Safety and Complications of Ocriplasmin

Ocriplasmin, Ocriplasmin; Oh, How Safe Art Thou?

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Our ability to examine the vitreoretinal interface has been greatly improved by the invention of spectral-domain optical coherence tomography (OCT). It has allowed earlier and more accurate diagnosis of abnormalities of vitreomacular adhesion (VMA) that may contribute to vision loss and may benefit from intervention. While subtle abnormalities of VMA may be observed, symptomatic VMA or that associated with full-thickness macular hole (FTMH) requires surgical intervention. With improvements in vitreoretinal surgical techniques and better understanding of these conditions, outcomes of surgical management of VMA-related disorders are excellent. However, even in the hands of the most experienced surgeon, there are associated surgical risks. There is also expected discomfort to the patient, delay in visual recovery, high cost, and, in cases of surgery for FTMH, postoperative positioning. Furthermore, advanced surgical skills are required for epiretinal membrane or internal limiting membrane peeling.

Ocriplasmin (Jetrea) is a recombinant truncated form of human plasmin with a molecular weight of 27.2 kDa. It is a recombinant protease with activity against fibronectin and laminin, which are components of the vitreoretinal interface. In 2 phase 3 clinical trials comparing a single intravitreal injection of ocriplasmin (0.125 mg/0.1 mL) with a placebo injection (drug vehicle diluted with saline) in patients with symptomatic VMA, where the primary end point was resolution of VMA at day 28, 26.5% of ocriplasmin-injected eyes had resolution compared with 10.1% of placebo-injected eyes ($P < .001$). Nonsurgical closure of macular holes was achieved in 40.6% of ocriplasmin-injected eyes, as compared with 10.6% of placebo-injected eyes ($P < .001$). Consequently, ocriplasmin was approved by the US Food and Drug Administration (FDA) for use in symptomatic VMA in October 2012.

It is notable that ocriplasmin is a first-in-class pharmacologic agent that has been FDA approved to manage symptomatic VMA. Furthermore, the primary end point in the pivotal studies was based on OCT changes rather than on visual acuity improvement, the first time, to my knowledge, that OCT has been used as the primary outcome for a clinical trial in ophthalmology. Finally, even when patients do not achieve release of abnormal VMA or closure of FTMH following intravitreal ocriplasmin injection, they can still undergo surgical management. Therefore, ocriplasmin offers clinicians an additional tool to manage the anatomical abnormalities of symptomatic VMA in a less invasive manner than with surgery in select cases.

However, since the real-world use of the drug began, there have been unfavorable anecdotal reports of visual disturbances after ocriplasmin injection, including transient but profound visual decline, raising concerns regarding its safety. While it is not possible to know the frequency of these events in postmarketing surveillance, it is worthwhile to pay attention to safety-related reports.

In the report of phase 3 trials of ocriplasmin, ocular adverse events such as vitreous floaters, photopsia, conjunctival hemorrhage, blurred vision, and visual impairment were found to be significantly higher in the treatment group compared with the placebo group. However, the authors state that “most of the adverse events were transient and mild in severity.” The Warnings and Precautions section of the package insert for ocriplasmin includes decrease of 3 or more lines of best-corrected visual acuity in 5.6% of patients treated with ocriplasmin (compared with 3.2% in the control group), intravitreal injection procedure–associated effects (intraocular inflammation, intraocular hemorrhage, increased intraocular pressure), potential for lens subluxation, retinal breaks, and dyschromatopsia. It states that “dyschromatopsia (generally described as yellowish vision) was reported in 2% of all patients injected with Jetrea. In approximately half of these dyschromatopsia cases there were also electroneuretographic ERG changes reported (a- and b-wave amplitude decrease).” According to the FDA Advisory Committee briefing document, 9 patients receiving ocriplasmin in various clinical trials were reported to have experienced an acute decrease in vision within 24 hours of injection, some to the hand motions level. In 8 of 9 patients, vision returned to baseline with a median recovery time of 2 weeks. Dyschromatopsia reportedly resolved within a median time of 3 months. Of the 141 ocriplasmin-treated patients who underwent ERG testing, 11 (7.8%) had ERG changes and 9 of these patients also had dyschromatopsia. Among the 11 patients with ERG changes, the ERG changes resolved in 6 patients (median time, 6 months), 3 did not have follow-up ERGs, 1 was still undergoing follow-up, and 1 case did not resolve and was thought to be due to concurrent vitelliform dystrophy.

Recently, there was a report of a patient with symptomatic VMA, epiretinal membrane, and an impending FTMH who experienced transient vision loss after ocriplasmin injection. The patient was found to have disruption of the outer retina, in particular the ellipsoid zone (previously known as the inner segment/outer segment junction), on spectral-domain OCT.
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Betts et al.7 describe a patient who experienced darkening of vision in dim illumination for 4 months after intravitreal ocriplasmin injection, even though there was release of VMA and improvement in visual acuity. They also found widespread disruption in the ellipsoid zone as well as reduced ERG amplitudes, with greater reduction in scotopic function compared with photopic function, indicating possible panretinal abnormality with greater adverse effects on the rod photoreceptors. Fahim et al.8 document a case of acute panretinal dysfunction after ocriplasmin injection in an eye with VMA and a small macular hole. This patient was found to have visual acuity loss, pupillary abnormality, visual field constriction, OCT abnormality of outer segments, and ERG abnormality affecting b-waves more than a-waves when examined 9 days after injection. These findings suggest that there is widespread retinal dysfunction. The authors postulate that these widespread abnormalities occur after intravitreal injection of ocriplasmin owing to its effect on laminin, which is found not only in the vitreous but also throughout multiple layers of the retina, including the Bruch membrane, the interphotoreceptor matrix, the external limiting membrane, the outer plexiform layer, the inner plexiform layer, and the internal limiting mem-
brane. Therefore, the protease effect may be diffuse throughout the retina and not limited to the macula.

These reports add to our understanding of potential adverse effects and the mechanism of toxic effects of this new drug. Because ocriplasmin is a small molecule that may be able to penetrate well into the retina where laminin is present throughout, it is possible that the enzymatic effect of ocriplasmin may be panretinal and not limited to the vitreoretinal interface at the macula. While outer-segment anatomical changes and visual acuity decline appear to be transient, there may be prolonged effect on the rod photoreceptor function. The articles also highlight the need to further investigate risk factors for adverse events, the duration and extent of recovery, and ways to minimize toxic effects following ocriplasmin injection.

Intravitreal injection of ocriplasmin provides clinicians with far less invasive means than surgery to manage symptomatic VMA in select cases, and many patients have been successfully treated. However, judicious use, thorough pretreatment discussion, and careful follow-up are needed in light of these potential adverse effects. Finally, while there are serious limitations to postmarketing surveillance of drugs, reports such as these provide yet another example of the importance of postmarketing surveillance for better understanding of the effectiveness and safety of new drugs to provide the best care to our patients.

REFERENCES