The Microplasmin for Pediatric Vitrectomy Study

Ocriplasmin has been evaluated in children in a phase 2 trial; results have not been announced.

BY KIMBERLY DRENSE, MD, PHD

Pharmacologic vitreolysis is a promising prospect for manipulation of the vitreous and retina. Recently a proteolytic enzyme, ocriplasmin (formerly microplasmin; Jetrea, Thrombogenics Inc.) received US regulatory approval for treatment of symptomatic vitreomacular adhesion. This recombinant protein, containing the active protease site of human plasmin, can be used either alone or as a surgical adjunct to induce posterior vitreous detachment (PVD).1

The vitreous has characteristics that make it ideal for enzymatic manipulation: It is predominantly water, mostly acellular, and allows rapid diffusion of drugs. In the vitreoretinal interface, primarily the boundary between the posterior vitreous hyaloid and the internal limiting membrane (ILM), molecular adhesion principally occurs via linkages among heparin sulfates, proteoglycans, and opticin. Plasmin enzyme can induce liquefaction of the vitreous and weaken hyaloid attachment at the vitreoretinal interface.

Enzymes have been used to facilitate vitreous surgery for more than a decade.2 Autologous plasmin enzyme has been shown to facilitate cleavage of the vitreoretinal interface in adult patients with diabetic macular edema without previous PVD.3

Early investigations used autologous human plasmin enzyme, with the disadvantage that this substance must be derived from a blood product in a laboratory and prepared specifically for each case. The advent of a recombinant microplasmin has introduced greater ease of use, with a product provided in a single-use vial using reproducible technology.1

Figure 1. Stage 5 familial exudative vitreoretinopathy with retinal detachment; optical coherence tomography shows tight adhesions at the vitreoretinal interface.
Children’s eyes are significantly different from adult eyes; hyaloid adhesion is stronger in the eyes of children and infants, and this often leads to complicated or difficult vitreoretinal surgery. Surgical approaches and results are different in children from those in adults.

The use of autologous or maternal plasmin has been evaluated in pediatric patients for a number of conditions, including the treatment of traumatic macular holes, tractional retinal detachments, rhegmatogenous retinal detachments (RRDs), retinoschisis, and retinopathy of prematurity (ROP).4-6 These investigations have led to the understanding that often in the past surgical treatment of pediatric retinal disease was not successful due to failure to effectively remove the hyaloid from the underlying retinal junction.

A number of pediatric retinopathies requiring surgical intervention are marked by very adherent vitreoretinal adhesions. Tractional retinal detachments (such as those seen in familial exudative vitreoretinopathy [FEVR] or hyaloid contraction), RRDs in young children, and retinoschisis (as seen in congenital X-linked retinoschisis) may benefit from enzymatic cleavage of laminin and fibronectin at the vitreoretinal junction. Autologous plasmin enzyme has been used for several years in these cases with improved surgical results.5

The figures show examples of challenging cases. Figure 1 shows a child with FEVR with a tractional retinal detachment. Optical coherence tomography shows the complexity of the vitreoretinal interfaces and highlights how difficult it can be intraoperatively to successfully remove the hyaloid and its structures safely and cleanly without creating an iatrogenic break in the underlying retina. Traumatic RRDs in children are also challenging (Figure 2), and it is frequently difficult to fully clean the hyaloid off the retinal surface. The hyaloid often splits, leading to increased proliferative vitreoretinopathy. Figure 3 shows the hyaloid contraction that can occur when split hyaloid is left behind. If split hyaloid remains along the surface of the retina, it can contract and redetach the retina, even though it appeared that the hyaloid was completely dissociated at the initial surgery. Figure 4 shows an example of congenital X-linked retinoschisis. A schisis cavity is threatening the macula. Traumatically removing the hyaloid from the schisis cavity using mechanical extrusion will possibly cause the schisis cavity to extend and involve the macula. Often an inner wall retinectomy is used to try to avoid these tractional changes.

**Clinical Trial**

The safety and effectiveness of ocriplasmin in pediatric patients has not been established.1 The Microplasmin in Children (MIC) trial was conducted to evaluate the safety and preliminary efficacy of intravitreal ocriplasmin as an adjunct to conventional vitrectomy for the treatment of pediatric patients.7 This phase 2 trial was begun in January 2010 and completed in April 2012.

The MIC was a phase 2 randomized, placebo-controlled, double-masked clinical trial investigating the safety and efficacy of a single injection of 175 µg intravitreal ocriplasmin in pediatric patients scheduled to undergo vitrectomy. Twenty-four patients were enrolled and randomized 2:1 to ocriplasmin or placebo intravitreal injection. Patients included were male or female children 16 years of age or younger who were candidates for traditional 2- or 3-port vitrectomy for retinal detachment. Patients had to have evidence of attached vitreous in the posterior pole. Among the exclusion criteria were stages 1, 2, or 3 ROP not requiring vitrectomy; stage 5 ROP with retinal detachment at the time of surgery; and unclear media such as a cataract or vitreous opacity that would preclude evaluation of the poste-

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rior junction. Preoperatively and postoperatively all children underwent full ophthalmic examination, including slit-lamp and fundus exam, ultrasonography, fundus photography, and fluorescein angiography.

Efficacy was assessed by the surgeon, primarily at the time of surgery. During vitrectomy there were 2 main criteria: the level of PVD, indicated as a plus or minus; and the degree of liquefaction of the vitreous gel, indicated on a scale of 1 to 4, with 1 being closest to a formed gel and 4 being closest to the consistency of water.

Enrollment in MIC is complete. The last close-out examination was performed in May 2012, and the data are being analyzed. Thrombogenics has not committed to a date of release for the data.

We look forward to being able to use this agent in the future for children with complicated retinal detachments.

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