Characterization of Anatomic and Visual Function Outcomes in Patients With Full-Thickness Macular Hole in Ocriplasmin Phase 3 Trials

PRAVIN U. DUGEL, CARL REGILLO, AND DEAN ELIOTT

- PURPOSE: To characterize anatomic and visual outcomes in patients with full-thickness macular hole (FTMH) at baseline in ocriplasmin phase 3 clinical trials, focusing on the relationship between resolution of vitreomacular adhesion and FTMH closure.
- DESIGN: Two multicenter, randomized, double-masked clinical trials.
- METHODS: Pharmacologic FTMH closure was one of multiple secondary endpoints. OCT scans were obtained at baseline and at all postinjection visits, and for patients with baseline FTMH, evaluated for FTMH width, vitreomacular adhesion, and epiretinal membrane.
- RESULTS: FTMH closure was observed in a greater proportion of ocriplasmin- vs vehicle-injected patients with baseline FTMH width ≤250 μm (58.3% vs 16.0%, P < .001) and >250 to ≤400 μm (36.8% vs 5.3%, P = .009). Among FTMH patients in the ocriplasmin group, ≥2-line visual acuity gains at month 6 were achieved by a greater percentage of those who achieved hole closure at day 28 vs those who did not achieve this outcome (72.1% vs 25.4%).
- CONCLUSIONS: Ocriplasmin demonstrated efficacy in closure of small and medium FTMH, and in FTMH without epiretinal membrane at baseline. Visual acuity gains occurred more frequently when hole closure was achieved after ocriplasmin treatment compared to when this outcome did not occur. Ocriplasmin treatment is an additional option for the management of patients with FTMH and vitreomacular adhesion. (Am J Ophthalmol 2015;160(1):94–99. © 2015 by Elsevier Inc. All rights reserved.)

Incomplete posterior vitreous detachment from the macula (vitreomacular adhesion, VMA) can lead to vitreomacular traction and full-thickness macular hole (FTMH). An FTMH is a continuous lesion that interrupts all retinal layers from the internal limiting membrane to the retinal pigment epithelium, and is characterized according to multiple anatomic features, including but not limited to vitreous anatomy, hole diameter, presence of cystoid parafoveal changes, presence of epiretinal membrane, location of the hole center relative to the foveola, and configuration of the hole edges on the retina surface. Symptoms and signs of FTMH include metamorphopsia, reduced visual acuity, and central scotoma. Untreated FTMH can lead to irreversible retinal damage and vision loss. Delays in treatment can lead to suboptimal outcomes, and early diagnosis is therefore critical for preserving visual function.

Ocriplasmin (Jetrea; ThromboGenics, Leuven, Belgium) is a pharmacologic treatment option for patients with symptomatic VMA. The safety and efficacy of ocriplasmin for symptomatic VMA was demonstrated in 2 phase 3 clinical trials (the Microplasmin for Intravitreous Injection–Traction Release without Surgical Treatment, or MIVI-TRUST, trials). Ocriplasmin has proteolytic activity that degrades extracellular matrix components of the vitreous body and the vitreomacular interface, including collagen, laminin, and fibronectin. This activity is thought to induce vitreous liquefaction and separation of the vitreous cortex from the inner retina.

Ocriplasmin achieved the primary efficacy endpoint in the phase 3 trials: pharmacologic VMA resolution at day 28 after injection. Several secondary efficacy endpoints were also met, including pharmacologic closure of FTMH at day 28 after injection. The current analysis evaluates anatomic and visual outcomes in the subgroup of patients with VMA and concomitant FTMH in the ocriplasmin phase 3 clinical trials. This analysis will identify factors affecting FTMH closure and help define future treatment strategies.

