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CLINICAL INVESTIGATION

Flare changes after intravitreal injection of ocriplasmin in symptomatic vitreomacular traction syndrome

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Abstract

Purpose To evaluate the changes in anterior chamber flare after a single intravitreal injection of ocriplasmin (125 µg), in patients with symptomatic vitreomacular traction syndrome (VMT).

Study design An institutional review board-approved single-center not randomized prospective study.

Methods Fifteen eyes of fifteen patients (9 women, 6 men) underwent intravitreal injection with ocriplasmin for symptomatic VMT (width of attachment ≤ 1500 µm). Anterior segment flare was measured with a laser flare meter (Kowa) before intravitreal injection and 1 day, 1 week, 1 month after injection. The changes in flare were analyzed; the resolution of VMT was evaluated with spectral-domain OCT.

Results The mean anterior chamber flare was 10.5 ± 1.9 photons per millisecond (photons/ms) before the injection. After 1 day it increased to 13.6 ± 2.7 photons/ms (p = 0.027) and after 1 week to 14.4 ± 2.5 photons/ms (p = 0.005); after 1 month it decreased to 12.3 ± 2.3 photons/ms (p = 0.123). At 1 day and 1 week after injection, mean anterior chamber flare of fellow eyes was significantly lower than study eyes, while at 1 month this difference was not significant (12.3 ± 2.3 vs. 10.5 ± 1.8 photons/ms, p = 0.124, for study and fellow eyes). There was no statistically significant difference in the changes in flare between women and men or between phakic (N = 10) and pseudophakic (N = 5) eyes. No eye demonstrated intraretinal damage at any time-point. Also, 9 eyes showed resolution of VMT while 6 eyes demonstrated persistence of VMT.

Conclusion Our study shows that intravitreal injection of ocriplasmin can be a safe and effective approach to treat symptomatic VMT syndrome in selected patients.

Keywords Ocriplasmin · Laser flare photometry · Vitreomacular traction syndrome · Intravitreal injection

Introduction

Vitreomacular traction (VMT) syndrome is characterized by an incomplete posterior vitreous detachment (PVD) that exerts traction on the macula and may lead to a decrease in visual acuity [1]. The prevalence of isolated VMT syndrome is reported to be 22.5 per 100,000 population. The annual incidence of isolated VMT syndrome is 0.6 per 100,000 population. However, the prevalence and incidence of VMT are much higher in patients characterized by older age or in patients affected with diabetic retinopathy, diabetic macular edema, age-related macular degeneration (AMD) as well as other macular diseases [2]. Although partial PVD with asymptomatic vitreomacular adhesion (VMA) may be a normal transient stage of physiologic PVD, nonphysiologic persistence of VMA may result in VMT with visual symptoms [3]. A symptomatic VMT may cause tension on the retina leading to retinal distortion, macular edema, foveal detachment, and full-thickness macular hole (FTMH), with symptoms such as distortion or reduction in vision and photopsia. The introduction of high-resolution spectral-domain optical coherence tomography (SD-OCT) has allowed a better understanding and visualization of the vitreomacular interface. An optical coherence tomography (OCT)-based classification system was proposed in 2013 by the International Vitreomacular Traction Study Group [4], providing a clinically applicable prediction of therapeutic outcomes, and useful method for the execution and analysis of clinical

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studies of disorders of the vitreomacular interface. Recently pharmacological vitreolysis has been suggested as an alternative treatment option for VMT. The peptide bridges in laminin and fibronectin, molecules maintaining adhesion between the posterior vitreous face and inner limiting membrane, are broken down by vitreolytic agents. Ocriplasmin, a 27-kDa recombinant selective serine protease subunit of human plasmin, possesses the same catalytic properties of plasmin but is a far more stable product, and has, therefore, emerged as the vitreolytic agent of choice, being capable of cleaving collagen and laminin, as well as fibronectin. Ocriplasmin adverse events are likely caused by the release of VMA, including vitreous floaters and photopsia, and because of its pharmacological properties, such as dyschromatopsia, it may be associated with changes in the ellipsoid zone [5, 6]. Moreover, with SD-OCT analysis, subretinal fluid accumulation was described, and a toxic and inflammatory effect on the interphotoreceptor layer has been suggested [7]. Therefore, an evaluation of potential inflammatory ocular side effects following intravitreal injections of ocriplasmin should be mandatory. Flare or Tyndall effect, caused by the back-scattering of light by ''cloudy matters'' and first described by Lord John Tyndall in 1869 [8], is an optical phenomenon produced by an increased protein content in the aqueous humor. When examined with a slit lamp, measurements of intraocular inflammation remain subjective with considerable intra- and interobserver variations. In 1988, Sawa et al. [9] reported a new noninvasive and quantitative method to measure aqueous humor cells and protein. This new technology, laser flare and cell photometry, was developed by KOWA Company, Ltd.

