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

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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.

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, central macular thicknesst beyond 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 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).

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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, $P < .001$).

### 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.
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 approach.

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.

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REFERENCES


**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.