Italian real-life experience on the use of ocriplasmin

Francesco Barca, Dario Pasquale Mucciolo, Tomaso Caporossi, Gianni Virgili, Ruggero Tartaro, Stanislao Rizzo, The Italian Ocriplasmin Group

ABSTRACT

Objective To evaluate the success of an intravitreal injection of ocriplasmin to release symptomatic vitreomacular traction (VMT) and close a full-thickness macular hole.

Methods and analysis An observational retrospective multicentre study conducted in Italy. Patients with symptomatic distortion and loss of vision secondary to VMT were included in the study. The patients received a single injection of ocriplasmin and were followed up for 1, 3 and 6 months. Best-corrected visual acuity (BCVA) and spectral domain OCT (SD-OCT) were performed for patient assessment, and adverse events were recorded and analysed.

Results 74 patients (74 eyes) were included in the study. 44 of 74 eyes (59.5%) experienced complete release of the VMT. Macular hole closure was obtained in eight eyes (40%). BCVA improved about three lines after 3 months of follow-up in the patients with VMT resolution in comparison with the patients who did not have VMT resolution (p<0.0001). In 55/74 eyes of 55 patients (74.3%), no adverse events were reported, and most of them were transitory (17/19; 89.5%). The mean time to resolve VMT was 27.4±21.9 days. No cases of retinal tear, retinal detachment or lens destabilisation were observed.

Conclusion Ocriplasmin is a potential alternative treatment for patients with symptomatic VMT and has a good safety profile. A more careful selection of patients, in clinical practice, may increase the success rate.

INTRODUCTION

Vitreomacular traction (VMT) syndrome is a disorder of the vitreomacular interface characterised by an incomplete and pathological separation between the vitreous and the macula. Resulting alterations in retinal morphology may lead to symptomatic metamorphopsia and decreased visual acuity.1-3 The purpose of therapy is to release vitreous traction on the macula before structural retinal damage occurs.1 Ocriplasmin, a serine protease, is active against substrates, such as fibronectin and laminin, and is therefore able to cleave the vitreoretinal interface.3 The results of phase III studies demonstrated a clinically significant difference in favour of a single intravitreal injection of 125 mg of ocriplasmin over the placebo, and they achieved VMT resolution at day 28.3

Furthermore, release rates were found to be positively correlated with age less than 65 years, absence of an epiretinal membrane (ERM), VMT diameter of ≤1500 micra and phakic lens status.4 Concerning full-thickness macular hole (FTMH) treated with ocriplasmin, a closure rate of 40.6% was found versus 10.6% in the placebo group. Ocriplasmin was then approved for the non-surgical treatment of symptomatic VMT associated or not to FTMH less than 400 micra.5 Since the real-world use of the drug began, there have been favourable reports of visual improvement after ocriplasmin injection due to the release of VMT.6-7

In this study, we examine a multicentric clinical experience (18 centres) of ocriplasmin injection for VMT with or without macular hole (MH), and we report on data from 74 collected eyes.

METHODS

Patients and baseline assessment

Informed consent was obtained from subjects (or their guardians).
Seventy-four consecutive patients were included in this study; they underwent a complete ophthalmological evaluation, including extensive history and optical coherence tomography (OCT). All patients with symptomatic vitreomacular adhesion or VMT who had the ocriplasmin injection (a single intravitreal injection of 125 µg ocriplasmin) were included; no injected patients were excluded. The primary end-point was VMT release at the end of follow-up (range 30–180 months postinjection).

**Ocriplasmin injection protocol**

All patients received an intravitreal injection of ocriplasmin (125 µg in a 0.10 mL volume) via pars plana. All intravitreal injections were performed under sterile conditions, as per standard protocol. Patients were observed for 30 min after the injection and discharged if intraocular pressure was less than 30 mm Hg.

**Statistical analysis**

The patients were divided into subgroups according to traction width and MH size, if present. The effect of baseline predictors of surgical success was assessed at 30 days as the primary analysis; anatomical response was a dichotomous variable (resolution of traction and closing the hole) in a logistic regression model. In secondary analyses, the anatomical and functional response (visual acuity) was assessed up to a follow-up of 6 months with linear mixed models, considering repeated measurements within the patient.

**RESULTS**

**Findings at baseline**

Seventy-four eyes of 74 patients (28 males, 20.7% and 46 females, 30.0%) were included in the study. Key baseline characteristics are summarised in Table 1.

In 54 patients (73.0%), VMT was the only finding, while in 20 patients (27.0%), there was VMT combined with MH. The mean age of the studied cases was 71.3 ± 11.2 years (range 32–91 years).

Sixty-one patients were phakic (82.4%), while 13 patients were pseudophakic (17.6%). At baseline, the mean BCVA was 0.48 ± 0.31 logMar. Seventy-five patients (59.5%) had VMT resolution at the end of follow-up. The mean follow-up period was 112 ± 62.2 days (range: 30–180 days).

