Graefes Arch Clin Exp Ophthalmol (2016) 254:1247–1256
DOI 10.1007/s00417-016-3363-5

REVIEW ARTICLE

Ocriplasmin use for vitreomacular traction and macular hole: A meta-analysis and comprehensive review on predictive factors for vitreous release and potential complications

Irini Chatziralli[1,2] · George Theodossiadis[3] · Paraskevi Xanthopoulou[2,4,5] · Michael Miligkos[5] · Sobha Sivaprasad[1] · Panagiotis Theodossiadis[2]

Received: 5 November 2015 / Revised: 20 March 2016 / Accepted: 19 April 2016 / Published online: 30 April 2016

Abstract
Purpose We aimed to provide a meta-analysis of the factors affecting vitreomacular traction (VMT) resolution after ocriplasmin use. A comprehensive systematic review of the complications after ocriplasmin use for VMT and macular hole was also done.
Methods A literature search in PubMed was performed for studies about ocriplasmin published before 30 June 2015. Then a meta-analysis of the factors affecting the VMT resolution after ocriplasmin use was done, providing the pooled odds ratios for each factor and 95 % confidence intervals (CIs). We also described the potential adverse events after ocriplasmin use in a systematic review.
Results A total of 194 abstracts were screened and 19 eligible studies were included in the meta-analysis. Age <65 years, female gender, vitreomacular adhesion diameter <1500 μm, phakic lens status and epiretinal membrane absence were found as positive predictive factors for VMT resolution, while macular hole size <250 μm was significantly associated with macular hole closure at the meta-analytical level. Various complications after ocriplasmin use were reported by frequency, including mainly vitreous floaters, photopsias, visual acuity decrease, ellipsoid zone changes, subretinal fluid development, enlargement of macular hole, anterior segment changes and electroretinogram alterations. It has to be noted that significant methodological weaknesses were identified, such as the absence of control groups or lack of transparency in the recruitment process and the examination procedure.
Conclusions It is important to carefully select patients for ocriplasmin injection, taking into account the various predictive factors for VMT resolution. Patients should be informed about the potential adverse events of ocriplasmin, although they mainly seemed to be transient and usually mild/moderate in severity, suggesting that ocriplasmin is a safe and effective new treatment alternative for VMT and macular hole. However, due to the limited study quality, the uncertainty concerning the efficacy of this new approach is increased.

Keywords Ocriplasmin · Meta-analysis · Complications · Vitreomacular traction · Macular hole · Release · Optical coherence tomography

✉ Irini Chatziralli
eirchat@yahoo.gr

[1] NIHR Moorfields Biomedical Research Centre, Moorfields Eye Hospital, London, UK

[2] 2nd Department of Ophthalmology, Attikon Hospital, University of Athens, 1, Rimini street, Haidari, 12462 Athens, Greece

[3] 2nd Department of Ophthalmology, Henry Dunant Hospital, Athens, Greece

[4] Department of Ophthalmology, 401 Hellenic Army General Hospital, Athens, Greece

[5] Laboratory of Biomathematics, School of Medicine, University of Thessaly, Larissa, Greece

Introduction

The vitreous is an optically clear watery gel that occupies about 80 % of the eye, being mainly composed of water, collagen fibers, hyaluronan and extracellular matrix components [1]. The vitreous is normally attached to the anterior surface of the retina until young adulthood. Aging causes degeneration and liquefaction of the vitreous, leading to alterations in the vitreoretinal interface (VRI), which progressively end up to separation between the posterior vitreous cortex and the internal limiting membrane (ILM), a process known as posterior vitreous detachment (PVD) [1, 2].

Advances in retinal imaging provide better understanding of the VRI disorders, including vitreomacular adhesion (VMA), vitreomacular traction (VMT), lamellar and full-thickness macular hole (LMH and FTMH). According to the classification of the International Vitreomacular Traction Study Group, VMA has been defined as the asymptomatic persistent attachment of the vitreous at the macula, which can progress to VMT, when anatomical distortion of the foveal contour and symptoms occur [3, 4]. Therefore, in the literature, VMT has usually been referred to as symptomatic VMA. LMH is characterized by defect in the inner fovea and is typically located between the outer plexiform and the outer nuclear layer, while FTMH involves all macular layers from ILM to the retinal pigment epithelium (RPE) and may have or not have VMT [3, 4].

