

Microplasmin Shows Promise for Vitreomacular Traction Treatment

Microplasmin dissolves the protein structure linking vitreous to the retina.

REVIEWED BY PETER STALMANS, MD, PhD; AND DAVID M. BROWN, MD

Spontaneous posterior vitreous detachment (PVD) has been seen in some patients following injection of microplasmin (ThromboGenics, Leuven, Belgium). Prof. Peter Stalmans, of University Hospitals, Leuven, Belgium, presented data from the phase 2a Microplasmin in Surgical Vitrectomy (MIVI-IIT) trial, a randomized, double-masked, sham-controlled study in which 30 patients were assigned to receive either 75- or 125- μ g microplasmin or sham injection. Prof. Stalmans spoke at the American Society of Retina Specialists 25th Annual Meeting in Indian Wells, California.¹

Among the patients who were recruited across Europe, 24 received microplasmin, and six received sham injections. According to a news release from ThromboGenics, the trial showed clear benefits from therapy, with nine of the 24 microplasmin-treated patients having resolution of vitreomacular traction—including macular hole closure in two of the four macular hole cases—without the need for vitrectomy (Figures 1 through 8).

UNMASKING AT 1 MONTH

Included patients had vitreous traction on macula, according to Prof. Stalmans, macular thickness of ≥ 250 μ m, visual acuity of $\leq 20/40$ in the study eye, and $\geq 20/400$ in the fellow eye. The follow-up was 6

months, with unmasking at 1 month.

Microplasmin therapy was safe and well tolerated in the trial. There were no retinal tears, retinal detachments, cases of endophthalmitis, or other adverse

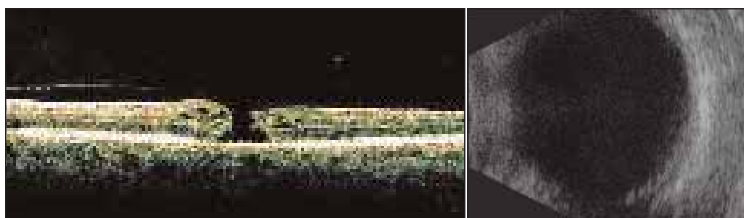


Figure 1. Macular hole in a patient with baseline vision of 20/63.

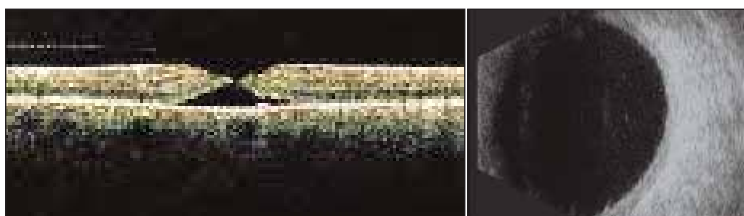


Figure 2. Same patient at day 3, visual acuity was still 20/63.

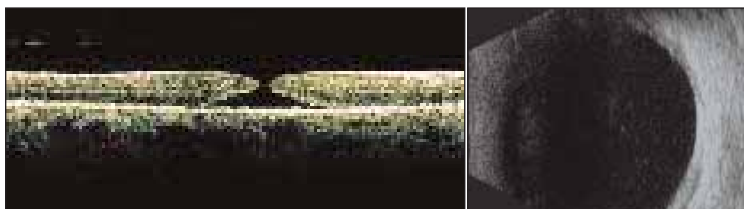


Figure 3. At day 7, the patient's visual acuity was stable at 20/63.

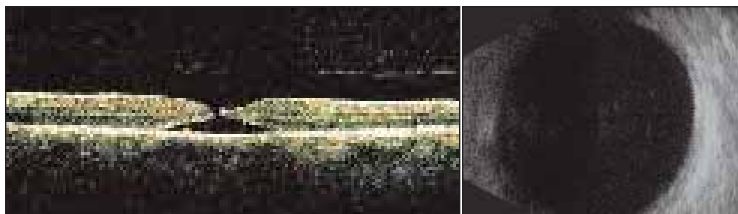


Figure 4. At day 14, the patient's visual acuity was still 20/63. Gas bubble was injected with face-down positioning.



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

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.

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 liquification.

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 vitrec-

tomy for diabetic retinopathy, macular holes, proliferative vitreoretinopathy, and retinopathy of prematurity.

