Original Investigation | CLINICAL SCIENCES

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

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IMPORTANCE Assessing the effect of ocriplasmin availability on the management of full-thickness macular holes (MHs) is important for vitreoretinal surgeons and their patients. Such an assessment can indicate whether the use of ocriplasmin will bring a paradigm shift in treating MHs or will be just an additional option relevant to a small group of patients.

OBJECTIVES To classify the MHs evaluated in our institute by their stage and the presence of vitreomacular adhesion (VMA) and to identify eyes that were suitable candidates for ocriplasmin injection according to guidelines published by the Microplasmin for Intravitreous Injection–Traction Release Without Surgical Treatment (MIVI-TRUST) study group.

DESIGN, SETTING, AND PARTICIPANTS All optical coherence tomographic studies of eyes with MHs performed between 2009 and 2013 were retrospectively reviewed. The scans were interpreted by 2 individuals, and for each hole the stage, size, and vitreomacular relationship were defined according to the definitions used in the MIVI-TRUST studies. One hundred thirty-five patients with full-thickness MHs evaluated at a public hospital were included in the study series. There were 82 women and 53 men, and the mean (SD) age was 67.3 (12.8) years.

MAIN OUTCOMES AND MEASURES The stage, size, and presence or absence of VMA were documented for each MH. The suitability for ocriplasmin intravitreal injection was determined according to the criteria described in the MIVI-TRUST reports.

RESULTS Vitreomacular adhesion was present in 19 eyes with MH (14.1%). Of these, the hole size was 400 µm or less in only 9 eyes (6.7% of the series). Using the criteria of the MIVI-TRUST study exclusively, only these eyes were candidates for ocriplasmin injection. Assuming a closure success rate of 40%, as described in that study, only 2.7% of the patients in our series would have benefited from ocriplasmin injection.

CONCLUSIONS AND RELEVANCE Our findings indicate that ocriplasmin injection is an adequate choice for few patients with MHs. Pars plana vitrectomy 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 vitreomacular traction.

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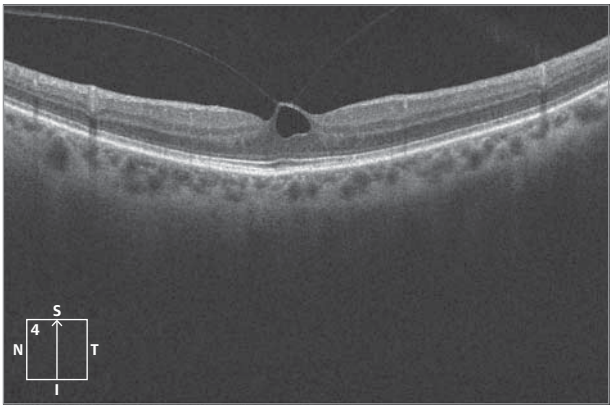
Ocriplasmin (Jetrea; ThromboGenics) is a recombinant truncated form of human plasmin that targets fibronectin, laminin, collagen, and other molecules. It enhances vitreous liquefaction and promotes separation of the vitreous from the internal limiting membrane.[1]

The Microplasmin for Intravitreous Injection–Traction Release Without Surgical Treatment (MIVI-TRUST) study group[2] 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).

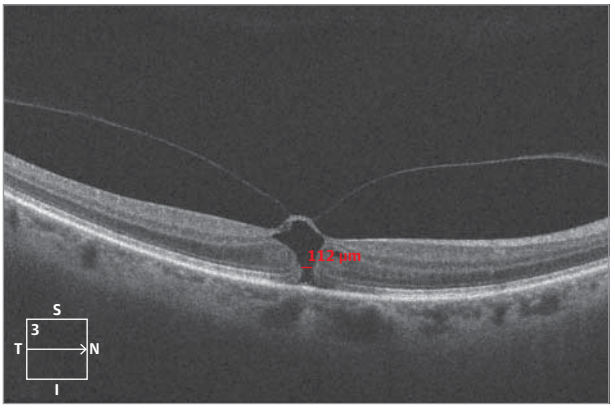
Replacing vitrectomy for MHs with one injection of ocriplasmin is in theory a very attractive option. However, the MIVI-TRUST group did not provide data regarding the relative incidence of holes 400 µm or smaller with VMA among all eyes with MHs. It was our impression that most MHs seen in our institute 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-

Figure 1. Vitreomacular Traction (VMT)



Presence of VMT and an inner foveal cavity but with existing outer layers was defined as VMT and not as a stage 1 macular hole; it was not included in the series. The box shows the location of the scan. I indicates inferior; N, nasal; S, superior; and T, temporal.

Figure 2. Stage 1 Macular Hole



A macular hole with an intact cap, with the cavity beneath the cap reaching all the way to the retinal pigment epithelium and the 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.

2013) and to identify MHs that were suitable candidates for ocriplasmin injection according to the guidelines published by the MIVI-TRUST study group.[2]

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 reinterpreted 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

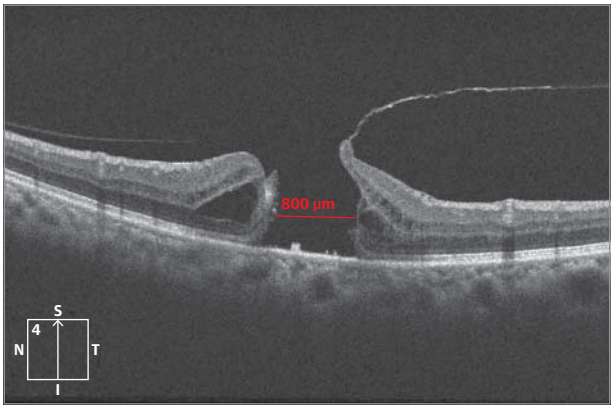
The following definitions were used in our study:

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 OCT scans.
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.[1] 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;

Figure 3. Example of Macular Hole Size Determination



The minimum width at any location along the hole was graded, and the largest of these minimum widths was recorded and used to define the size of the macular hole. The Microplasmin for Intravitreous Injection–Traction Release Without Surgical Treatment study included only macular holes with vitreomacular traction and a size of 400 µm or less. The box shows the location of the scan. I indicates inferior; N, nasal; S, superior; and T, temporal.