Until recently, the treatment alternatives for VMT were observation and pars plana vitrectomy (PPV). Observation remains an option for VMT treatment, since the natural history of VMT also includes spontaneous resolution in some cases, supporting its efficacy [5, 6]. On the other hand, PPV has been considered as the standard procedure for the treatment of VMT and FTMH, presenting a closure rate for MH of approximately 87.5 % and higher. Nevertheless, complications, such as cataract formation, bleeding, retinal detachment or infection can occur [7]. Nowadays, special interest has been shown to pharmacologic vitreolysis, which is a new approach for the treatment of VRI disorders. Ocriplasmin (Jetrea, Thrombogenics USA, Alcon/Novartis EU), a recombinant truncated form of a protease derived from human plasmin, has been recently approved by Food Drug Administration and European Medicines Agency for the nonsurgical treatment of symptomatic VMA. It retains proteolytic activity, targeting fibronectin and laminin, which are both extracellular matrix components and are thought to mediate the adhesion between the posterior vitreous cortex and the ILM. In fact, ocriplasmin is considered to work in a two-step mechanism, involving both vitreoretinal separation and vitreous liquefaction [8, 9].

The approval of ocriplasmin for clinical use was based on the MIVI-TRUST study, which was a randomized control trial evaluating the safety and efficacy of a single ocriplasmin injection compared to a placebo saline injection for the treatment of VMT and MH. The results of this trial demonstrated a 26.5 % resolution of VMA at day 28 in the ocriplasmin group versus 10.1 % in the placebo group [10], while release rate was found to be positively correlated with age less than 65 years, absence of epiretinal membrane (ERM), VMA diameter of less than or equal to 1500 μm and phakic lens status [11]. As far as the FTMH is concerned, a closure rate of 40.6 % has been mentioned in ocriplasmin group versus 10.6 % in the placebo group [10]. Various studies have been also performed after ocriplasmin approval for assessing its safety and efficacy in the real world clinical practice.

In light of the above, a meta-analysis was performed on the predictive factors affecting the release rate of VMT after ocriplasmin injection; namely age, gender, ERM presence, VMA diameter, and lens status. To our knowledge, this is the first meta-analysis on the field, estimating the pooled odd ratios (ORs) for the various predictive factors for VMT release after ocriplasmin use, summarizing the ORs from the individual studies, which were published after the pivotal MIVI-TRUST study. In addition, a systematic review was done to describe the potential adverse events after ocriplasmin injection, as they have been reported in the literature.

Materials and methods

Eligible articles were identified by a search of PubMed literature database using the terms: (ocriplasmin) OR (microplasmin). The end date of the search date was 30 June 2015. We also checked all the references of relevant reviews and eligible articles that our search retrieved. Language restrictions were not used.

We defined the eligibility criteria as randomized controlled phase III trials and cohort, case–control or cross-sectional studies reporting the release rate of VMT or the closure rate of FTMH in patients with VMT or FTMH after intravitreal ocriplasmin injection. Case reports were excluded from the meta-analysis, but were used for the systematic review regarding potential adverse events of ocriplasmin. It should be noted that only the treated arm in controlled trials was selected.

Data were extracted from each eligible study by two investigators working independently (IC, GT). For each study, the following data were collected: investigator name, year of publication, study design type, definitions of cases (and controls, where applicable), sample size, type of optical coherence tomography (OCT) used for the study, demographic characteristics of the population being studied (age, gender), clinical characteristics (presence of epiretinal membrane, diameter of VMA, lens status, size of FTMH) and release rate of VMT, as well as rate of FTMH closure.

According to the frequencies in patients who did and did not develop VMT resolution, the pooled proportions of eyes with VMT release after ocriplasmin injection with the corresponding 95 % confidence intervals (95%CI) were calculated, using the random effects model with arcsine transformation for proportions [12]. For the meta-analysis of predictive factors for VMT release or FTMH closure, the pooled ORs were estimated using the random-effects model estimated by the empirical Bayes method [13]. Statistical heterogeneity was assessed by the I^2 statistic [14]. Values below 25 % and 50 % indicate low and moderate heterogeneity, respectively, whereas values above 50 % indicate high heterogeneity. All analyses were performed with OpenMetaAnalyst (http://www.cebm.brown.edu/open_meta/). For the optimization of

this meta-analysis, the guidelines summarized in the PRISMA and the MOOSE statements were followed [15, 16].

