

RETINAL DISORDERS

Trials successful for vitreomacular adhesions, macular hole; may also help AMD

by Howard Larkin in Paris

Microplasmin, a compound that helps dissolve proteins that bind the vitreous to the retina, may soon be available as a non-surgical treatment for a variety of retinal disorders related to vitreous adhesions, said Marc D de Smet MDCM, PhD, FRCSC, Lausanne, Switzerland. Microplasmin may also be helpful for treating proliferative diabetic retinopathy, and managing or even preventing retinal complications for high-risk cataract patients.

“For anterior segment surgery it may be useful as a form of prophylaxis in high-risk patients, where you might consider injecting it to induce a posterior vitreous detachment (PVD) before surgery,” Dr de Smet told a symposium of the XXVIII Congress of the ESCRS.

This could lower the risk of developing cystoid macular edema (CME) or progression to proliferative diabetic retinopathy due to focal vitreous adhesions on the macula causing traction on the retina during and after surgery. Injecting microplasmin might also help prevent CME and other retinal complications after cataract surgery complications such as posterior capsule rupture, added Dr de Smet, who has participated in microplasmin pre-clinical and clinical trials.

Benefits of complete PVD Dr de Smet noted that while PVD is common in older patients, it results from a progressive process that typically takes years. It involves both synchysis, or detachment of the vitreous from the retinal surface, and syneresis, or liquefaction of the vitreous gel. When the two progress together, the vitreous separates cleanly and completely from the retina as the gel liquefies and collapses. But often the vitreous adheres firmly in the peripheral retina or around the macula producing traction on the retina as the vitreous liquefies and collapses. Vitreomacular traction syndrome and macular holes can directly result from these vitreomacular adhesions. They may also contribute to CME, and proliferative diabetic retinopathy. Firmly adherent vitreous in the periphery will contribute to the formation of tears.

A meta-analysis of published literature on the effect of PVD revealed that a complete posterior vitreous detachment



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is desirable in cataract patients because it reduces the chances of post surgery CME by a factor of three compared with no PVD, Dr de Smet said.

“After complicated cataract surgery if you have a complete PVD you are less likely to develop CME.”

For patients with proliferative diabetic retinopathy, the difference is even more dramatic. A complete PVD reduces the chances of progression to about 10 per cent compared with no PVD, whereas a partial PVD increases the risk by a factor of nearly 200 compared with no PVD.

Similarly, an absent PVD is often found in eyes with wet AMD. In the presence of a PVD, oxygen levels increase at the retinal surface helping to restore function to ischemic tissues.

