Effect of Ocriplasmin on the Management of Macular Holes: Assessment of the Clinical Relevance of Ocriplasmin

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Ocriplasmin (Jetrea; ThromboGenics) is a recombinant truncated form of human plasmin that targets fibronectin, laminin, collagen, and other molecules. It enhances vitreous liquefaction and promotes separation of the vitreous from the internal limiting membrane.1

The Microplasmin for Intravitreous Injection–Traction Release Without Surgical Treatment (MIVI-TRUST) study group recently reported the results of enzymatic vitreolysis with ocriplasmin for vitreomacular traction (VMT) and macular holes (MHs). Nonsurgical closure of MHs was achieved in 40.6% of ocriplasmin-injected eyes compared with 10.6% of placebo-injected eyes, and the difference was highly statistically significant. Only MHs of 400 μm or less were eligible for the study, provided they also had vitreomacular adhesion (VMA).

Replacing vitrectomy for MHs with one injection of ocriplasmin is in theory a very attractive option. However, the MIVI-TRUST group did not provide data regarding the relative incidence of holes 400 μm or smaller with VMA among all eyes with MHs. It was our impression that most MHs seen in our institute are already at stage 3 or 4 when first evaluated by optical coherence tomography (OCT) and therefore are not candidates for this pharmacologic vitreolysis. The purposes of this study were to evaluate the population of patients with MHs who presented to our institute during the past 4 years (2009-
Methods

All OCT studies coded as MH VMT between April 1, 2009, and March 31, 2013, were retrospectively reviewed after Sheba Medical Center Institutional Review Board approval was obtained. The scans were reinterpret by 2 individuals (J.M. and I.M.) and classified as either MH or VMT. Eyes classified as VMT without MHs were excluded from the study. The purpose of this first analysis was to identify cases of stage 1 MHs that were coded as VMT or cases of VMT that were coded as stage 1 MHs, because there is some overlap between the 2 diagnoses. The definitions used in our study for these 2 entities are detailed in the following paragraph. The data retrieved for the study eyes included age, sex, right or left eye, presence or absence of VMA to the edges of the MH, stage of the hole, size of the hole (measurement technique provided below), and fellow eye findings. We also obtained information on prior ocular conditions, as defined by the MIVI-TRUST group exclusion criteria,2 and only patients without associated retinal abnormalities were eligible for this series. The presence of an epiretinal membrane was not a criterion for exclusion.

Definitions

The following definitions were used in our study:
1. Vitreomacular adhesion was considered the posterior vitreous face adhered to the macula with vitreous separation around the adhesion, without any visible deformity of the macular contour.
2. Vitreomacular traction was considered the posterior vitreous face adhered to the macula with vitreous separation around the adhesion, with any change in the macular contour at the adhesion site that could be attributed to traction. A case with VMT and an inner foveal cavity but with existing outer layers (Figure 1) was classified as VMT—not stage 1 MH.
3. Posterior vitreous detachment (PVD) is usually considered complete if there is no visible vitreous adhesion to the macula or optic disc. If there is vitreous adhesion to the disc but not to the macula, the PVD is considered incomplete. Because the purpose of the present study was to identify MHs with and without vitreous adhesion, we categorized all eyes without vitreous adhesion to the edge of the MH as eyes with PVD, regardless of whether PVD was complete or incomplete.
4. Stage 1 MH (Figure 2) was considered a closed-cap MH, with the cavity beneath the cap reaching all the way to the retinal pigment epithelium, with vitreous attached to the surface of the cap. There could be no discontinuity in the cap in any of the optical coherence tomographic scans. The box shows the location of the scan. I indicates inferior; N, nasal; S, superior; and T, temporal.
5. Stage 2 MH was considered a full-thickness MH with vitreous attached to the edges of the hole or to the cap as long as the cap was still attached to the rim of the hole.
6. Stage 3 or 4 MH was considered a full-thickness MH with no VMA to the hole. The PVD could be only over the macula (stage 3) or complete (stage 4).
7. For the size of the MH (Figure 3), the readers in the MIVI-TRUST study basically graded 2 dimensions of the MH: the maximum width at the level of the retinal pigment epithelium and the minimum width at any location along the hole.3 The largest of these minimum widths was recorded and used to define the size of the hole. Eyes with minimum width measurement greater than 400 μm were not eligible for the MIVI-TRUST study. The MIVI-TRUST study included only MHs with VMT and a size of 400 μm or less. Thus, only eyes with stage 1 or 2 MHs were eligible. We adopted the same criteria for our study.