In our study,¹ 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

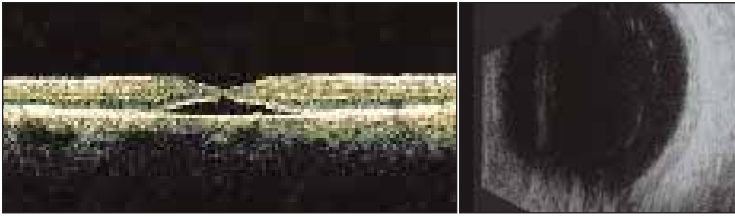


Figure 6. On day 28, the patient's visual acuity was 20/50.

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

traction, no active neovascular disease, and at least 6 months follow-up.

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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1. Hassan TS, Quiram PA, Sund NJ. In-office pharmacologic vitreolysis with intravitreal autologous plasmin enzyme plus intravitreal bevacizumab to treat refractory macular edema. Presented at the American Society of Retina Specialists 25th Annual Meeting. Dec 1-5, 2007. Indian Wells, California.

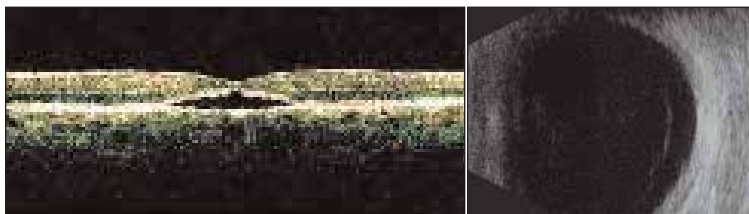


Figure 7. Three months after treatment, visual acuity was 20/32.

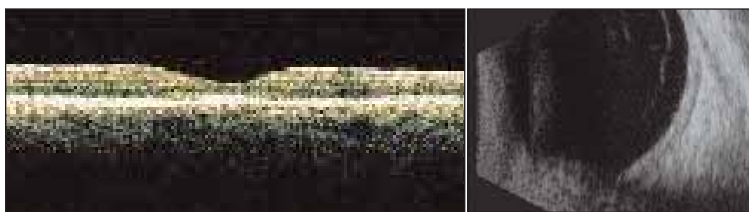


Figure 8. At 6-month follow-up, the patient's visual acuity was 20/25.

population, leading to estimates of approximately 400,000 cases in the United States and up to 1 million in the industrialized world, according to the company. Potential nonsurgical applications for microplasmin include treatment of DME and DR. DR is the leading cause of blindness among working-age adults, whereas DME is the leading cause of decreased vision in patients with DR. Approximately 750,000 patients in the United States suffer from DME.

Macular hole occurs in about 0.14% of the general population, leading to estimates of approximately 400,000 cases in the United States and up to 1 million in the industrialized world.

MIVI III TRIAL

David M. Brown, MD, an investigator for the MIVI III trial, presented cases from this trial at the Retina Society Annual Meeting in Boston.² MIVI III is a placebo-controlled trial being performed in the United States among patients scheduled to undergo vitrectomy.

Options in these patients consist of continued observation, pars plana vitrectomy with a hyaloid peel, or enrollment in the MIVI III phase 2b trial, in which the patient would be randomized to one of three dilutions of microplasmin or normal saline intravitreal injection.

Postmortem and in vivo experiments with

microplasmin in four separate animal models demonstrated safety and dose-dependent efficacy, Dr. Brown said. Pharmacologic vitreolysis was achieved, showing detachment of vitreous from retinal surface and liquefaction of the vitreous gel.

Patients with nonproliferative vitreoretinal disease, in whom vitrectomy is indicated, are being randomized in a placebo-controlled, double-masked, parallel-group, dose-ranging study. The 120 patients are being randomized to one of four arms: placebo, 25 µg, 75 µg, and 125 µg. A pars plana vitrectomy will be performed 7 days after injection (unless the induction of a PVD prior to surgery accomplishes the anatomic goal without surgery). Patients are followed for 6

months, and the primary analysis will be based on a 28-day postoperative time point (subsequent secondary analysis for safety based on 6-month follow-up time point).

There will be continued follow-up of the US and worldwide studies for safety and efficacy, Dr. Brown said. This treatment could potentially be used as first-line therapy for cases of vitreomacular traction and impending macular hole, as an adjunct for vitreoretinal surgery, as well as play a role in the diabetic vitreous. ■

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1. Stalmans P, van Calster J, de Smet MD, et al. MIVI-2T Trial: A randomized, double-masked clinical trial of microplasmin intravitreal injection for nonsurgical treatment of vitreomacular traction. Presented at the American Society of Retina Specialists 25th Annual Meeting. Dec 1-5, 2007. Indian Wells, California.

2. Brown D. MIVI III trial. Presented at the Retina Society Annual Meeting. Sept. 27-30, 2007. Boston.

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