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Acute Ocriplasmin Retinopathy

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Ocriplasmin, a recombinant truncated form of the enzyme plasmin, was approved by the Food and Drug Administration in October 2012 as a first-in-class drug for the nonsurgical treatment of vitreomacular traction (VMT).[1] The potential advantages of pharmacologic vitreolysis over surgical vitrectomy include the induction of a “clean” and complete PVD without vitreoschisis, greater ease, lower cost, avoidance of surgical risk, and faster visual rehabilitation, possibly with better visual outcomes. Many retina specialists were hopeful that ocriplasmin was the long-awaited silver bullet—a safe and effective vitreolytic agent that would fulfill the promise of this new treatment approach. Real-life experience with the drug, however, has raised serious safety concerns.

The safety profile of ocriplasmin reported in the phase 3 registration trials included adverse events related to the intravitreal injection procedure and to the induction of posterior vitreous detachment, as well as photopsias and acute reduction in visual acuity.[1] A more detailed review of safety data from both phase 2 and phase 3 trials published in this issue of the journal *Retina*[2] documents additional adverse events, including dyschromatopsia, electroretinography (ERG) changes, macular hole enlargement, subretinal fluid development, and lens instability. Furthermore, numerous postmarketing reports, including 3 papers appearing in this issue, reveal that ocriplasmin injection may cause substantial acute panretinal structural and functional abnormalities that typically improve over time.[3–15] Although these anatomical changes in the outer retina with their associated visual symptoms are especially likely to develop in eyes that experience vitreomacular separation, they are not uncommon in eyes with no change in the vitreoretinal relationship.[2–5,11,12,14]

The symptoms and signs of acute ocriplasmin retinopathy are numerous and can in some cases be very frightening to patients and clinicians. They include varying degrees of the following: acute reduction in visual acuity (sometimes to very low levels such as hand motions or light perception), bizarre photopsias (eg. continuous bright curved or kaleidoscopic lines, sparkles, white floaters on a dark background), dyschromatopsia (eg. chromatic tinting, black and white or “negative” vision), nyctalopia, visual field constriction, afferent pupillary defect, anisocoria, retinal vascular attenuation or constriction, disruption/

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loss of outer retinal signals on spectral domain optical coherence tomography (SD-OCT) imaging, macular hole enlargement, macular detachment, and reduced (sometimes flat) ERG responses.[2–15] Signs that are likely very rare include autofluorescence abnormalities as well as lens subluxation or phacodonesis, which have been seen primarily in vitrectomized eyes.[2,3] Similar findings, including ERG suppression, retinal vascular attenuation, pupillary abnormalities, retinal atrophy, and lens subluxation were seen in dose-dependent fashion after intravitreal ocriplasmin injection in toxicology studies involving several animal species such as rabbits and monkeys.[16,17]

The precise mechanism of acute ocriplasmin retinopathy remains unclear. Although acute reductions in visual acuity have been attributed to progression of VMT,[2] this mechanism cannot explain the constellation of findings that comprise ocriplasmin retinopathy. As recently noted by Beebe,[18] plasmin and its derivative ocriplasmin are nonspecific serine proteases that cleave peptide bonds located after a lysine or an arginine residue. Although their intended targets for pharmacologic vitreolysis are laminin and fibronectin at the vitreoretinal interface, they are capable of cleaving dozens of other proteins.[18] Furthermore, intravitreous ocriplasmin, a relatively small protein with a molecular weight of 27 kDa, has been shown to penetrate all layers of the retina in rat eyes, causing degradation of laminin and fibronectin in outer retinal layers as well as at the vitreoretinal junction.[19] It should not be surprising that an enzyme capable of accessing and digesting a large diversity of proteins in the eye could cause widespread dysfunction throughout the retina and other tissues such as lens zonules.

Although cleavage of more than 1 protein may be responsible for the various manifestations of ocriplasmin retinopathy, there is plausible evidence that degradation of intraretinal laminin plays a key role.[7,10,20] In addition to its distribution in vitreous gel and lens zonules,[21] laminin is found in multiple retinal layers, including the internal limiting membrane, the outer plexiform layer (where it localizes to synapses between photoreceptor and bipolar cells), the external limiting membrane, and the interphotoreceptor matrix.[22,23] The specific adverse effects of ocriplasmin appear to correlate with the anatomical distribution of laminin within the retina and zonules.[7,20] For example, laminin degradation in synapses of the outer plexiform layer may explain ERG B-wave suppression, while cleavage of laminin in the interphotoreceptor matrix and photoreceptor cell layer is consistent with such findings as visual acuity loss, dyschromatopsia, nyctalopia, afferent pupillary defect, visual field constriction, ERG A-wave suppression, disruption of ellipsoid and interdigitation lines, and macular detachment.[7,10,20] The observations that subretinal fluid developing after ocriplasmin injection strongly correlates with ellipsoid zone changes[11,12] and can persist for over 6 months[3] have led previous authors[10,13,15] to suggest that ocriplasmin causes weakening of retinal adhesion by degrading laminin and possibly other constituents of the interphotoreceptor matrix, which is known to mediate photoreceptor-RPE adhesion in primate eyes.[24]

There are intriguing parallels between ocriplasmin's acute adverse effects in human eyes and the anatomical and functional abnormalities seen in congenital laminin deficiency states. In laminin β2 chain knockout mice, histology demonstrates shortened photoreceptor outer segments and disorganized photoreceptor synapses in the outer plexiform layer.[23] In

addition, laminin deficient mice display a negative waveform ERG with severely reduced B-waves. Laminin deficiency in zebrafish results in reduced A- and B-waves on ERG.[25] Histologic findings in these eyes include severe photoreceptor outer segment shortening and dysmorphic photoreceptor-bipolar synapses, in addition to abnormalities of the lens and other tissues. Pierson syndrome, a human disorder caused by mutations in the laminin β2 gene, can cause a range of ocular abnormalities, including a high incidence of retinal detachment in young children.[26] This adds further evidence that laminin function likely is important for normal retinal attachment.