Apart from the meta-analysis of the predictive factors for VMT release and FTMH closure, a systematic review of the potential adverse events after ocriplasmin use has been performed, including not only the reported adverse events in the large studies, but also all published case reports concerning side-effects of ocriplasmin use.

Results

The flow chart describing the successive steps for the selection of eligible articles is depicted in Fig. 1. It is worth mentioning that the studies by Varma et al. [17] and Gandorfer et al. [18] were excluded due to overlapping population with the MIVI-TRUST trials, while the results reported by Haller et al. [11] were also incorporated in the study by Stalmans et al. [10] and presented in detail by Dr Ray at the American Academy of Ophthalmology Retina Subspecialty Day (Ray S. Independent baseline features predictive of pharmacologic VMT resolution in the Phase III ocriplasmin clinical program. Presented at: AAO Retina Subspecialty Day, 10 November 2012; Chicago). In addition, two studies had to be excluded for reporting reasons, as they presented the results from the MIVI I and II trials, which were phase I/II studies, being out of the scope of this study [19, 20], while six "letters to the editor" were excluded, as they only commented on previously published data [21–26]. Moreover, it has to be noted that only two prospective randomized controlled trials were included in the meta-analysis [10, 27], while all other studies were observational.

Table 1 presents the characteristics of the 19 eligible studies [10, 27–44]. Table 2 demonstrates the results of the meta-analyses; the forest plots are provided in Figs 2 and 3. The overall proportion of eyes exhibiting VMT release was found to be 0.46 (95 % CI: 0.36–0.55) with release rate ranging from 10 % to 71 % in the included studies, while the overall proportion of eyes with FTMH closure was 0.33 (95 % CI: 0.26–0.39) with closure rate ranging from 12 % to 50 %. It should be noted that two of the 19 studies enrolled only patients with macular hole combined with VMT [29, 40], while one study included only patients with VMT and concomitant age-related macular degeneration [27].

The diameter of VMA was indicated as the most significant positive predictive factor for VMT release; noticeably, VMA with diameter <1500 μm has about 7.85 times (95 % CI: 3.80-16.24) higher odds of resolution compared to VMA with diameter >1500 μm. Absence of ERM, phakic lens status, age <65 years and female gender are also statistically significant positive predictive factors for VMT release. Regarding FTMH closure, macular hole <250 μm has 2.25 times (95 % CI: 1.12-4.53) higher odds to close than macular hole >250 μm, pointing out the size of macular hole as a positive predictive factor for closure.

A test for heterogeneity of studies included in the meta-analyses showed low heterogeneity for age, VMA diameter, ERM, phakic lens status and macular hole size, while studies examining female gender moderate heterogeneity.

Apart from the meta-analyzed predictive factors, Chatziralli et al. found that the increased vitreofoveal angle, the V-shaped and loose VMA, the small VMA surface and the thin vitreous strands at the site of VMA could additionally positively affect the outcome of VMT release [31].