METHODS

The efficacy and safety of Ocriplasmin for the treatment of symptomatic VMA was demonstrated in 2 pivotal phase 3 randomized, double-masked, vehicle-
controlled trials.\textsuperscript{7} The trials are registered in the US National Institutes of Health clinicaltrials.gov database (NCT00781859 and NCT00798317). Study design, Institutional Review Board approval, and Informed Consent approval were previously reported.\textsuperscript{7} Enrolled patients were analyzed by time-domain optical coherence tomography (TD-OCT) at a central reading center (CRC) to confirm the presence of VMA. The eligibility of the patients was assessed by the study investigators; however, assessment of the images was also performed independently by the central reading center. The CRC measurements are standardized across all sites and patients, and for statistical analysis those measurements were used. In some instances, measurements made by the investigator on site differed from the measurement by the CRC.

A total of 652 patients were treated with a single intravitreal injection of ocriplasmin 125 \( \mu \text{g} \) (\( n = 464 \)) or vehicle (\( n = 188 \)).\textsuperscript{7} A post hoc analysis was performed to evaluate visual and anatomic outcomes after ocriplasmin injection in patients from the phase 3 trials who had symptomatic VMA with FTMH at baseline (106 in the ocriplasmin group and 47 in the vehicle group). Visual acuity was measured as Early Treatment Diabetic Retinopathy Study (ETDRS) letters. OCT scans were analyzed from baseline and all postinjection visits through the end of the study. Macular hole diameter was defined as the shortest linear distance between the edges of the hole using a line parallel to the retinal pigment epithelium. The shortest linear distance was chosen based on previous work that analyzed and defined success for macular hole closure based on a size determined from the shortest distance across the full-thickness defect.\textsuperscript{4,10-11} The measurement was based on 6 radial scans as defined in the clinical study protocol commonly used for Stratus OCT. Ocular features derived from OCT imaging included FTMH diameter, VMA resolution status, and epiretinal membrane presence.

Summary statistics for continuous variables included number of observations (\( n \)), mean, standard deviation (SD), median, minimum, and maximum. Categorical variables were summarized using group counts and percentages for each category. Results of statistical testing included values for each treatment, crude and stratified differences between treatments (categorical variables only), and 2-sided 95% confidence interval (CI) and \( P \) values. For categorical endpoints, differences between treatments were evaluated using the Cochran-Mantel-Haenszel test, stratified by study (integrated studies). For continuous endpoints, differences between treatments were evaluated using analysis of variance (ANOVA) with factor for study in the integrated analysis.

### RESULTS

- **BASELINE OCULAR CHARACTERISTICS AMONG PATIENTS WITH FULL-THICKNESS MACULAR HOLE AT BASELINE:** The mean FTMH diameter from patients enrolled in the phase 3 trials who presented with an FTMH at baseline was 282.7 \( \mu \text{m} \) and 247.0 \( \mu \text{m} \) in the ocriplasmin-treated and vehicle-treated groups, respectively (Table). Out of a total of 153 patients who presented with FTMH, 73 (48\%) presented with a small FTMH (diameter \( \leq 250 \mu \text{m} \), 48 of 106 [45.3\%] in the ocriplasmin group and 25 of 47 [53.2\%] in the vehicle group). Although large FTMH (diameter \( > 400 \mu \text{m} \)) was an exclusion criterion, 19 of 106 (17.9\%) patients in the ocriplasmin group and 3 of 47 (6.4\%) patients in the vehicle group had large FTMH at baseline (Table). These 22 patients were ultimately included in the analysis population.

- **OVERALL RATES OF FULL-THICKNESS MACULAR HOLE CLOSURE:** After injection, 43 of 106 (40.6\%) patients in the ocriplasmin group and 5 of 47 (10.6\%) patients in the vehicle group achieved FTMH closure by day 28 (\( P < .001 \)).\textsuperscript{7} The proportion of patients with FTMH closure at month 6 was 40.6\% in the ocriplasmin group and 17.0\% in the vehicle group (\( P = .004 \)).\textsuperscript{7}