The purpose of this study was, therefore, to evaluate the changes in anterior chamber flare in patients with symptomatic VMT (width of attachment ≤ 1500 µm), using a Kowa laser flare meter, after a single intravitreal injection of ocriplasmin (125 µg); and to assess adverse effects and the resolution of VMT using SD-OCT.

Patients and methods

This was an institutional review board-approved single-center prospective study. A total of 15 eyes of 15 patients (9 women, 6 men), who applied to our Department between October 2016 and November 2017, were included in the study. Their mean age was 62.7 years with a standard deviation (SD) of 4.6 years (range 55–71 years). Patients were included if they presented symptomatic VMT syndrome (width of attachment ≤ 1500 µm). Exclusion criteria were any condition which could alter flare measurement, and included central corneal opacity, mature cataract, very shallow anterior chamber, a history of uveitis with or without posterior synechiae, prior ocular surgery, diabetes and concomitant therapy with prostaglandin analogues. Aqueous flare was evaluated using a laser flare meter before pupillary dilatation at baseline, 1 day, 7 days and 1 month after the injection. Flare was measured using the Kowa FM-700 laser flare meter (Kowa) and reported as photons per millisecond. At baseline and at each time-point all patients underwent spectral-domain optical coherence tomography (SD-OCT) (Spectralis; Heidelberg Engineering) with automated central macular thickness (CMT) measurements, generated by using a 19-horizontal line protocol (6×6 mm area), each consisting of 1024 A-scans per line. Also, the subfoveal choroidal thickness was measured from the outer portion of the hyperreflective line corresponding to the retinal pigment epithelium (RPE) to the hyporeflective line or margin corresponding to the sclerochoroidal interface. The possible risks of intravitreal injection and the side-effects of ocriplasmin were explained and written informed consent was obtained from all patients. The study procedures were performed in accordance with the Declaration of Helsinki.

Technique of intravitreal ocriplasmin injection

Under sterile conditions, ocriplasmin was prepared from a vial containing 0.5 mg of ocriplasmin in 0.2 mL solution. After dilution with 0.2 mL of sodium chloride 9 mg/mL (0.9%) solution for injection, 0.1 mL of the diluted solution contained 0.125 mg ocriplasmin, the dose used in this study. A 30-gauge needle was used for the injection. The eyes were anesthetized with a topical administration of a 0.4% oxybuprocaine hydrochloride eye drops. After sterilization of the periocular area with 10% povidone iodine and irrigation of conjunctival sac with 5% povidone iodine solution, the patient was draped. An eyelid speculum was placed and a caliper was used to determine the correct localization. An injection of 0.125 mg ocriplasmin was administered intravitreally from 3.5–4.0 mm posterior to the limbus. All injections were performed in an operating room under sterile conditions. The patients were prescribed topical ofloxacin 0.3% eye drop, five times per day for 5 days.

Measurement technique with a laser flare meter

The laser flare meter used in this study was Kowa FM-700, using a semiconductor 640 nm diode laser and a measurement window of 0.5×0.3 mm. Because pupillary dilatation causes an alteration in flare values, aqueous flare was evaluated before pupillary dilatation. Flare results are expressed in photon counts per millisecond (ph/ms). The recorded flare was an average of at least ten acceptable measurements. Measurements were deleted if they were selected by the machine's "rigorous" error level setting as outliers, if they had an error code, an abnormal wave form, a background reading of > 100 or $= 0$, or a background

percent > 10%. The machine automatically calculated the mean and the SD of the readings and the mean flare values were recorded. If the SD of the ten or more measurements was > 5, the patient was excluded. Although readings have been shown to be highly reproducible [12], measurements were performed by a single operator. A single flare meter was used and was calibrated as specified by the manufacturer. Measurements were done in a darkened room.

Statistical analysis

Statistical calculations were performed using Statistical Package for Social Sciences (version 17.0, SPSS Inc.). Comparisons of mean anterior chamber flare CMT and choroidal thickness, between baseline and each time-point, for the overall group of patients and for different groups of patients (male or female, phakic or pseudophakic, with VMT resolution or persistence), were performed using the Student's *t* test with Bonferroni correction. Pearson correlation analyses were performed between mean anterior chamber flare, CMT and choroidal thickness parameters. The chosen level of statistical significance was $p < 0.05$.