OCT Scanners

Two scanners were used on eyes included in the study (Cirrus HD [high-density]–OCT, version 6; Carl Zeiss Meditec, Inc;...
or Spectralis SD [spectral-domain]-OCT, version 5; Heidelberg Engineering, Inc). All patients had a macular map scan and high-density raster lines performed over the foveal region. With the Cirrus HD-OCT, a macular cube scan of 512 × 128 lines was performed and a high-density, 5-line raster (1024 A scans), 6-mm line over the central foveal area was taken. With the Spectralis SD-OCT, a Fast Map 512 × 25 lines and 7-line (1536 A scans), 9-mm scans were performed. The images were analyzed, and the width of the MH was measured in the middle portion of the hole, in the narrowest area. The largest diameter recorded in all scans going through the MH was used for the study.

Results

There were 148 eyes of 148 patients coded as either MH or VMT. Reassessment of all scans resulted in final coding of 13 eyes as having VMT without MH, and these eyes were excluded. Of the 135 patients included in the study series, there were 53 men and 82 women, and the mean (SD) age was 67.3 (12.8) years (range, 18-91 years). Vitreomacular adhesion was present in 19 eyes graded as stage 1 (10 eyes) or stage 2 (9 eyes) MH. The other 116 eyes were graded as stage 3 or 4 MH, not having any evidence for VMA. The data on the 19 patients with VMA are presented in Table 1. Of the 10 stage 1 MHs, 7 were smaller than 400 μm and 3 were wider than 400 μm. Of the 9 stage 2 eyes, there were only 2 smaller than 400 μm, and 7 were wider. The fellow eye data in this group revealed VMA in 8 eyes, VMT in 3 eyes, PVD in 4 eyes, MH in 3 eyes, and epiretinal membrane with PVD in 1 eye. The data on the 116 eyes with MH and no VMT are presented in Table 2. There was no statistically significant difference between the study group and the stage 3 and 4 group regarding age, sex, or the distribution of macular findings in the fellow eyes.

Only 19 eyes (14.1%) in our series had MH with VMA. There were 9 eyes (6.7%) with an MH of 400 μm or less and 5 eyes (4.2%) with an MH of 250 μm or less. Thus, only 6.7% of the MHs in our series were eligible for ocriplasmin injection according to the MIVI-TRUST study.2 Assuming a 40% success rate (hole closure) as reported in that study, only 2.7% of our patients would have benefited from ocriplasmin injection. If the indications for ocriplasmin use are expanded to include all eyes with stage 1 MHs, regardless of size, together with the stage 2 eyes with MHs of less than 400 μm, 12 eyes (8.9%) in our series would be eligible for this therapy.

Discussion

Patients were eligible for the MIVI-TRUST study2 if they had focal VMA, defined as vitreous adhesion to the macula within a 6-mm central retinal field surrounded by elevation of the posterior vitreous cortex, as seen on OCT, and a best-corrected visual acuity (VA) of 20/25 or less in the study eye according to the Early Treatment Diabetic Retinopathy Study acuity chart.2 Our study was a retrospective review of medical records, and the VA acuity data were not obtained by study coordinators and probably were not the best-corrected VA for these patients. We therefore chose to exclude VA from the analysis of our data and to focus instead on anatomic data as identified by the OCT scanners. This omission does not undermine our results, because the upper limit for VA (20/25) is most likely met even by patients with stage 1 MHs. We adopted the other exclusion criteria mentioned above.

In the MIVI-TRUST study,2 nonsurgical closure of MHs was achieved in 40.6% of ocriplasmin-injected eyes compared with
Table 2. Eyes With MH and No VMA Compared With the Study Group

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No. (%)</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>MH, No VMA</td>
</tr>
<tr>
<td>No. of patients</td>
<td>116</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>46 (39.7)</td>
</tr>
<tr>
<td>Female</td>
<td>70 (60.3)</td>
</tr>
<tr>
<td>Age, mean (SD), y</td>
<td>67.5 (13.2)</td>
</tr>
<tr>
<td>Macular findings in fellow eye</td>
<td></td>
</tr>
<tr>
<td>VMA</td>
<td>53 (45.7)</td>
</tr>
<tr>
<td>VMT</td>
<td>4 (3.4)</td>
</tr>
<tr>
<td>PVD and normal macula</td>
<td>32 (27.6)</td>
</tr>
<tr>
<td>MH</td>
<td>11 (9.5)</td>
</tr>
<tr>
<td>After PPV for MH</td>
<td>4 (3.4)</td>
</tr>
<tr>
<td>ERM/PVD</td>
<td>10 (8.6)</td>
</tr>
<tr>
<td>Macular scar</td>
<td>1 (0.9)</td>
</tr>
<tr>
<td>Vitelliform lesion</td>
<td>1 (0.9)</td>
</tr>
</tbody>
</table>