- **FULL-THICKNESS MACULAR HOLE CLOSURE BY HOLE SIZE AT BASELINE:** The rate of FTMH closure at day 28 was determined in subgroups of patients by the FTMH diameter at baseline. The prespecified analysis plan was to evaluate hole closure rates in holes with diameter \( \leq 250 \mu \text{m} \) and \( > 250 \mu \text{m} \). An additional post hoc analysis was done to include the subgroup of patients who presented with holes with diameter \( > 250 \mu \text{m} \) and \( \leq 400 \mu \text{m} \). The following subgroups showed differential responses to ocriplasmin treatment compared to vehicle treatment: the small FTMH subgroup (58.3\% vs 16.0\%, \( P < .001 \)) and the medium FTMH subgroup (diameter \( > 250 \mu \text{m} \) to \( \leq 400 \mu \text{m} \), 36.8\% vs 5.3\%, \( P = .009 \)) (Figure 1). The study subgroup of \( > 250 \mu \text{m} \) showed a rate of FTMH closure of

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**TABLE.** Selected Baseline Characteristics of Full-Thickness Macular Holes From the Ocriplasmin Phase 3 Trials, as Determined by Time-Domain Optical Coherence Tomography

| Baseline OCT Characteristic                        | Vehicle\textsuperscript{4} (\( N = 47 \)) | Ocriplasmin\textsuperscript{7} (\( N = 106 \)) |
|-----------------------------------------------|-----------------------------------------------|
| Mean FTMH diameter (\( \mu \text{m} \))       | 247.0                                         | 282.7                                         |
| FTMH diameter \( \leq 250 \mu \text{m} \), n (%) | 25 (53.2\%)                                   | 48 (45.3\%)                                   |
| FTMH diameter \( > 250 \mu \text{m} \leq 400 \mu \text{m} \), n (%) | 19 (40.4\%)                                   | 38 (35.8\%)                                   |
| FTMH diameter \( > 400 \mu \text{m} \), n (%) | 3 (6.4\%)                                     | 19 (17.9\%)                                   |
| Presence of epiretinal membrane, n (%)        | 5 (10.9\%)                                    | 18 (18.0\%)                                   |

FTMH = full-thickness macular hole; OCT = optical coherence tomography.

\textsuperscript{4}One patient in the ocriplasmin group did not have an FTMH diameter measurement at baseline. One patient in the vehicle group and 6 patients in the ocriplasmin group were not evaluable for epiretinal membrane status at baseline.
24.6% in the ocriplasmin group vs 4.5% in the placebo group (P = .031). No large (>400 µm) FTMH patients achieved hole closure with either ocriplasmin or vehicle treatment.

**FULL-THICKNESS MACULAR HOLE CLOSURE BY EPIRETINAL MEMBRANE STATUS AT BASELINE:** Patients with FTMH at baseline were evaluated for the rate of FTMH closure by baseline epiretinal membrane status. A total of 23 patients were determined to have epiretinal membrane at baseline, with 18 of 100 (18.0%) patients in the ocriplasmin group and 5 of 46 (10.9%) patients in the vehicle group (P < .001). Among patients with medium (250 to ≤400 µm) FTMH at baseline, the percentage that achieved hole closure at day 28 was also significantly higher in the ocriplasmin group compared to the vehicle group (P = .009).

**VISUAL ACUITY OUTCOMES:** Success in achieving FTMH closure was strongly associated with visual acuity improvement. For FTMH patients treated with ocriplasmin who achieved hole closure at day 28, 31 of 43 (72.1%) patients gained at least 2 lines at month 6, and 21 of 43 (48.8%) gained at least 3 lines at month 6. Interestingly, some FTMH patients without hole closure at day 28 also showed improvement in visual acuity: 16 of 63 (25.4%) ocriplasmin-treated patients gained at least 2 lines and 8 of 63 (12.7%) ocriplasmin-treated patients gained at least 3 lines at month 6. In FTMH patients with vehicle injection who achieved hole closure at day 28, 2 of 5 (40.0%) patients gained at least 2 lines and 2 of 5 (40.0%) gained at least 3 lines at month 6. In vehicle-injected patients without hole closure at day 28, 12 of 42 (29.3%) patients achieved hole closure at day 28. Among patients with absence of epiretinal membrane (ERM) at baseline, the percentage that achieved hole closure at month 6 was significantly higher in the ocriplasmin group compared to the vehicle group (P = .002).

