events related to the study agent. According to the company, the safety results from clinical data to date have led to a decision to recruit 15 additional patients to evaluate a higher dose (175 µg) of microplasmin.

Microplasmin alone may be sufficient to induce PVD—preventing the need for vitrectomy—and be beneficial in the prevention of serious posterior segment disorders, including macular holes, diabetic retinopathy (DR), and diabetic macular edema (DME).

Microplasmin is a truncated form of plasmin, an enzyme that dissolves protein formations that are crucial to thrombus formation; similar protein formations are seen linking the vitreous to the retina in the eye.

Figure 4. At day 14, the patient’s visual acuity was still 20/63. Gas bubble was injected with face-down positioning.

Figure 5. Three days after injection of gas bubble (day 17), visual acuity was 20/40.

Is There a Role for In-Office Vitreolysis With Autologous Plasmin Enzyme?

In this group of cases, eyes were refractory to previous treatments with other available intravitreal agents.

BY TAREK S. HASSAN, MD

The cleaving of vitreous from the retinal surface is an obvious surgical goal for many indications. It is likely desired for an improved natural history of diabetic and other macular edemas, proliferative diabetic disease, and maybe even neovascular age-related macular degeneration.

Plasmin is a fibrinolytic serum protease enzyme with dose-dependent activity that degrades the matrix proteins fibronectin and laminin, the major adhesives between the vitreous and the internal limiting membrane (ILM); activates matrix metalloproteinase 2; and breaks down vitreous macromolecules, thereby leading to the cleavage of the vitreous from the retinal surface and vitreous liquefication.

AUTOLOGOUS PLASMIN

In its clinically useful forms, we have autologous plasmin enzyme, which is extracted from a patient several days prior to intravitreal injection, and microplasmin, a 29-kD human recombinant form of the protease active site of plasmin from ThromboGenics (Leuven, Belgium), which is currently in phase 2 trials (see main article). Autologous plasmin has been successfully used as an adjunct to vitrectomy for diabetic retinopathy, macular holes, proliferative vitreoretinopathy, and retinopathy of prematurity.

In our study, we sought to determine the efficacy of autologous plasmin, injected intravitreally in the office setting, to obtain a pharmacologic posterior vitreous detachment (PVD), which could then enhance the ability of intravitreally injected bevacizumab (Avastin; Genentech, South San Francisco, California) or triamcinolone to treat eyes with clinically significant macular edema due to diabetic retinopathy and cystoid macular edema due to central retinal vein occlusion (CRVO) that were refractory prior to treatment with these intravitreal agents.

Our goal was to create a safe, atraumatic nonsurgical PVD which could allow patients to potentially avoid the operating room when combined with currently known therapies to improve vision and reduce anatomic abnormalities. We looked at eyes that were unresponsive to other current therapies, had refractory macular edema, no clinical PVD, and had failed prior intravitreal steroid or bevacizumab injections. We defined failure as no significant improvement during their postinjection and laser course. Patients had no clinically discernible vitreoretinal
Prof. Stalmans, the study’s principal investigator, said: “The results from the study . . . clearly indicate the potential for microplasmin to become a more convenient, less invasive, hence more patient-friendly treatment for vitreomacular traction. The fact that we have been able to clearly show that microplasmin can achieve clinically important outcomes such as traction release and macular hole closure without surgery augurs well for the future development of this novel treatment.”

**CLINICAL TRIAL BACKGROUND**

A phase 2 trial with microplasmin as a surgical adjunct for vitrectomy and the induction of PVD has been completed. This trial, MIVI I, demonstrated that microplasmin was generally well tolerated, with PVD induction observed in some patients (including five of 10 patients in whom microplasmin was injected 7 days before surgery).

Macular hole occurs in about 0.14% of the general population. It is most common in adults older than 60 years of age. The macular hole itself is a break in the retinal tissue that causes a loss of vision.

INCLUDED EYES

For our investigation, we ended up with five eyes that had appropriate follow-up—three with macular edema from diabetes and two from CRVO; all had a number of prior interventions. We drew blood from the patients 5 to 7 days before its use and separated out the plasmin using an infinity chromatography process. We then measured the activity of the plasmin and tested it for bacterial contamination.

We injected 1.6- to 2-IU of plasmin in a volume of 0.09 to 0.1 mL using a standard intravitreal procedure. The patients were given a combination of steroid-antibiotic drops for 1 week following injection and before the injection of intravitreal triamcinolone or bevacizumab. The mean visual acuity continued to improve in all eyes, although three of the eyes required an additional intravitreal steroid injection. All five of the eyes developed what appeared to be a clinically visible PVD, seen at an average of 5 weeks following plasmin injection. Statistically significant improvement in the mean foveal thickness was noted early by ocular coherence tomography and remained stable throughout follow-up.

**SHORTCOMINGS, IMPLICATIONS FOR THE FUTURE**

This was small series of eyes that was not controlled or randomized. We need longer follow-up in these patients and we also still have many unanswered questions: Are we really creating true PVDs (not vitreoschisis) with plasmin enzyme and no vitrectomy? From one of the surgical examples, it appears we are not likely doing that in all eyes. We do not know the optimal dose of autologous plasmin or if there is a potential for repeated use. It may be that treating these eyes earlier in the disease process will give better results, and perhaps plasmin can be combined with other treatments. The new recombinant microplasmin may have different properties, and perhaps we can potentially combine this concept with an in-office vitrectomy procedure.

We showed that this office procedure can lead to reduction or resolution of refractory macular edema and give some visual improvement in eyes able to respond to the same therapies that previously failed to show efficacy. Something about the action of plasmin enzyme on the vitreomacular interface has likely had an impact on the outcomes in these patients. Clearly, we are at the tip of the iceberg of a paradigm shift in which we will learn to manipulate the vitreous pharmacologically. In the future, I think we will learn much more about disease prophylaxis and the alteration of the natural history of a number of vitreoretinal diseases.

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