There are many things we do not yet know about ocriplasmin-induced retinal toxicity. Importantly, complete information about the incidence and severity of acute retinal dysfunction after ocriplasmin injection is not yet available. Changes in the ellipsoid zone and other signals in the outer retinal were not reported in the phase III ocriplasmin clinical trial program, which used time domain rather than spectral domain OCT.[1,2] Similarly, ERG testing was not regularly obtained in ocriplasmin clinical trials, so the rate of panretinal dysfunction in this study group is unknown.[3] Furthermore, as pointed out by Hahn and co-authors in this issue of *Retina*,[3] post-market analyses based on voluntary reporting are inherently flawed when estimating the incidence of adverse events, due to gross underreporting.

However, recently published reports suggest that acute retinal alterations occur in a large proportion of eyes receiving intravitreal injection of ocriplasmin. In retrospective studies of consecutive eyes imaged with SD-OCT, ocriplasmin-associated loss of the ellipsoid zone is typically seen in 40-50% of eyes.[4,5,9,11,12,14] Quantitative OCT image analysis[5,12] may detect subtle ellipsoid layer loss not seen with visual inspection alone. Attenuation/disruption of outer retinal signals is typically accompanied by reduction in visual acuity within the first weeks after injection, which has been reported in as many as 80% of eyes in one retrospective series.[5] And while such SD-OCT and visual acuity data demonstrate that acute macular dysfunction is common after ocriplasmin injection, a small single-center phase 2 study found full-field ERG changes in 69% of eyes, suggesting that acute ocriplasmin retinopathy, when it occurs, routinely is panretinal in extent.[3] Clearly, further research is needed to understand the true incidence of the various findings comprising acute ocriplasmin retinopathy.

Also lacking is complete information about the extent and time course of recovery from ocriplasmin-induced retinal damage. In animal toxicology studies, acute findings such as retinal vascular attenuation and ERG suppression showed reversibility over time, but with persistence beyond 8 weeks in eyes receiving doses of 125 μg or greater.[16,17] Similarly, most of the retinal adverse effects in human eyes have been reported to be transient or mostly reversible over time, typically within 2 months after injection.[1,2,4,11,12,14] Even cases of severe visual acuity and visual field loss have been reported to resolve quite completely over extended periods of 4 to 36 months.[10,13] However, other reports have shown that visual acuity loss, ERG changes, ellipsoid zone alterations and/or subretinal fluid may persist in some patients beyond 3 to 6 months of follow-up.[2,3,5,9,12,15] The largest published analysis of pre-marketing ocriplasmin safety data[3] found that adverse effects such as

dyschromatopsia, reduced visual acuity, and ERG abnormalities remained unresolved at study end (6 months follow-up) in 12 to 40% of the eyes affected.

Many eyes recover from acute ocriplasmin retinopathy with good visual acuity.[10,11,13] However, we agree with Hahn and co-authors[3] that further studies are needed to fully understand the impact of ocriplasmin on long-term visual function. In the phase 3 clinical trials of ocriplasmin for VMT and macular hole, the mean change in VA at 6 months did not differ significantly between placebo and ocriplasmin groups, despite a higher percentage of ocriplasmin-treated eyes experiencing release of vitreomacular traction and macular hole closure.[1] In published retrospective series, visual outcomes in ocriplasmin-treated eyes are disappointing, with mean final post-injection visual acuities worse than,[5] the same as,[11] or only modestly (approximately one Snellen line) better than[4,14,27] pre-treatment acuities. Based on growing anecdotal clinical experience and several published reports[5,9,15] suggesting that some treated eyes have visual outcomes worse than expected based on the initial macular condition, we are concerned that ocriplasmin's enzymatic activity may permanently compromise visual function in a subset of eyes. However, alternative therapies for VMT and macular hole, such as vitrectomy and pneumatic vitreolysis, also have adverse effects, and comparative studies with long follow-up are needed to definitively establish preferred treatment paradigms.

It is currently not understood why ocriplasmin produces clinically evident retinal damage in some patients but not in others. In humans, laminin is comprised of five alpha, three beta, and three gamma chains, which produce 15 different isoforms.[28] It is therefore possible that genotype plays a role in determining vulnerability to ocriplasmin-induced vision loss. Other factors, such as variable dilution by the vitreous and variations in drug preparation and injection technique, might also influence drug safety. Unfortunately, it is not possible at this time to predict in advance whether acute ocriplasmin retinopathy in a given patient will be undetectable, mild and reversible, or severe and partially persistent. Until it is possible to identify which patients are susceptible to significant damage, injecting ocriplasmin is fraught with uncertainty. Fortunately, several phase 4 evaluations of ocriplasmin are ongoing and should provide us with additional safety information. We believe that ocriplasmin should be used with caution pending further study results about the mechanism, incidence, and reversibility of its harmful effects on the eye.

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Summary Statement

Review of safety data from clinical trials and post-marketing reports demonstrates that intravitreal ocriplasmin results in temporary and occasionally lasting panretinal structural and functional abnormalities in a subset of eyes. These acute effects are likely due to enzymatic degradation of laminin and possibly other proteins within the retina.