**EYES WITH PHARMACOLOGIC VITREOMACULAR ADHESION RESOLUTION AND FULL-THICKNESS MACULAR HOLE CLOSURE:** Another clinical consideration is the relationship between VMA resolution and FTMH closure. For ocriplasmin-treated patients who achieved FTMH closure at month 6, 24 of 43 (55.8%) patients also achieved VMA resolution at day 28, whereas 19 (44.2%) did not (Figure 3).

**HOLE REOPENING AFTER FULL-THICKNESS MACULAR HOLE CLOSURE:** The proportion of patients with FTMH reopening after FTMH closure was low: 4 of 43 (9.3%) patients in the ocriplasmin group and 0 of 8 (0.0%) patients in the vehicle group at month 6.
gained at least 2 lines and 4 of 42 (9.8%) gained at least 3 lines at month 6. None of the FTMH patients treated with ocriplasmin achieved hole closure at day 28. Among patients without hole closure at day 28, some FTMH patients showed a decrease in visual acuity: 9 of 63 (14.3%) ocriplasmin-treated patients lost at least 2 lines and 7 of 63 (11.1%) ocriplasmin-treated patients lost at least 3 lines. For FTMH patients with vehicle injection who achieved hole closure at day 28, 1 of 5 (20.0%) patients lost at least 2 lines, while none lost 3 lines or more. In patients without hole closure after vehicle injection, 6 of 42 (14.6%) patients lost at least 2 lines and 5 of 42 (12.2%) lost at least 3 lines at month 6.

Selection Case: The following example is a patient from the phase 3 trials with VMA and FTMH with hole closure and visual acuity improvement after ocriplasmin treatment. Visual acuity was 20/63 at baseline (Figure 4, Top left). The FTMH had vitreous attachment to the inner retinal flap and the presence of cystoid spaces. Following ocriplasmin treatment, VMA resolution and initiation of FTMH closure occurred within 7 days (Figure 4, Top middle). Subretinal fluid was observed at days 7 and 14 (Figure 4, Top middle and Top right, respectively) but diminished over time (Figure 4, Bottom left and Bottom middle panels) and completely resolved by month 6 (Figure 4, Bottom right). Complete closure of the FTMH was evident at 6 months and the final visual acuity improved to 20/32.

Discussion

Spontaneous FTMH closure has historically been shown to occur in 5%–11% of cases. In the randomized controlled ocriplasmin phase 3 clinical trials, FTMH closure occurred in 10.6% of patients in the vehicle group, similar to what is reported for spontaneous closure in the absence of treatment. Pharmacologic FTMH closure was achieved by a significantly greater proportion of patients in the ocriplasmin group (40.6%) compared to this vehicle group.

This subgroup analysis demonstrated the efficacy of ocriplasmin for patients with VMA and small or medium FTMH. Small to medium FTMHs are usually early-stage and amenable to treatment. More than half of eyes with VMA and small FTMH achieved hole closure at day 28 after ocriplasmin injection, while more than a third with VMA and medium FTMH had closure at day 28 after injection. Large FTMH was an exclusion criterion in the phase 3 trials, but a small number of eyes with VMA and large FTMH were nevertheless enrolled and treated. None of these eyes achieved hole closure during the study, suggesting that the pharmacologic vitreolytic activity of ocriplasmin is not likely to facilitate hole closure in symptomatic VMA patients with large FTMH. Hole closure rates were similar between ocriplasmin-treated patients who had epiretinal membrane at baseline and those without epiretinal membrane at baseline. This is in contrast to findings from a recent study by Haller and associates. Results of post hoc subgroup analyses should be interpreted with the understanding that such patient subpopulations can represent a small number of eyes, often analyzed by TD-OCT. Future analyses including
larger numbers of patients with FTMH and epiretinal membrane, or using spectral-domain OCT imaging, may yield different results.