Table 1 Mean anterior chamber flare (photons/ms), central macular thickness (μm) and choroidal thickness (μm) measurements at any time-point from the ocriplasmin injection

Parameter	Baseline	Day 1	Day 7	Day 30
Anterior chamber flare	10.5 ± 1.9	13.6 ± 2.7	14.4 ± 2.5	12.3 ± 2.3
p value		0.027	0.005	0.123
CMT	385.5 ± 65	374 ± 73.2	354.5 ± 83.3	343.3 ± 76.3
p value		0.129	0.062	0.023
Choroid	195 ± 69.8	197.8 ± 66.2	186.7 ± 55.9	195 ± 68.9
p value		0.318	0.235	0.991

Anterior chamber flare mean laser flare measurements in the anterior chamber, *CMT* central macular thickness, *Choroid* choroidal thickness in the subfoveal area

Results

Fifteen eyes of 15 patients were analyzed. Of the 15 patients, 9 were women and 6 were men; the mean age was 62.7 ± 4.7 years (range 55–71 years). The mean anterior chamber flare value measured by the laser flare meter was 10.5 ± 1.9 photons/ms before the injection. After 1 day mean anterior chamber flare increased to 13.6 ± 2.7 photons/ms, after 1 week it became 14.4 ± 2.5 photons/ms and after 1 month it decreased to 12.3 ± 2.3 photons/ms (Table 1). There was a statistically significant difference in mean values of flare between baseline and day 1 ($p = 0.027$), baseline and day 7 ($p = 0.005$) while no statistically significant difference was found between baseline and day 30 ($p = 0.123$) (Table 1). At baseline, mean CMT was 385.5 ± 65 μm and progressively decreased during the follow-up period (Table 1). Mean subfoveal choroidal thickness did not demonstrate any particular changes throughout the follow up period (Table 1). Moreover, no retinal layer alterations were found at any time-point, particularly at the level of ellipsoid zone-retinal pigment epithelium complex.

There was no statistically significant difference in the changes in flare between women and men or between phakic (N = 10) and pseudophakic eyes (N = 5) (Table 2). Moreover, 9 eyes showed complete resolution of VMT (Fig. 1a, b) and demonstrated higher flare values than the group of eyes (N = 6) characterized by persistence of VMT (Fig. 2a, b), even though not significantly (Table 3).

Mean anterior chamber flare of fellow eyes was 10.2 ± 1.5 photons/ms at baseline; at 1 day it increased to 10.5 ± 1.6 photons/ms ($p = 0.678$) and at 1 week to 10.6 ± 2.2 photons/ms ($p = 0.655$). At 1 month, it decreased to 10.5 ± 1.8 photons/ms ($p = 0.682$). At baseline, mean anterior chamber flare values were similar between eyes subjected to ocriplasmin injection (study eyes) and fellow eyes, while at 1 day and 1 week mean anterior chamber flare values of study eyes were significantly higher than fellow eyes (Table 4). Interestingly, at the 1-month follow up, flare values of study eyes were not significantly higher than fellow eyes (Table 4).

No significant correlations were found between the anterior chamber flare and central macular thickness. There was also no significant correlation between anterior chamber flare and choroidal thickness. Reported adverse effects were

Table 2 Mean anterior chamber flare (photons/ms) measurements at any time-point from ocriplasmin injection, depending on gender and phakic or pseudophakic status

Parameter	Male N = 6	Female N = 9	p value	Phakic N = 10	Pseudophaki N = 5c	p value
Baseline	11.1 ± 1.5	10.2 ± 2.1	0.414	9.9 ± 1.8	11.7 ± 1.7	0.082
Day 1	14.2 ± 2.7	13.3 ± 2.8	0.547	12.7 ± 2.4	15.4 ± 2.4	0.066
Day 7	14.8 ± 2.7	14.2 ± 2.5	0.715	14 ± 2.3	15.3 ± 2.8	0.332
Day 30	12.6 ± 2.3	12.2 ± 2.4	0.735	12.1 ± 2.3	12.8 ± 2.5	0.600