All patients without metamorphopsia at the baseline remained asymptomatic (9/74 eyes; 12.2%). Among patients that complained of metamorphopsia at the baseline, in 30 patients it was reduced (30/65 eyes; 30.8%); in 13 patients it disappeared (13/65 eyes; 20%); in 2 patients it worsened (2/65 eyes; 3.1%); and in 28 patients it was stable (28/65 eyes; 43.1%). In particular, among the patients with metamorphopsia at the baseline (40 eyes) who had a complete resolution of the VMT, 29 eyes also had metamorphopsia improvement, while among patients with metamorphopsia at baseline and no VMT resolution (25 eyes) metamorphopsia improved only in four eyes.

The VMT mean extension in the success group (resolution of the VMT) was 360 ± 313.9 µm; in the group with no success (no resolution of VMT), it was 524 ± 304.7 µm (p = 0.0481) Figure 1. In particular, we analysed the success rate (VMT resolution) in the four subgroups according to the baseline extension of the traction (each group differed by 499 µm; range 0–1600 µm). Regarding the VMT extension group (0–499 µm) success was obtained in 37 patients (37/54 eyes, 68%); regarding the second group (500–999 µm) in five patients (5/14 eyes; 35.7%); regarding the third group (1000–1499 µm), success was obtained in only one case (1/1 eyes; 100%) (p = 0.0007). Regarding the VMT extension group (>1500 µm), composed of only three eyes, no success was obtained.

| Table 1 Findings at baseline |
|-----------------------------|
| **Cases** 74 | % |
| **Sex** 46 F | 20.7 |
| 28 M |
| **Age (mean)** 71 years (range 32–91 years) | |
| **Eye** 44 left eye | 59.5 |
| 30 right eye | 40.5 |
| **Metamorphopsia** 65 yes | 87.3 |
| 9 no | 12.1 |
| **Lens status** 61 phakic | 82.4 |
| 13 pseudophakic | 17.6 |
| **VMT extension (mean, median)** 426 ± 310 µm, 352 µm (range 40–1600 µm) | |
| **FTMH** 20 | 27.0 |
| **FTMH size (mean)** 258 ± 131 µm (range 82–550 µm) | |
| **ERM** 12 yes | 16.2 |
| 62 no | 83.8 |
| **BCVA (logMar)** 0.48 ± 0.31 (range 0–1.30) | |

BCVA, best-corrected visual acuity; ERM, epiretinal membrane; FTMH, full-thickness macular hole; VMT, vitreomacular traction.
In the success group, the mean age was 66.8±11.8 years, while in the no-success group, it was 76.6±7.8 years (p 0.0001).

The association between ERM or FTMH presence and VMT release was not significant (p 0.098 and p 0.9319). Furthermore, in this study, the association between lens status and VMT release after the injection of ocriplasmin (p 0.089) was not significant.

FTMH closure occurred in eight patients (8/20 eyes; 40%). The patients with macular hole (MH) diameter >400 µm did not present MH closure (0/4, 0%); regarding the holes of diameter <250 µm 7/13 closed (53.8%); the holes of diameter 250–400 µm closed in a percentage of 33.3% patients.

Vitrectomy was performed on 12 patients, 12/74 (16.2%).

The distribution of logMar BCVA is summarised in figure 2 and in figure 3 and subdivided according to success (resolution of VMT) or no success. The mean (BCVA) at baseline in the success group was 0.51±0.32 logMar; in the no-success group, it was 0.46±0.38 logMar (p 0.5153).

In 55/74 eyes of 55 patients (74.3%), no adverse events related to the ocriplasmin injection were reported; most of the adverse events were transitory (17/19, 89.5%). The mean time of adverse event resolution was 27.4±21.9 days. Furthermore, no cases of retinal tear, retinal detachment, lens destabilisation and infections were found in this study. All the adverse events were reported within 1 week in table 2.

DISCUSSION

Spontaneous release rate of VMT is achieved only in 11%–47% of the cases over a mean time frame of 8–60 months,7 8 and even with spontaneous release abnormal structural changes in the macula and decreased visual acuity can persist, especially in chronic and/or severe cases of VMT. For VMT associated with FTMH, spontaneous closure rates are much lower (3%–11% of cases).9 10 Most MHs enlarge, with a progression rate of 84% from stage II to stage III/IV.8 Untreated FTMHs can result in significant and persistent decrease in visual acuity. The closure rates of MHs with current vitrectomy techniques are typically 88% or higher.11

In VMT, treatment observation is shown to be ineffective; however, PPV is, today, the best treatment, but there is a higher risk of cataract formation, glaucoma, infection, retinal tears and detachment; for this reason, less invasive but effective treatment options are being developed.