Best-corrected visual acuity improvement was observed in patients with successful hole closure after ocriplasmin treatment. In some patients, BCVA still improved even though hole closure did not occur after ocriplasmin treatment, which may be attributable to VMA resolution. Interestingly, VMA resolution is not necessary for FTMH closure, as almost half of the patients whose holes closed following ocriplasmin treatment did not have VMA resolution. One possibility is that partial VMA release, or some degree of enhanced vitreous liquefaction, may be theoretically sufficient to allow hole closure.

While VMA is thought to be involved in the development of idiopathic macular holes, there is no clear understanding of how or whether VMA resolution influences the closure of macular holes. Based on the data presented here, there does not seem to be an obvious association.

The high percentage of patients who did not have hole closure but did have visual acuity improvement (25.4% and 29.3% in the ocriplasmin and vehicle groups, respectively) may also suggest that visual acuity testing in the presence of a macular hole has a lower coefficient of repeatability than visual acuity testing in individuals without maculopathy. Indeed, it has been shown that postoperative visual results vary significantly with the size of macular holes in patients with stage 3 macular holes of duration 1–4 months, suggesting that the intervention in the study (either vehicle or ocriplasmin injection) affected the vitreous architecture and/or macular hole size or configuration in a way that affected visual acuity.

One important consideration when discussing visual acuity outcomes is potential changes in lens status. In the pivotal phase 3 studies, ocriplasmin did not appear to affect cataract formation differently from vehicle. The incidence of cataract (any event) in the pivotal studies combined was 26 of 465 (5.6%) in the ocriplasmin group compared with 17 of 187 (9.1%) in the vehicle group. In phakic eyes, progression of cataracts was observed in 24 of 293 (8.2%) eyes injected with ocriplasmin and in 16 of 134 (11.9%) eyes injected with vehicle ($P = .32$). Among patients who did not undergo vitrectomy, the proportion of patients with cataract progression was similar in the ocriplasmin and placebo groups (4.8% and 5.2%, respectively; $P = .97$).

Ocular features associated with hole closure after ocriplasmin injection in this subgroup analysis will be useful for physicians considering treatment options for patients with symptomatic VMA and concomitant FTMH.

**FIGURE 4.** Case of small full-thickness macular hole and vitreomacular adhesion with successful anatomic and visual outcomes after ocriplasmin injection. (Top left) Baseline: Patient presented with a small (±250 μm) full-thickness macular hole (FTMH); vitreous was attached to the inner retinal flap of the hole and intraretinal cystoid spaces were detected; visual acuity was 20/63. The eye was treated with a single intravitreal injection of 125 μg ocriplasmin. (Top middle) Day 7 post injection: Vitreomacular adhesion was resolved and hole closure appeared to have initiated, with subretinal fluid present; visual acuity was 20/50. (Top right) Day 14 post injection: Subretinal fluid present; visual acuity was 20/63. (Bottom left) Day 28 post injection: Subretinal fluid appears to be resolving; visual acuity was 20/40. (Bottom middle) Month 3 post injection: Subretinal fluid continues to resolve; visual acuity was 20/40. (Bottom right) Month 6 post injection: Hole closure was complete, and subretinal fluid also completely resolved; visual acuity was 20/32.
REFERENCES


Biosketch

Dr Pravin U. Dugel is an internationally recognized clinical researcher, awarded with Senior Honors by the AAO. He is Managing Partner of Retinal Consultants of Arizona, Founding Member of Spectra Eye Institute and Clinical Professor at USC Eye Institute, Keck School of Medicine. Dr Dugel was recently named to the Board of Directors of A New Vision and is Chairman of the ORBIS International Medical Advisory Board, providing free surgery to preventable blindness sufferers worldwide.