Management of Symptomatic Vitreomacular Adhesion

Emerging pharmacologic strategies have potential implications for age-related macular degeneration.

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Age-related macular degeneration (AMD) is the primary cause of severe visual impairment in industrialized nations. Over 1.22 million Americans have neovascular AMD in at least 1 eye. The proportion of the population most at risk is growing, and therefore the number of patients seeking and requiring treatment is also increasing. The pathogenesis of AMD involves a defect in the outer retina and retinal pigment epithelium and a genetic predisposition that may control the immune responses in the posterior segment. AMD largely involves the outer retinal layers, although intraoperative observations first implicated involvement of the vitreous. Further anomalies in the relationship between the retina and vitreous have been investigated, particularly abnormal posterior vitreous detachment (PVD) and its association with AMD. Recent studies have reported that PVD is linked to less severe AMD, and that symptomatic vitreomacular adhesion (sVMA) plays a significant role in the progression to the exudative (wet) form of the disease. Additionally, it has also been found that the incidence of VMA is higher in eyes with exudative AMD—38% compared with 10% in eyes with nonexudative AMD.

It has been suggested that persistence of VMA and traction may have a role in conversion of nonexudative AMD to the exudative form. A number of factors have been proposed to link VMA to AMD progression, including: low-grade inflammation caused by vitreal traction, a macula that has been exposed to free radicals or cytokines by the bordering vitreous, or limited access to required oxygen and nutrition at the adhesion site. Repeated intravitreal injections of anti-vascular endothelial growth factor (VEGF) injections are currently the standard of care for patients with neovascular AMD, which can be a burden to patients, both in terms of frequency and cost. Additionally, there are data showing that almost 50% of patients have a suboptimal response to anti-VEGF therapy. Vitrectomy has been reported to slow the development of AMD; however, the associated risks of surgical intervention must be seriously considered.

A PHARMACOLOGIC OPTION FOR sVMA

Pharmacologic options for the treatment and resolution of sVMA have been proposed and studied as independent modalities or adjuncts to surgery for more than a decade. The ultimate goal of a pharmacologic intervention is to induce appropriate liquefaction of the vitreous (synchisis) and produce dehiscence (syneresis), facilitating a smooth PVD without damage or toxicity to the retina. Early enzymatic agents, such as hyaluronidase, were used with the intention to cleave hyaluronan and the collagen complex and produce liquefaction of the vitreous. In rabbit eyes, hyaluronidase was unable to produce the desired PVD. Subsequently, a highly purified hyaluronidase (Vitrase, Ista Pharmaceuticals), was developed, and its effect on vitreous hemorrhage was studied. The purified hyaluronidase achieved 30% success in the clearance of hemorrhages and liquefaction of vitreous gel, but successful dehiscence was not achieved. Other treatments were proposed and studied, with limited results in animal or donor postmortem eyes. These included chondroitinase, which produced conflicting findings, and dispase and collagenase, both of which caused damage or toxicity to the retina. Plasmin, when used as an adjunct to surgery in human eyes, facilitated PVD and provided a clean surface on the
internal limiting membrane of the retina.17 Although these findings were promising, plasmin provided additional challenges. It is both highly unstable and not easily available, as plasminogen must be converted in vitro by streptokinase prior to surgery.

MICROPLASMIN

Most recently, microplasmin (Ocriplasmin, ThromboGenics) has been evaluated for safety and effectiveness in the treatment of sVMA, with promising results. Ocriplasmin is a recombinant agent that contains only the catalytic domain of human plasmin, sharing all its catalytic properties.18 It has powerful and effective proteolytic activity against major components of the vitreoretinal interface and induces both liquefaction and vitreous detachment. The results of a randomized, double masked, phase 2 trial (MIVI-III) was conducted at 19 centers in the United States, evaluating three doses of microplasmin (25, 75, and 125 µg) vs placebo in 125 patients scheduled for vitrectomy. The trial assessed the efficacy and safety of microplasmin intravitreal injection 7 days prior to vitrectomy, and showed that ocriplasmin was well tolerated with a defined dose response curve.20

These results prompted the development of two large, phase 3, international, multicenter, randomized, placebo-controlled, double-masked, dose-ranging clinical trial (MIVI-TRUST) to further evaluate 125 µg of ocriplasmin vs placebo administered via an intravitreal injection for the treatment of patients with sVMA. The study met its primary and secondary endpoints with high statistical and clinical significance. These findings are important because the resolution of sVMA can play an important role in the treatment of many retinal diseases, including macular hole, diabetic retinopathy, symptomatic vitreomacular traction syndrome, and AMD.

Eyes with VMA-related disorders can experience rapid deterioration of vision and function if not managed in an effective and timely fashion.21 The prevalence of many of these serious ocular disorders is rising, and effective care and management of many patients is often limited to vitrectomy. This surgical intervention, however, is accompanied by potential complications and is indicated for a limited number of patients. Earlier intervention may limit progression of disease and prevent deterioration of visual acuity and visual function. A pharmacologic option to manage patients with VMA would satisfy a clinical need to provide an earlier, safer, and more effective treatment by relieving vitreoretinal adhesion and its sequelae and eliminating the complications associated with surgery and the need for prolonged monitoring. Microplasmin has been well tolerated and effective in a phase 3 program at the defined optimal dose of 125 µg. These results are promising for the future management of many retinal disorders.

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