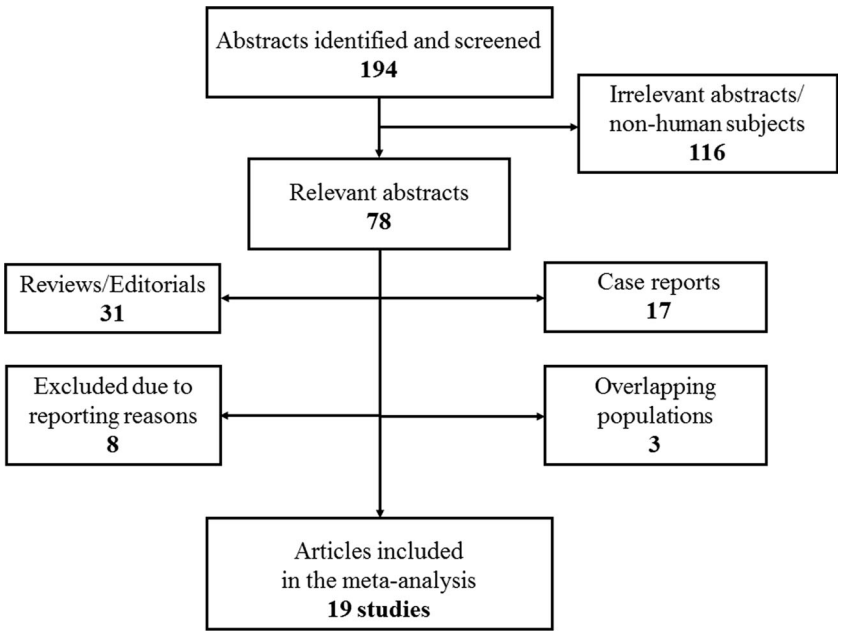

Fig. 1 Flow chart showing the selection of eligible studies

Table 1 Characteristics of the eligible studies

Study (Year)	Country	Study design	Number of eyes examined	VMA release rate	Analyzed factors	Comments
Maier (2015)[28]	Germany	Prospective	21	71 %	VMA diameter	
Steel (2015)[29]	UK	Prospective	12	58 %	MH size	Only patients with MH
Quezada-Ruiz (2015)[30]	USA	Retrospective	23	48 %		
Chatziralli (2015)[31]	Greece	Prospective	24	67 %	Gender, age, VMA diameter, lens status, ERM, MH size	
Reiss (2015)[32]	USA	Retrospective	10	10 %		6 DR and 1 AMD
Willekens (2015)[33]	Germany	Retrospective	38	71 %	Gender, age, VMA diameter, lens status, ERM, MH size	
Meyer (2015)[34]	USA	Retrospective	22	44 %	Gender, age, lens status, ERM, MH size	
Sharma (2015)[35]	USA	Retrospective	58	50 %	Age, lens status, ERM, MH size	
Novack (2015)[27]	USA	Prospective	74	24 %		All patients had AMD
Hager (2015)[36]	Germany	Retrospective	5	20 %	Age, lens status, ERM, MH size	
Warrow (2015)[37]	USA	Retrospective	35	43 %	Gender, age, VMA diameter, ERM lens status	5 AMD, 5 DR, 3 DME, 1 BRVO, 1 vitelliform
Chin (2014)[38]	USA	Retrospective	7	0 %	Gender, age, lens status	
Itoh (2014)[39]	USA	Retrospective	19	47 %		
Miller (2014)[40]	USA	Retrospective	8	57 %	MH size	Only patients with MH
Knudsen (2014)[41]	Saudi Arabia	Retrospective	8	62 %		
Lommatzsch (2014)[42]	Germany	Retrospective	14	64 %		
Singh (2014)[43]	USA	Retrospective	17	47 %	Age, VMA diameter, lens status, ERM	
Kim (2014)[44]	USA	Retrospective	19	42 %	Gender, age, VMA diameter, lens status, ERM	Patients with DR and AMD were included
Stalmans (2012)[10]	USA	Prospective	464	27 %	Age, gender, VMA diameter, lens status, ERM, MH size	

VMA: vitreomacular adhesion; ERM: epiterinal membrane; MH: macular hole; AMD: age-related macular degeneration; DR: diabetic retinopathy; DME: diabetic macular edema; BRVO: branch retinal vein occlusion

Table 3 summarizes the potential adverse events that have been reported in the literature after ocriplasmin use. The most common adverse events occur in the first week after ocriplasmin use and include vitreous floaters, photopsias and acute visual acuity decrease in about 17.5 % of patients. Subretinal fluid development has been observed in 8.8 % of patients and was usually associated with VMT resolution, along with ellipsoid zone changes, which occurred in 8.2 % of patients. These changes were transient and usually resolved during the first month post injection. Macular hole development and macular hole enlargement were noted in 5 % and 0.7 %, respectively, in the literature, while distortion/metamorphopsia has been reported in 1.9 % of patients, particularly after VMA release [45, 46]. Macular edema, especially in cystoid form, has been developed in 1.6 % of patients. ERG changes were observed in phase 2 MIVI studies, but were not reported in the results of phase 3 trials. Post marketing results showed ERG changes in about 0.3 %, accompanied with dyschromatopsia and ellipsoid zone changes.