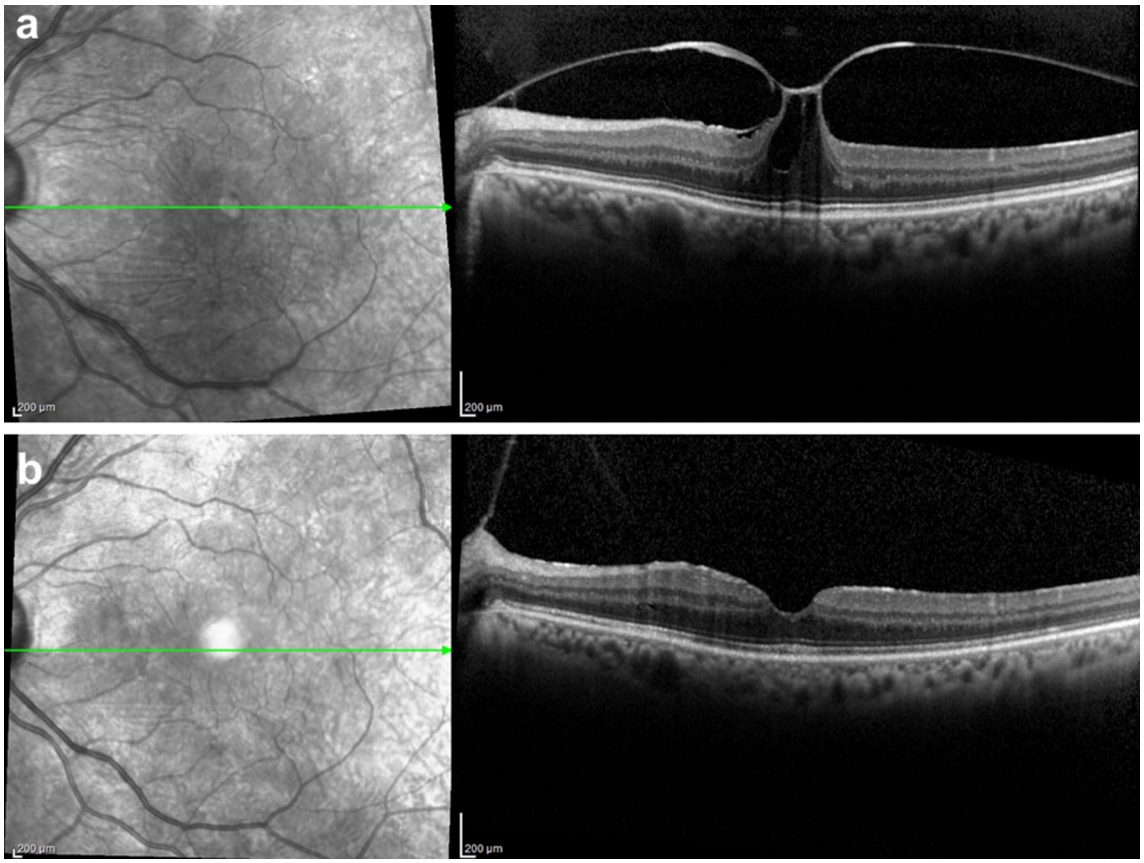

Fig. 1 SD-OCT imaging demonstrating the presence of VMT one day before the ocriplasmin injection (**a**) and one month after the ocriplasmin injection, showing complete resolution of VMT (**b**). Flare values of this patient (woman, 72 years old) were 11.1 photons/ms at baseline and 12.5 photons/ms after one month from intravitreal treatment

only vitreous floaters and/or conjunctival hemorrhage in 5 patients.

Discussion

There are no previous articles about evaluation of anterior chamber flare after a single intravitreal injection of ocriplasmin. Measurement of flare post intravitreal injection of anti-VEGF drugs is reported [13], but the inflammatory reaction after intravitreal therapy shows many aspects which have still to be completely understood. Disruption of the blood–ocular barrier, due to disease or surgical treatment, results in an increase in intraocular inflammatory parameters, such as aqueous flare and cells.

The anterior chamber is, normally, an optically empty and clear space. The disruption of blood–ocular barrier leads to spillover of inflammatory cells and leakage of serum proteins in the anterior segment, resulting in changes in the optical properties of the aqueous. Intraocular inflammation is characterized by cells and flare that can be measured and quantified by laser photometry. Reproducibility and accuracy of laser flare and cell photometry measurements are demonstrated in several studies, and the values correlated well with protein concentrations in serial dilutions of plasma and aqueous humor samples obtained from patients undergoing intraocular surgery [10, 11].

