

Common Questions Regarding the Safety of Ocriplasmin

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Ocriplasmin (Jetrea, Thrombogenics), the formulation of a proteolytic enzyme administered as an intravitreal injection, was approved by the US Food and Drug Administration (FDA) for the treatment of symptomatic vitreomacular adhesion (sVMA) last year. This treatment represents a potential therapeutic option, along with observation and vitrectomy, for a subgroup of patients with pathology of the vitreoretinal interface, mainly vitreomacular traction (VMT) and small macular holes in the presence of sVMA.

With the introduction of a new drug physicians must ask whether it is safe before asking whether it works. As such, beyond efficacy data, it is incumbent on treating physicians to be familiar with the safety profile of new therapies so as to provide patients with a comprehensive overview of risks and benefits during the informed consent process. In the following article we hope to give an overview of the available data that addresses some of the common questions we have heard from patients, as well as fellow clinicians, regarding the safety of intravitreal ocriplasmin.

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What are some of the common adverse events reported?

In combined data from the phase 3 studies, the common adverse events reported with ocriplasmin as compared with controls (injection of vehicle alone) in days 0-7 post injection were vitreous floaters (12.9% vs 2.7%), eye pain (10.5% vs 3.2%), photopsia (10.1% vs 1.1%), and blurred vision. All of these resolved to levels lower or equal to controls by 6 months.¹

Is there any significant postinjection inflammation associated with intravitreal ocriplasmin injection?

In pooled data from the controlled clinical trials, the rate of postinjection inflammation was 7.1% in the treatment group and 3.1% in the controls.

The onset was during days 0 to 7 for most events in the ocriplasmin group and during day 8 to the end of the study in the placebo group. None of the drug-related events were considered serious adverse events, and most were of mild intensity. The majority of events resolved spontaneously.^{1,2}



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Is there any increased risk of retinal tears (RT) or retinal detachments (RD) with ocriplasmin?

No. In the combined phase 3 data, the rate of combined retinal tear (without detachment) and/or retinal detachment was 0.4% in the ocriplasmin group, as compared with 0.5% in the vehicle group. In patients who underwent vitrectomy, the rates of postvitrectomy RT and RD were comparable between groups, with 8.5% (6.1% RT, 2.4% RD) in the ocriplasmin group and 14% (8.0% RT, 6.0% RD) in the vehicle group.²

Is there an increased incidence of cataract progression in patients undergoing intravitreal ocriplasmin injection?

In the pooled phase 3 study data there was progression of cataracts in 8.2% of phakic eyes injected with

Patient education in regard to expectations and safety is an important part of the [ocriplasmin] injection process.

ocriplasmin and in 11.9% of phakic eyes injected with vehicle. Among patients who did not undergo vitrectomy, the proportion of patients with cataract progression was similar in the ocriplasmin and vehicle groups (4.8% and 5.2%, respectively). There were no cases of acute postinjection cataract formation.³

Ocriplasmin is a proteolytic enzyme with potential effects on the lenticular zonules. Is there any evidence to date of significant induced lens instability or subluxation in human subjects?

Although there is evidence of spontaneous lens subluxation in animal studies with higher than currently recommended doses and with repeated intravitreal injections, there is no significant evidence at this time in human subjects. There has been only 1 reported case of lens subluxation in a human subject following intravitreal ocriplasmin injection (reported during a phase 2 trial). This instance occurred during vitrectomy for 4A retinopathy of prematurity in which the infant received 0.175 mg of ocriplasmin (1.4 times the current recommended dose of ocriplasmin) 1 hour prior to injection.⁴ There has been 1 case of reported lens instability during vitrectomy approximately 1 month postinjection. Further prospective studies looking to qualify and quantify lens instability after ocriplasmin injection are currently under way.

Have there been any cases of significant vision loss following injection of ocriplasmin?