Injection related adverse events have been also reported. Eye pain and conjunctival hemorrhage were the most common in about 8.5 %, while cataract development and intraocular pressure increase were noted in 3.5 % of patients. Severe adverse events, such as retinal tear/retinal detachment were reported in 1.8 % of patients [47], while endophthalmitis was noted in one case (0.1 %). Photophobia was present in 2.5 %, and anterior segment abnormalities, such as tearing, discharge, foreign body sensation, dry eye, blepharitis, corneal edema, and anterior uveitis, were observed in less than 1.5 %.

Rare adverse events, which were reported as isolated cases in the literature were lens subluxation, retinal vessels changes (attenuation/constriction), changes in autofluorescence, visual field constriction, afferent pupillary defect, sterile endophthalmitis and subfoveal vitelliform-like drusenoid deposits in less than 0.2 % [48–50].

Discussion

The principal message of this meta-analysis is that VMT release was positively associated with VMA diameter less than 1500 μm, ERM absence, phakic lens status, age <65 years and

Table 2 Results of the meta-analyses for vitreomacular traction resolution and macular hole closure. Bold cells denote statistical significance

Variables assessed for VMT release	Odds Ratio (95%CI)	Test for heterogeneity (I^2, p value)
Age <65 years	**2.69 (1.79-4.03)**	$I^2 = 0$ %, $p = 0.91$
Female gender	**2.37 (1.23-4.57)**	$I^2 = 27.91$ %, $p = 0.25$
VMA diameter <1500 μm	**7.85 (3.80-16.24)**	$I^2 = 0$ %, $p = 0.99$
Phakic lens status	**3.02 (2.02-4.50)**	$I^2 = 0$ %, $p = 0.47$
ERM absence	**4.75 (3.06-7.37)**	$I^2 = 0$ %, $p = 0.77$
Variables assessed for macular hole closure	**Odds Ratio (95%CI)**	**Test for heterogeneity (I^2, p value)**
Macular hole size <250 μm	**2.25 (1.12-4.53)**	$I^2 = 0$ %, $p = 0.77$

VMT: vitreomacular traction; CI: confidence interval

female gender. Regarding the macular closure rate, it has been found that macular hole size less than 250 μm was significantly associated with macular hole closure. The above confirm and essentially expand at a meta-analytical level the findings by the MIVI TRUST trial, which pointed out to the above-mentioned factors as predictors for VMT release [10]. The release rate of VMT ranged between 0 and 71 % in various studies, while the macular closure rate was 12–50 %. However, it should be noted that some studies included patients with other ocular comorbidities, such as age-related macular degeneration [27, 32, 37, 44], diabetic retinopathy [32, 37, 44] or branch retinal vein occlusion [37], which seemed to affect the VMT release and macular hole closure rate.