Laser flare photometry is, therefore, an objective quantitative method that enables accurate measurement of inflammatory parameters with very high reproducibility, allowing detection of subclinical alterations in the blood–ocular barrier, identifying subtle pathological changes that cannot be recorded otherwise. With this method, it is possible to compare the effect of different surgical techniques, surgical adjuncts, and anti-inflammatory medications on intraocular inflammation. We chose to evaluate flare using a laser flare meter that measures intraocular protein concentrations using an orthogonal laser source to measure light scatter in units of photons per millisecond.

The main strength of this study is that quantitative differences in flare (and therefore in inflammation) had not been reported before. Our study found a statistically significant difference in mean flare between baseline and day 1, and

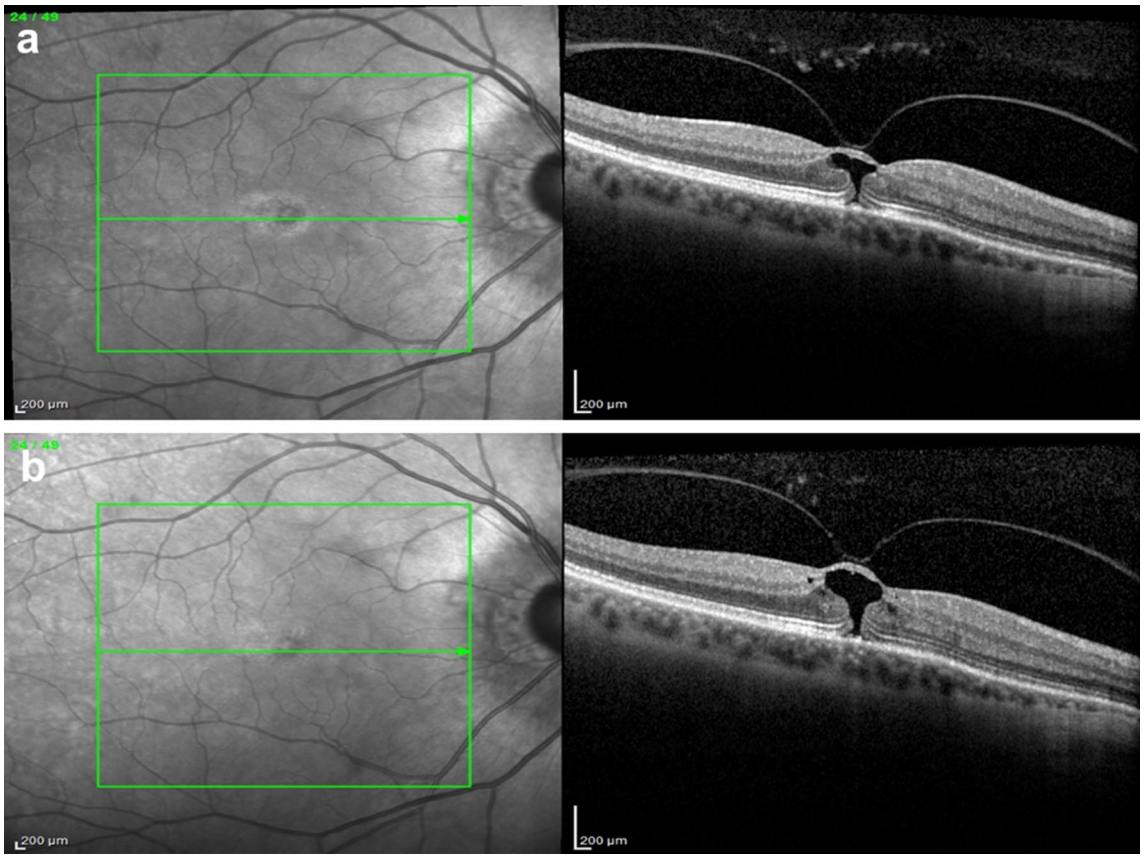

Fig. 2 SD-OCT imaging showing the presence of VMT one day before the ocriplasmin injection (**a**) and one month after the ocriplasmin injection, without resolution of VMT (**b**). Flare values of this patient (woman, 64 years old) were 10.1 photons/ms at baseline and 10.9 photons/ms after one month from intravitreal treatment

Table 3 Mean anterior chamber flare (photons/ms) measurements at any time-point from ocriplasmin injection, depending on resolution or persistence of vitreomacular traction (VMT)

Parameter	VMT persistence N = 6	VMT resolution N = 9	p value
Baseline	9.9 ± 1.9	10.9 ± 2.1	0.368
Day 1	13.2 ± 2.1	14.1 ± 2.2	0.454
Day 7	13.5 ± 2.1	15.1 ± 1.9	0.178
Day 30	11.5 ± 1.8	12.9 ± 1.9	0.312

Table 4 Comparison between mean anterior chamber flare (photons/ms) measurements of study eyes and fellow eyes, at any time-point from ocriplasmin injection

	Study eyes N = 15	Fellow eyes N = 15	p-value
Baseline	10.5 ± 1.9	10.2 ± 1.5	0.768
Day 1	13.6 ± 2.7	10.5 ± 1.6	0.003
Day 7	14.4 ± 2.5	10.6 ± 2.2	0.001
Day 30	12.3 ± 2.3	10.5 ± 1.8	0.124

baseline and day 7; no statistically significant difference was found between baseline and day 30.