Abbreviations: ERM, epiretinal membrane; MH, macular hole; PPV, pars plana vitrectomy; PVD, posterior vitreous detachment; VMA, vitreomacular adhesion; VMT, vitreomacular traction.

Ocriplasmin injection is offered as a pharmacological alternative to PPV in eyes with MHs. Our findings indicate that this treatment is suitable for few patients with MHs. The first limitation is that the hole must have VMA; therefore, it must be stage 1 or 2. Many of the patients present with stage 3 or 4 full-thickness MHs. This may be the result of delays in obtaining ophthalmic consultation (patient or medical system responsibility) as well as late referral for retinal consultation. In our series 85.9% of the patients presented with stage 3 or 4 full-thickness MHs and could not benefit from ocriplasmin injection. It is possible that expediting the evaluation of patients with vision problems could result in a larger proportion of MHs being identified at stage 1 or 2, and ocriplasmin thus could be offered to more patients. In addition, the MIVI-TRUST group2 included only MHs of 400 μm or less. Therefore, of the 14% of patients in our series with MHs and VMA, some were not eligible for pharmacologic vitreolysis. In our series only 6.7% of the patients had MHs of 400 μm or smaller associated with VMT. That is a very small proportion of the series, and if one projects on these patients the figure of 40% closure by ocriplasmin, it becomes evident that only 2.7% of our patients (4 eyes) could benefit from the treatment. Because stage 1 MHs are not full thickness, having an uninterrupted cap with VMA, it could be argued that all stage 1 MHs are candidates for pharmacologic vitreolysis regardless of size. Size is probably more important for stage 2 MHs. Even if we thus broaden the eligibility criteria, we could offer treatment to only 12 eyes (8.9%) in our series. However, if the cutoff size of 250 μm is chosen, only 4.2% of the patients in our series would be candidates for ocriplasmin.

The scans in our series were all performed with SD machines; however, the MIVI-TRUST study2 used time-domain OCT machines. It could be argued that the use of SD-OCT instead of time-domain OCT could change the evaluation of these eyes, but the MIVI-TRUST group compared the measures of MHs (vitreomacular interface findings and size estimates) obtained with the 2 types of scanners and found no statistically significant difference between them (except for epiretinal membrane).5

The main limitations of our work are that it was retrospective and there were no best-corrected VA results. However, all scans were performed within one institute, and the series included all MHs evaluated in our imaging service during a 48-month period; in our opinion, these factors reflect medical reality. The 2 study groups—with and without VMA—were similar in age, sex, and fellow eye abnormalities. It seems, therefore, that our series represents an unbiased cohort of patients with MHs.

Conclusions

The present study did not address the possible complications of ocriplasmin that were reported in detail by the MIVI-TRUST group and therefore did not evaluate the risks and benefits of ocriplasmin as compared with vitrectomy. Our only purpose was to gain some understanding of the effect of ocriplasmin on the management of MHs, because these data were not provided by the MIVI-TRUST group. We believe that few eyes with MHs would be good candidates for ocriplasmin treatment and that PPV will probably remain the treatment of choice for most eyes with MHs. This situation could change if MHs are detected earlier and treated while they are still small and have VMT.


**OPHTHALMIC IMAGES**

**Inadvertent Corneal Intrastral Intraocular Lens Implantation During Phacoemulsification**

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Inadvertent intrastral intraocular lens implantation at the time of wound-assisted intraocular lens delivery with successful retrieval and eventual reimplantation of the intraocular lens in the capsular bag. The postoperative visual outcome was good at 6 months' follow-up (spectacle prescription: −0.75 cylinder at 105° with visual acuity of 6/6 Snellen equivalent in meters).

Figure 1. Intrastral implantation of intraocular lens with surrounding corneal striae.

Figure 2. Six-month postoperative image showing clear cornea.