucoma, retinal tears, vitreous hemorrhage, or any systemic adverse events, were not observed in any of the cases. Biomicroscopy and OCT confirmed a complete posterior detachment in all the eyes treated with APE (Figure 1).

CENTRAL MACULAR THICKNESS
All patients displayed an important decrease in retinal thickness within 1 month of APE injection (Table 2, Figure 2, and Figure 3). At baseline, the mean (SD) CMT was 494.875 (68.82) µm. The mean CMT was 226.375 (28.67) µm 1 month after APE injection and 228.570 (21.53) µm after 6 months (Wilcoxon signed rank test, P < .001).

Table 2. CMT Measured by Optical Coherence Tomography and Best-Corrected Visual Acuity Before APE Injection and at 1 and 6 Months After Injection

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Duration of BRVOa</th>
<th>CMT, µm</th>
<th>BCVA, logMAR Edema</th>
<th>1 Month After APE</th>
<th>6 Months After APE</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>11</td>
<td>432</td>
<td>Nonperfused</td>
<td>210</td>
<td>211</td>
</tr>
<tr>
<td>2</td>
<td>9</td>
<td>576</td>
<td>Nonperfused</td>
<td>224</td>
<td>234</td>
</tr>
<tr>
<td>3</td>
<td>10</td>
<td>520</td>
<td>Nonperfused</td>
<td>241</td>
<td>229</td>
</tr>
<tr>
<td>4</td>
<td>12</td>
<td>464</td>
<td>Perfused</td>
<td>182</td>
<td>191</td>
</tr>
<tr>
<td>5</td>
<td>8</td>
<td>516</td>
<td>Perfused</td>
<td>276</td>
<td>258</td>
</tr>
<tr>
<td>6</td>
<td>13</td>
<td>398</td>
<td>Perfused</td>
<td>213</td>
<td>234</td>
</tr>
<tr>
<td>7</td>
<td>13</td>
<td>610</td>
<td>Nonperfused</td>
<td>259</td>
<td>271</td>
</tr>
<tr>
<td>8</td>
<td>9</td>
<td>443</td>
<td>Perfused</td>
<td>210</td>
<td>202</td>
</tr>
</tbody>
</table>

Month, mean (SD) 494.875 (68.82) 0.552 (0.17) 226.375 (28.67) 0.197 (0.087) 228.570 (21.53) 0.217 (0.087)

Abbreviations: APE, autologous plasmin enzyme; BCVA, best-corrected visual acuity; BRVO, branch retinal vein occlusion; CMT, central macular thickness; logMAR, logarithm of the minimal angle of resolution.
aIndicates months since diagnosis of branch vein occlusion and plasmin treatment.

BEST-CORRECTED VISUAL ACUITY
Improvement of visual acuity was evident within the first month of intravitreal injection of APE (Table 2). The mean (SD) BCVA at baseline was 0.552 (0.17) (20/80-20/63). The BCVA was 0.197 (0.087) (20/25-20/32) at 1 month and 0.217 (0.087) after 6 months of follow-up (mean of 20/32, Snellen equivalent) (Wilcoxon signed rank test; P < .001 at 6 months compared with baseline). All patients displayed an improvement (>10 letters) in visual acuity at the last follow-up visit.
Because of the limited results with laser treatment, patients with vision loss secondary to ME associated with vitreous detachment remains the standard method of treatment for ME. Recently, new results from the Branch Vein Occlusion Study Group showed a benefit with grid photocoagulation in some patients with ME but also identified a subset of patients with limited benefit from it. Vascular endothelial growth factor and inflammation may also play an important role in the pathology of BRVO and could constitute the reason why photocoagulation has yielded limited benefits. Recently, new results from the Standard Care vs Corticosteroid for Retinal Vein Occlusion study have been published, and grid laser photocoagulation remains the standard method of treatment for patients with vision loss secondary to ME associated with BRVO.

The preliminary results of this prospective controlled study suggest a beneficial effect, at least for several months, on ME due to BRVO of intravitreal injection of APE prepared by a simplified method, at least in cases of an associated attachment of the vitreous cortex to the macula. Results appeared to persist at least 6 months after only 1 intravitreal injection of APE. The pharmacologic vitreolysis and posterior detachment of the vitreous cortex produced by this method may be equivalent to performing a pars plana vitrectomy while minimizing the adverse effects associated with a surgical procedure.

The BRVO study group showed a benefit with grid photocoagulation in some patients with ME but also identified a subset of patients with limited benefit from it. Vascular endothelial growth factor and inflammation may also play an important role in the pathology of BRVO and could constitute the reason why photocoagulation has yielded limited benefits. Recently, new results from the Standard Care vs Corticosteroid for Retinal Vein Occlusion study have been published, and grid laser photocoagulation remains the standard method of treatment for patients with vision loss secondary to ME associated with BRVO. Because of the limited results with laser treatment, it is important to find new strategies to treat ME, which is an important cause of retinal vascular disorder and loss of visual acuity. Six months after treatment we observed no cataract progression, intraocular pressure elevation, or any other major complications (retinal detachment, vitreous hemorrhage, or endophthalmitis) associated with intravitreal APE injection.

Until now, one of the limitations of the use of APE was the relatively time-consuming and expensive preparation of the enzyme. The advantage of the simplified technique is that the APE can be prepared 1 hour before injection, which accelerates and simplifies the procedure, lowers its cost, and, perhaps most important, could make it accessible to most retina practices. The concentrations of APE obtained by this simplified method are substantially lower than those obtained by an alternative method described by several authors. Nevertheless, it appears to be effective enough to induce a complete vitreous detachment.

The current study has several limitations, the most important being its relatively small number of patients evaluated in a condition with a variable response (limiting the treatment to those with substantial loss of visual acuity) and the absence of control individuals (making it impossible to determine how these patients would have fared with no treatment or with grid laser photocoagulation if indicated). More studies with a larger number of patients enrolled are needed because this study’s findings are not substantial enough to confirm the efficacy of this new treatment.

In conclusion, intravitreal injection of APE appeared to have substantial effects on ME due to BRVO associated with improvement in visual acuity, at least during a 6-month period. Further controlled studies are warranted to assess the long-term efficacy and safety of this approach.

Submitted for Publication: September 10, 2009; final revision received April 28, 2010; accepted May 1, 2010.

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Financial Disclosure: None reported.

REFERENCES


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**Correction**

Error in Figure 8 Labeling. In the Clinical Sciences article titled “Anti–Retinal Pigment Epithelium Antibodies in Acute Exudative Polymorphous Vitelliform Maculopathy: A New Hypothesis About Disease Pathogenesis,” by Koreen et al, published in the January issue of the Archives (2011;129[1]:23-29), an error occurred in the labeling of Figure 8 on page 27, right-hand column. The farthest left lane should have been unlabeled. “Retina” should have been placed only over relabeled lanes A and B with an enclosing bracket. Lane designators A and B at the top and the first 7 and 41 pair at the bottom should have been shifted 1 lane to the right. A correct version of the figure is reproduced herein. This article was corrected online.