Several studies report a transient increase in anterior chamber flare following the injection of different intravitreal drugs [13–15]. Blaha et al. compared the changes in anterior chamber flare before and one day after intravitreal injections of the anti-vascular endothelial growth factor agents bevacizumab, aflibercept, and ranibizumab. The authors report a statistically significant increase in flare after bevacizumab injection compared with ranibizumab [13]. Uzun et al. evaluated aqueous flare levels in 81 eyes of 79 patients following intravitreal ranibizumab injection for neovascular AMD; demonstrating a subtle increase of flare at day 1, even though not significantly [14]. Similarly, Morioka et al. evaluated anterior flare intensity values after intravitreal injection of different drugs in 100 patients affected by diabetic macular edema, reporting a significant temporary increase at one day after aflibercept injection in phakic eyes [15].

We also evaluated mean anterior chamber flare in the fellow eyes that did not significantly change during the entire follow-up period. Interestingly, mean anterior chamber flare

values were significantly higher in eyes subjected to ocriplasmin injection (study eyes) at 1 day and 1 week, but at the 1-month follow up flare values of study eyes were not significantly higher than fellow eyes (12.3 ± 2.3 vs. 10.5 ± 1.8 photons/ms, $p = 0.124$), indicating that after a transient increase of anterior chamber inflammation following ocriplasmin injection, flare values tend to regress to normal values.

In our study there was no statistically significant difference in the change in flare between women and men or between phakic and pseudophakic eyes. In 9 eyes there was resolution of VMT; moreover, in this group higher flare values were reported at every measurement, although the difference was not found to be statistically significant. Microplasmin-induced posterior vitreous detachment leads to a difference in vitreous oxygen concentrations in animals [16], therefore we think that oxygen variations may play a role in the regulation of inflammatory cascade after intravitreal ocriplasmin injection.

Ocriplasmin enzymatic activity is, moreover, another aspect whose role and relationship with changes in flare should be clarified in future research. Multiple studies show diminished electroretinogram (ERG) recordings, structural OCT changes, and persistent subretinal fluid (SRF) after intravitreal ocriplasmin injection [17, 18].

The long-term side-effects, including ultra-structural abnormalities seen on OCT, remain to be completely understood. The panretinal extent of adverse events is believed to be consistent with global protease activity against fibronectin and laminin, present not only within the vitreoretinal interface at the macula but diffusely throughout the retina and its layers, including Bruch membrane, the interphotoreceptor matrix, the external limiting membrane, the outer plexiform layer, the inner plexiform layer, and the internal limiting membrane [18]. This may explain the ellipsoid layer attenuation seen on OCT and resultant ERG changes [19].

An analysis of the different layers of the retina on SD-OCT by Kaiser et al. [18] revealed changes in the ellipsoid zone-retinal pigment epithelium status which correlated with an increase in SRF at week 1, further supporting the theory that the SRF origin could be related to the inflammation of photoreceptor outer segments [20]. It is noteworthy that, whereas previous studies report these intraretinal alterations, no eye in our sample showed any intraretinal damage at each time-point. The long-term implications of these findings still remain to be elucidated in prospective research.

Reported adverse effects in the patients evaluated in our study were only vitreous floaters and/or conjunctival haemorrhage in 5 patients.

In conclusion, our cases demonstrated that a single intravitreal injection of ocriplasmin (125 μg), in selected patients with symptomatic VMT, is an effective and safe way to treat patients with this condition. A limitation of this paper is the relatively small sample size. A collaborative multicentric study assessing short and long-term outcomes of ocriplasmin injection in symptomatic VMT may provide more cases and robust judgment regarding the role of this procedure in the management of this condition.

Conflicts of interest V. Pirani, None; P. Pelliccioni, None; C. Cesari, None; G. Carrozzi, None; E. Cavallero, None; C. Mariotti, None.

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