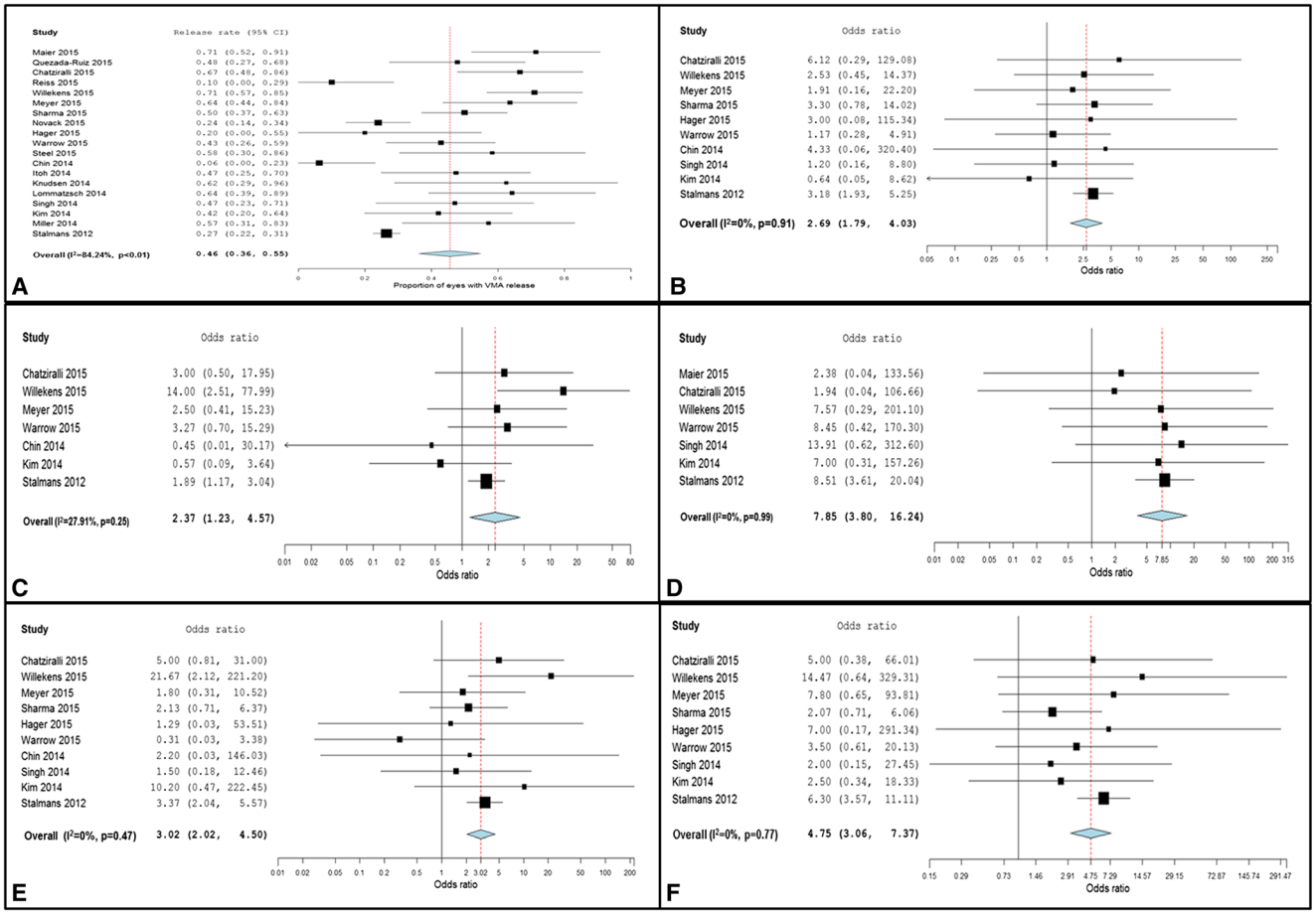

Fig. 2 Forest plot depicting the overall percentage of vitreomacular adhesion release (**a**) and the association between the vitreomacular adhesion release and age <65 years (**b**), female gender (**c**), vitreomacular adhesion diameter <1500 μm (**d**), phakic lens status (**e**) and absence of epiretinal membrane (f). Each study is shown by the point estimate of the odds ratio (the size of the square is proportional to the weight of each study) and 95 % confidence interval; the pooled odds ratios are shown as diamonds

