Practical Retina
Incorporating current trials and technology into clinical practice

In our first *Practical Retina*, Dr. Michael Ober from Southfield, Mich., was asked to comment on the FDA registration trials leading to the approval of ocriplasmin, or Jetrea, for symptomatic vitreomacular adhesion (sVMA). This unique agent is slated to be a very important tool to address the “wait and see” population of patients who have sVMA. These patients are not yet candidates for vitrectomy surgery because their relatively good vision does not warrant surgical risks.

Jetrea is unique from our other currently available intravitreal agents as it is an enzyme. This requires specialized handling and storage. Furthermore, theoretically, location of injection may play a role in efficacy. Lastly, given the unique mechanism of action, there may be a side effect profile unique to this agent compared to our other commonly used intravitreal injections.

Dr. Ober will comment on Jetrea — the first commercially available, FDA-approved intravitreal injection that is a proteolytic enzyme indicated for the treatment of symptomatic vitreomacular adhesion.

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The introduction of Jetrea (ocriplasmin, ThromboGenics) represents the first pharmacological treatment option for symptomatic vitreomacular adhesion, including vitreomacular traction and macular holes.

This drug has the potential to expand our treatment indications to include patients whose disease was previously addressed either through surgery or a wait-and-see approach. In particular, this drug offers a new option for patients in whom the risks of surgery were thought to outweigh the potential benefits.

Because the high threshold for surgery has historically excluded patients with mild disease, the standard of care has been based on monitoring for progression. In these cases, patients with visual symptoms now have a lower-risk option to address their condition at an earlier stage.

However, we await real world experience to determine how beneficial a product this will ultimately be. Before incorporating this drug into their practices, retinal specialists will need to weigh the advantages against the potentially significant barriers to widespread adoption.

**Ocriplasmin Benefits**

Ocriplasmin is a truncated form of the human serine protease plasmin. This recombinant protease dissolves the proteins that adhere the vitreous to the retina and is administered by intravitreal injection.

It has been studied in two phase 3 trials involving 652 patients with vitreomacular adhesion (VMA). These studies found that 26.5% of patients treated with ocriplasmin experienced resolution of VMA at 28 days, compared with 10.1% of patients receiving placebo ($P < .01$).

Ocriplasmin achieved nonsurgical closure of macular holes in 40.6% of injected eyes, compared with 10.6% of placebo-injected eyes.

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(P < .001). The phase 3 trials also found ocriplasmin to be largely well tolerated; the adverse events were temporary and mild.\(^1\)

Ocriplasmin offers a nonsurgical approach to patients with symptomatic VMA. Some patients with vitreomacular traction will likely be treated with ocriplasmin as an initial step, with failure leading to surgical intervention. In other patients, this drug will obviate the need for surgery.

I am eager to expand upon the indications in the clinical trials and try ocriplasmin prior to surgery in eyes with diabetic traction detachment and a diffusely attached vitreous. Perhaps this will aid in hyaloid separation, thus allowing a faster, easier, less complex surgery.

**ADOPTION BARRIERS**

Although ocriplasmin holds the promise of expanding treatment indications for symptomatic VMA, there are obstacles that may delay early adoption.

Ocriplasmin is much more stable than its parent molecule, plasmin, but it still must be stored at \(-4° F (\text{\textdegree}C)\).\(^2\) Failure to maintain the proper temperature will lead to degradation of the drug, and ThromboGenics will provide freezers to ensure proper storage. Furthermore, the retail cost of one vial is $3,950. For such costly inventory requiring below-freezing temperatures, a power outage could be catastrophic. For this reason, physicians might be compelled to invest further in a backup power generator and/or insurance coverage. All of this adds up to significant investment and expense for a product that has not yet been proven in a real-world situation.

Ocriplasmin works by lysing fibronectin, laminin, and other structural components of the vitreoretinal interface. Posterior hyaloid detachment will occur by two mechanisms following injection: (1) lysis of the vitreoretinal interface adhesions and (2) vitreolysis with liquefaction of the vitreous itself leading to contraction.\(^3,4\) In the presence of persistent vitreoretinal adhesions, pharmacologic vitreolysis alone can actually increase traction, at least in theory. For enzymatic degradation of the vitreoretinal adhesion to take place, the drug must reach the intended site. Given this fact and that ocriplasmin is quickly denatured in the body by naturally occurring enzymes as well as autolysis,\(^5\) an injection into the midvitreous is less likely to be effective than an injection under the posterior hyaloid. Thus, a high level of precision may be required for optimal effectiveness. It is therefore possible that with improved delivery techniques, the drug could be more effective than the clinical trial results indicate.

**ASSESSING THE DATA**

The phase 3 clinical trial results demonstrated a 26.5% anatomic improvement in VMA. Taken by itself, this result would be underwhelming for an expensive, invasive treatment; however, comparison to the placebo group (natural history) showed a statistically significant difference. The results for nonsurgical macular hole closure were more impressive, but treatment will be limited to the subset of macular holes with persistent vitreofoveal adhesion.

**ADVERSE EVENTS**

Ocular adverse events occurred in 68.4% of ocriplasmin-injected eyes versus 53.5% of placebo-injected eyes (P < .001), but this included expected events such as vitreous floaters, subconjunctival hemorrhage, and injection-related pain. The incidence of serious ocular adverse events was similar in the two groups (P = .26).\(^1\)

It should also be noted that in preclinical studies, lens subluxation was found in multiple animal species following a single injection of 0.175 mg ocriplasmin. After a second dose of 0.175 mg ocriplasmin injection, 100% of monkeys injected developed lens subluxation.\(^2\) Only a single case of lens subluxation was reported during the clinical trials of the FDA-approved dose (0.125mg/mL).\(^1\) Seven patients in a separate phase 2 trial received a second sequential injection of 0.125mg/mL ocriplasmin.\(^7\) None of these patients reported lens complications at 6 months; however, the preclinical data make me wonder whether eyes treated with ocriplasmin will have a greater incidence of late lens subluxation, dislocation, zonular dehiscence, and/or cataract surgery complications. Repeat injections could increase the potential for these complications.

**CONCLUSION**

Based upon this information, I believe retina specialists will be cautious in their early use of ocriplasmin. Whether it becomes adopted for widespread use will depend on real world experience. As clinicians, we do not like to talk about the bottom line, but some aspects of this product may catch our attention. It
will likely require an investment in infrastructure and carry some element of risk. Personally, I plan to limit early use and engage in discussions with my colleagues regarding our shared experiences before offering ocriplasmin to the bulk of potential candidates. This will enable a more informed decision on how to limit the risks and maximize the potential of ocriplasmin.

REFERENCES


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