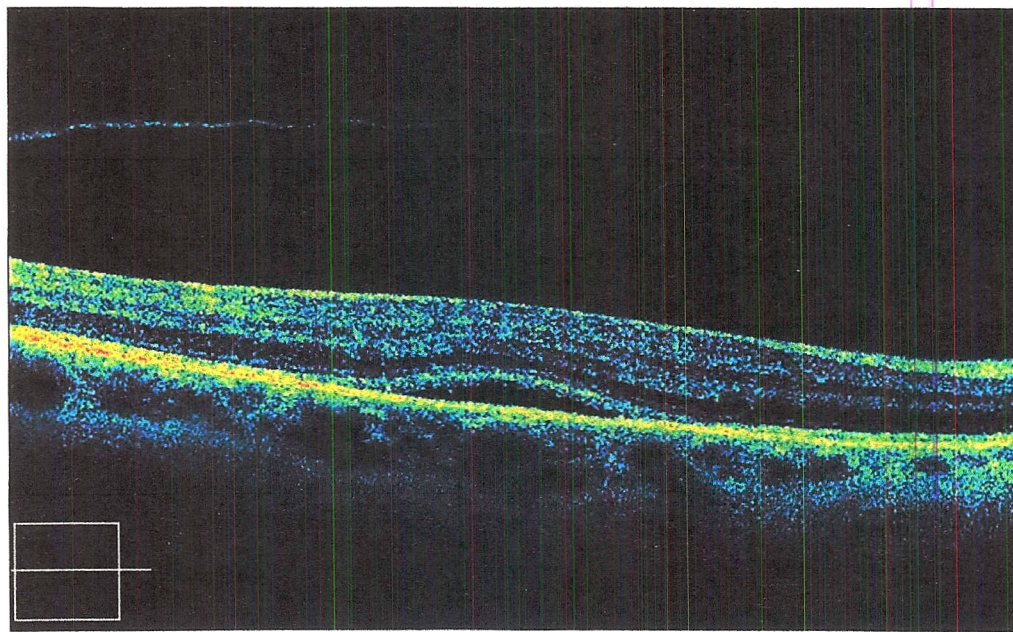
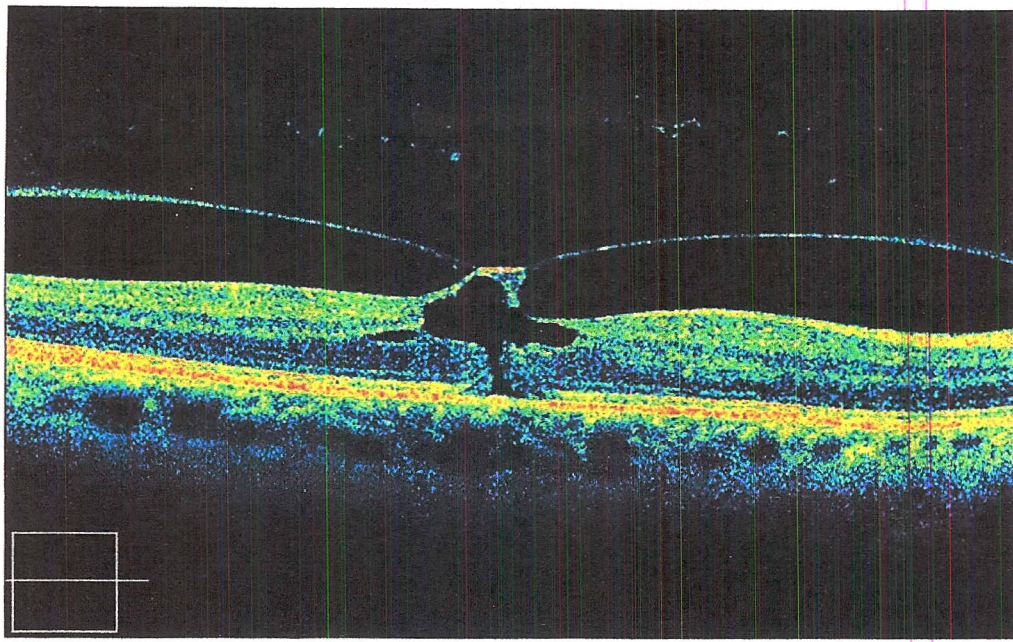
Benefits of pharmacological vitreolysis Dr de Smet noted that the proteins laminin and fibronectin are involved in binding the vitreous to the retinal surface.

“Weakening these adhesions can lead to a complete PVD. This is what we call pharmacological vitreolysis.”

Several compounds, including dipase, tPA/urokinase and hyaluronidase have been tried, but either didn't work or caused intolerable side effects. Plasmin showed promise. But it is a very large molecule that is difficult to synthesise in a stable form, Dr de Smet said.

However, researchers discovered that plasmin's enzymatic activity in degrading laminin and fibronectin was produced by one small area at the tip of the molecule. This compound, called microplasmin, was successfully produced recombinantly by the manufacturer, ThromoGenics.

Injecting microplasmin in pig eyes made



Courtesy of Marc D de Smet MD, PhD, FRCS

The first OCT image (top) was taken prior to surgery in a patient with a small macular hole. The second OCT shows that the hole is closed 14 days later though there is a residual serous macular detachment

the vitreous hazy, followed by complete vitreous separation, usually within an hour or two, Dr de Smet said. Post-mortem exams of human eyes revealed “a very smooth separation, much better than what you can achieve by natural separation or by surgery,” he added. This clean separation may prevent growth of epiretinal membranes, which can result from small amounts of material left behind after what appears to be a complete PVD.

In a phase II trial involving 60 patients with vitreomacular adhesions causing traction, 44 per cent receiving a 125 microgram dose achieved a complete separation by day 28, with 58 per cent doing so when a 125 microgram dose was repeated up to three times at four-week intervals.

In two recently concluded phase III trials involving 652 patients with vitreomacular adhesions, 26.5 per cent had complete resolution at 28 days following a single 125

microgram injection of microplasmin, vs 13 per cent in the placebo group. Of those subjects without an epiretinal membrane, 34.5 per cent treated with microplasmin had complete resolution. Of subjects with a full thickness macular hole, 40.6 per cent saw complete resolution. Of all subjects, 13.4 per cent had a complete PVD.

The drug was also well tolerated. A transient increase in floaters was the most common complaint, Dr de Smet said. The incidence of retinal detachment was about the same in those injected and those who were not.

“This drug appears to have a good safety profile. It is not on the market yet, but I’m pretty sure it will get there. There are novel approaches to treat macular traction on the way. Among these microplasmin holds great promise. We can expect a significant change in our approach to macular traction in years to come.”