Phase 3 study data revealed a decrease in vision of 2 lines or more (7.7% in the ocriplasmin group vs 1.6% in the placebo group) within 1 week of injection. By the end of the studies (6 months), most patients noted visual improvement to within 1 line or better of baseline best corrected visual acuity (BCVA) with a median recovery time of 14 days; the percentage of those who did not show improvement was comparable (1.3% ocriplasmin vs 1.1% placebo). A total of 9 patients treated with ocriplasmin from all studies (3 were from the phase 3 and part of that 7.7%) had temporary serious or severe adverse events related to acute vision decrease within 24 hours of injection, in which their vision decreases ranged from 20/150 to hand motion. The acute vision decreases resolved in all but 1 patient, and the lack of

resolution was attributed to the patient's concurrent disease (macula-off RD and exudative age-related macular degeneration). The median time to full recovery of visual acuity was 14 days. Rapid VMA resolution was observed by optical coherence tomography in 8 of the 9 cases, and VMA status is unknown for the remaining patient.²

I have heard of cases of dyschromatopsia and electroretinogram (ERG) changes following ocriplasmin injection in clinical trials. Is there cause for concern?

Of a total of 820 ocriplasmin-treated patients in phase 2 and phase 3 clinical trials, 16 (2%) reported alterations of color vision, generally described as mild and as a yellowish discoloration of vision. Time to onset of the subjective change was typically within the first 48 hours postinjection. Of note is that the majority of these cases came from 2 phase 2 studies conducted at the same site (in which patients were prospectively asked about changes in color vision). Median time to resolution of dyschromatopsia was 3 months for the 14 patients who had definitive resolution. In the remaining 2 patients, 1 was lost to follow-up and 1 died 18 months after the injection date of an unrelated cause.^{2,5}

ERG changes were reported in 11 of 141 (7.8%) treated patients who had ERG evaluations. These were described as a- and b-wave amplitude decreases occurring during the first month after injection. Nine of these patients also had dyschromatopsia. As in the aforementioned dyschromatopsia cases, the majority of these cases came from the same 2 phase 2 studies conducted at 1 site. In 6 of the 11 cases, the ERG changes resolved (median time, 6 months); 1 patient did not resolve, 1 patient is currently being followed, and 3 patients did not have follow-up ERGs. In the 1 case that did not resolve, the patient was diagnosed with concurrent vitelliform macular dystrophy. This preexisting condition was thought to be a factor for the lack of resolution. Visual acuity in all patients returned to baseline values with the exception of the 1 patient with vitelliform dystrophy.^{2,5}

An ongoing, fully enrolled phase 3b trial (OASIS) has color-vision testing (Roth-28) as a safety assessment for all 220 subjects. It also includes a full-field ERG in a substudy of 62 patients. This masked, sham-controlled trial evaluated 1 injection of intravitreal ocriplasmin for sVMA.⁶ The study follow-up is 2 years and is expected to be completed in November 2014.

DISCUSSION

In summary, ocriplasmin is an FDA-approved intravitreal injection for resolution of sVMA. These indications are well

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suited for the drug due to the fact that most retina specialists have been reluctant in the past to operate on this subset of patients. Ocriplasmin may allow us to avoid macular hole surgery in these eyes, but the long-term stability of macular hole closure in ocriplasmin-treated eyes remains unknown. The clinical trials appear to demonstrate benefit in patients experiencing vitreous traction on impending and stage 1 macular holes, but the drug would not be expected to eliminate the tangential traction caused by macular puckers around the edges of macular holes. Therefore, retina surgeons must recognize the proper indications for injection and educate their patients accordingly.

In terms of adverse events, the retina surgeon should apprise the patient of immediate potential issues within the first 48 to 72 hours:

1. The patient will experience a display of photopsias and new floaters. These are highly likely consequences and are an indication that the medication is relieving the vitreous traction via a sort of "chemical vitrectomy."
2. The risks of inflammation, cataract progression, and incidence of RT/RD are comparable with those of other intravitreal injections.
3. Initial vision decline has been reported infrequently as the vitreous traction is relieved, and in the majority of cases this resolves spontaneously.

Overall, ocriplasmin is an effective and safe treatment for the indications for which it has been approved. Patient education in regard to expectations and safety is an important part of the injection process. ■

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2. Data on file. ThromboGenics, Inc. 2012.

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