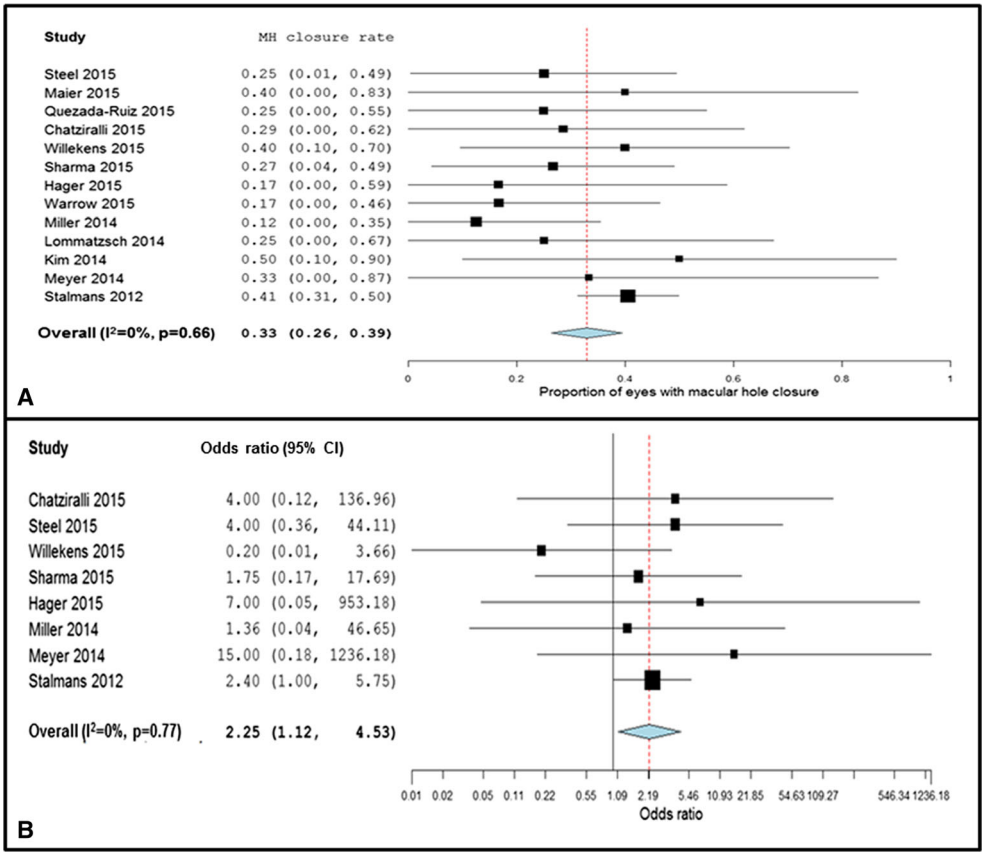

Fig. 3 Forest plot illustrating the overall percentage of macular hole closure (**a**) and the association between the rate of macular hole closure and the size of macular hole (**b**)

The ERM coexistence and the VMA diameter were factors that were expected to affect the VMT release, as ocriplasmin does not dissolve membranes, while it seems to have maximal impact on small adhesions [9]. In addition, it is well established that female gender is a risk factor for PVD, and therefore the likelihood for VMT release is higher in female patients [51]. Moreover, males were found to have greater VMA area than females in their fifth to eighth decade of life (Palacio A, Gupta A, Jadav P, Nesmith B, Schaal S. Vitreomacular Adhesion and Posterior Vitreous Detachment Evolution during Normal Aging of Human Eyes. Presented at ARVO meeting, May 3–7, 2015; Denver, Colorado), reinforcing the fact that female gender is a positive predictive factor for VMT release.

On the other hand, pseudophakia and young age are not documented in the literature to be more predictive of VMT resolution. In fact, the progression of PVD is more likely to happen after cataract surgery, especially if the posterior lens capsule is open [52]. Therefore, one could expect that VMA release will be higher in pseudophakic patients and in older patients. Stalmans et al. mentioned that a potential explanation for this discrepancy could be attributed to selection bias. The majority of pseudophakic patients and of those aged >65 years may already have developed PVD, and therefore patients enrolled in MIVI-TRUST trials might be more resistant cases of VMT [10, 11]. Another explanation could be that the liquefaction of vitreous following cataract surgery decreases the drug concentration at the VRI below a critical threshold level for drug efficacy. Therefore, further experimental studies are needed to scrutinize this phenomenon.

In this comprehensive review of the literature, apart from efficacy, ocriplasmin was found to be generally well-tolerated, while the reported adverse events were mainly ocular and no systemic. The systemic adverse events included nausea, headache and bronchitis in 3 % of patients. Severe adverse events i.e., retinal tears/retinal detachment or endophthalmitis, were also rare (1.8 % and 0.1 % respectively) [47]. Moderate adverse events, including acute visual acuity reduction, development of subretinal fluid, ellipsoid zone changes, ERG changes or distortion were found in about 8-17 %, but they were transient and usually occurred in the first week after injection, while most commonly resolving over time during the first month after injection [53–58]. Other mild adverse events, like the presence of photopsias, vitreous floaters or anterior segment abnormalities, were also reported, although they were transient [58]. On the other hand, more severe events, such as macular hole development or enlargement, were noticed in about 5 % of patients and needed surgical intervention to be treated [45, 46].