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, then 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.

Table 1. Nineteen Eyes With MH and VMT

Patient Sex/ Age, y	Study Eye			Macular Findings in Fellow Eye
	R/L	Hole Size, µm	Stage	
F/74	L	345	1	MH
M/66	L	168	1	ERM and PVD
F/82	L	364	1	VMA
M/82	L	544	1	MH
M/67	R	492	1	VMA
F/67	R	168	1	VMA
F/65	R	136	1	VMT
F/62	L	80	1	MH
F/70	R	503	1	VMT
M/68	L	144	1	PVD
F/67	R	760	2	PVD
M/55	L	800	2	VMA
F/59	L	760	2	VMA
F/60	L	376	2	PVD
F/36	R	544	2	VMA
F/69	L	688	2	VMT
M/64	R	420	2	VMA
M/72	L	344	2	VMA
F/64	R	512	2	PVD

Abbreviations: ERM, epiretinal membrane; L, left; MH, macular hole; PVD, posterior vitreous detachment; R, right; VMA, vitreomacular adhesion; VMT, vitreomacular traction.

Discussion

Patients were eligible for the MIVI-TRUST study[2] 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

Characteristic	No. (%)	
	MH, No VMA	MH, VMA
No. of patients	116	19
Sex		
Male	46 (39.7)	7 (36.8)
Female	70 (60.3)	12 (63.2)
Age, mean (SD), y	67.5 (13.2)	65.7 (9.9)
Macular findings in fellow eye		
VMA	53 (45.7)	8 (42.1)
VMT	4 (3.4)	3 (15.8)
PVD and normal macula	32 (27.6)	4 (21.1)
MH	11 (9.5)	3 (15.8)
After PPV for MH	4 (3.4)	0
ERM/PVD	10 (8.6)	1 (5.3)
Macular scar	1 (0.9)	0
Vitelliform lesion	1 (0.9)	0

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

10.6% of placebo-injected eyes, and the difference was highly statistically significant. In oral presentations[4] a subgroup analysis revealed that nonsurgical closure was dependent on the size of the MH. Nonsurgical closure of MHs that were 250 µm wide or less was achieved in 58% of the eyes with ocriplasmin compared with 16% with placebo. Nonsurgical closure of MHs that were 250 to 400 µm wide was successful at a much lower rate—25% compared with 4% with placebo injection.

Ocriplasmin injection is offered as a pharmacologic 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 group[2] 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 study[2] 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.

ARTICLE INFORMATION

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Author Contributions: Drs Moisseiev and Moroz contributed equally to the study. Dr Moisseiev had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Moisseiev, Katz.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: All authors.
Critical revision of the manuscript for important intellectual content: Moisseiev, Moroz.
Statistical analysis: Moisseiev, Moroz.
Administrative, technical, or material support: Moroz, Katz.

Conflict of Interest Disclosures: None reported.

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OPHTHALMIC IMAGES

Inadvertent Corneal Intrastromal Intraocular Lens Implantation During Phacoemulsification

Arun Kumar Jain, MD; Adit Gupta, MS; Raghav Gupta, MD; Nishant Nawani, MS

Inadvertent intrastromal 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).

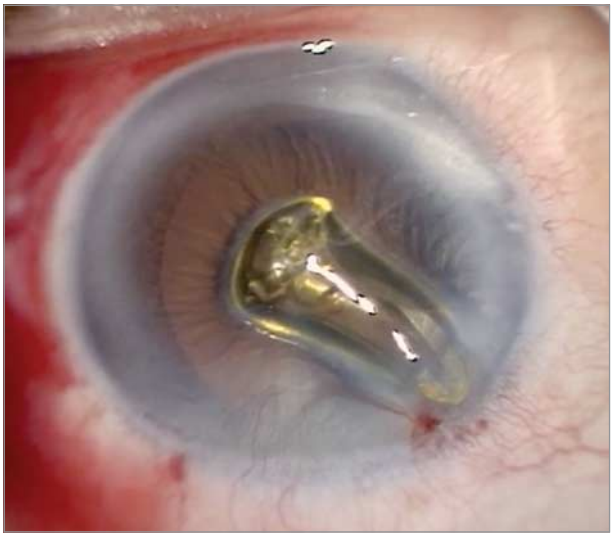

Figure 1. Intrastromal implantation of intraocular lens with surrounding corneal striae.

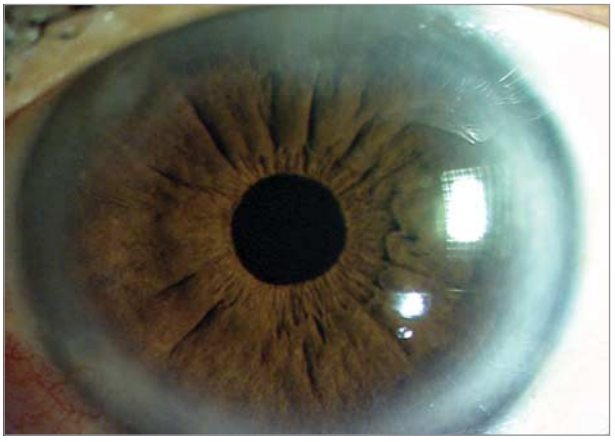

Figure 2. Six-month postoperative image showing clear cornea.