Through the recently approved ocriplasmin (Jetrea; Thrombogenics, USA, Alcon/Novartis EU), pharmacological vitreolysis shows a possible safer alternative to surgery in patients affected by VMT.5

In our study, we report the Italian clinical experience using ocriplasmin for VMT with or without an MH. In phase III testing, the efficacy of ocriplasmin for VMT release was 26.5%,3 but this percentage can be higher (42%–67%) depending on the presence of positive predictive criteria like: age less than 65 years, focal adhesions ≤1500 mm, presence of FTMH, phakic status and absence of epiretinal membrane.4 Our results showed that VMT release occurred in 44 eyes (44/74 eyes; 59.5%). In 22 eyes (22/44, 50%), success occurred within the first month of follow-up. This difference between the clinical trials and the results of postmarketing studies could be due to our selection of the patients.

The closure rate of FTMH in our study was 40%; this finding is also consistent with data of the Microplasmin for intravitreous injection-traction release without surgical treatment (MIVI-TRUST) trials (40.6%).3 4 The MH diameter was shown to be an important prognostic factor; in fact, eyes with FTMH width of ≤250 µm at baseline were more likely to achieve pharmacological FTMH closure (53.8%) compared with those with FTMH width of >250 µm, who achieved closure only in 7% of the cases. Furthermore, our group included four patients with FTMH >400 µm, in whom the closure rate was 0%.

Figure 1 Histogram presenting the distribution of Vitreomacular traction (VMA) extension by surgical success outcome.

Figure 2 Boxplots of logMAR visual acuity at baseline and at 1, 3 and 6 months by surgical success outcome.
with FTMH width between 250 µm and 400 µm at baseline achieved a closure rate of 33.3%. These results are similar to those obtained by the clinical trials. In other reports, different closure rates were presented (17%-27%-28.6%-40%).

In figure 3, successful and unsuccessful cases are presented using OCT images.

VMT extension was shown to be, according to the clinical trials, an important prognostic factor; in fact, the success rate was 0% in the eyes with VMT extension ≥1500 micra. However, the association between ERM presence at baseline and VMT release was not significant (p 0.931). This result is not in agreement with the clinical trials, in which the prevalence of ERM may have been underestimated. In the clinical trials, an old generation time-domain OCT was used, so patients with very evident epiretinal membrane were also included. Although we used the SD-OCT (more capacity of detection of epiretinal membranes), the prevalence of ERM in our patients was lower (16.2% vs 38.7%). This discrepancy is more probably due to improved patient selection for the ocriplasmin injection.

Regarding visual function, ocriplasmin showed important results: an improvement or complete resolution of metamorphopsia was achieved in 50.8% of the eyes. Furthermore, in our results, visual acuity at baseline did not influence VMT resolution after the injection (p 0.5153). The patients in which there was VMT resolution had better visual acuity; in fact, if we consider the difference between BVCA after 3 months of follow-up among the success and no-success groups, in the first group, there was significant improvement (about three lines) (p<0.0001) figure 4.

This result could be explained in part by the complete restoration of the ellipsoid zone (EZ) integrity after the
ocriplasmin injection, which takes about 3 months. In fact, it has been described in literature that transient OCT-based alterations were identified in a substantial number of the eyes after ocriplasmin therapy.14 These transient changes are particularly prominent in the EZ. In addition, the accumulation of subretinal fluid has also been described and appears to be closely linked to the changes in the EZ. The phase III trials used time-domain OCT, so the detection of these changes was difficult. The integrity of the EZ has been identified as an important factor for VA in multiple vitreoretinal conditions.15–17

In two cases, we encountered a strong adhesion between the posterior hyaloid and the optic pit; however, performing active aspiration with the vitrectomy probe, even though after approximately 1 min of suction, we obtained the vitreous separation from the posterior pole.

In our series, we observed adverse events in only 25.7% of the eyes; the majority of these were transitory, and VMT resolution was observed in about 27 days; no serious adverse events were registered.

CONCLUSION
In conclusion, pharmacological vitreolysis with intravitreal ocriplasmin is a new, non-surgical option for the treatment of VMT, with or without FTMH. In our study, we have reported a high rate of success and a low rate of adverse effects. A more careful selection of patients could increase the percentage of success.
12. Moisseiev J, Meroz I, Katz G. Effect of ocriplasmin on the management of macular holes: assessment of the clinical relevance of ocriplasmin. *JAMA Ophthalmol* 2014;132:709–13.

13. Kadonosono K, Itoh N, Uchio E, *et al*. Staining of internal limiting membrane in macular hole surgery. *Arch Ophthalmol* 2000;118:1116–8.

14. Itoh Y, Ehlers JP. Ellipsoid zone mapping and outer retinal characterization after intravitreal ocriplasmin. *Retina* 2016;36:2290–6.

15. Singh R, Reddy DM, Barkmeier AJ, *et al*. Long-term visual outcomes following lens-sparing vitrectomy for retinopathy of prematurity. *Br J Ophthalmol* 2012;96:1395–8.

16. Freund KB, Shah SA, Shah VP. Correlation of transient vision loss with outer retinal disruption following intravitreal ocriplasmin. *Eye* 2013;27:773–4.

17. Nudleman E, Franklin MS, Wolfe JD, *et al*. Resolution of subretinal fluid and outer retinal changes in patients related to ocriplasmin. *Retina* 2016;36:738–43.