The fact that most adverse events occur during the first week after ocriplasmin injection and resolve in about 1–2 months post injection can be explained by the pharmacokinetic profile

Table 3 Summary of adverse events after ocriplasmin use sorted by frequency, as reported in 874 eyes in the literature

	Total number (percentage)
Vitreous floaters	153 (17.5)
Visual acuity decrease (acute)	152 (17.4)
Photopsias	151 (17.3)
Subretinal fluid development	77 (8.8)
Eye pain	76 (8.7)
Conjunctival hemorrhage/Redness	75 (8.6)
Ellipsoid zone changes	72 (8.2)
Macular hole development	44 (5)
Cataract	32 (3.7)
Increase of intraocular pressure	25 (2.9)
Photophobia	22 (2.5)
Distortion	17 (1.9)
Retinal tear/retinal detachment	16 (1.8)
Cystoid macular edema	14 (1.6)
Dry eyes	12 (1.4)
Dyschromatopsia	8 (0.9)
Macular hole enlargement	6 (0.7)
Tearing	5 (0.6)
Blepharitis	4 (0.5)
Corneal edema	4 (0.5)
ERG changes	3 (0.3)
Foreign body sensation	3 (0.3)
Dimming of vision	3 (0.3)
Subfoveal vitelliform-like drusenoid deposits	2 (0.2)
Anterior uveitis	2 (0.2)
Sterile inflammation	2 (0.2)
Lens subluxation	2 (0.2)
Visual field constriction	2 (0.2)
Afferent pupillary defect	1 (0.1)
Discharge	1 (0.1)
Endophthalmitis	1 (0.1)
Retinal vessels changes (attenuation/ constriction)	1 (0.1)
Fundus autofluorescence changes	1 (0.1)

of ocriplasmin, as it has been determined at different time points after a single intravitreal injection [59, 60]. Specifically, at day 7, the mean active ocriplasmin concentration in the vitreous was below the lower level of quantification compared with the concentration seen immediately after the injection. This finding suggests that a process of autolysis occurs immediately after injection, while ocriplasmin follows a second-order kinetics thereafter, until its total removal from the eye [59].

The studies thus far have shown that ocriplasmin may cause "acute panretinal structural and functional abnormalities" that typically improve over time [58]. Of note, these observations were more common in patients exhibiting VMT release, but they may also be present in patients without any change in VMT condition [58]. The precise mechanism of acute retinopathy after ocriplasmin remains unknown. In fact, the acute decrease in visual acuity has been attributed to further progression of VMT. Beebe has noted that ocriplasmin is nonspecific serine protease, cleaving peptide bonds located after a lysine or an arginine residue [21]. Therefore, even if their target to cause pharmacologic vitreolysis is laminin and fibronectin at the VRI, they cleave various other proteins as well. In addition, ocriplasmin has a relatively small molecular weight of 27 kDa and is capable of penetrating in all retinal layers, resulting in degradation of laminin and fibronectin in outer retinal layers and at the vitreoretinal junction [61]. Accordingly, ERG changes in b-wave could be explained by laminin degradation in the synapses of the outer plexiform layer, while nyctalopia, dyschromatopsia, visual field constriction, ERG a-wave suppression, disruption of ellipsoid zone and macular detachment are consistent with the cleavage of laminin in the interphotoreceptor matrix and photoreceptor cell layer [52–58, 62].

It is also worth noting that ocriplasmin has been reported to rarely cause lens subluxation or phacodonesis in cases that underwent combined phacoemulsification and PPV shortly after ocriplasmin injection [48]. A potential explanation for this observation could be the idiosyncratic distribution of the drug, which may reach the zonules of the lens and degrade their elastic glycoprotein fibrils in some patients [48]. This can also be related to the depth of the injection, resulting in pooling of ocriplasmin in the Cloquet space [48].

An interesting question that has not yet been answered is why ocriplamin causes abnormalities in a subset of patients and not in others. Probably genetic susceptibility may play a role in the vulnerability of some patients to acute retinopathy, along with other factors, such as the variable dilution by the vitreous and variations in drug preparation. In addition, a potential limitation of adverse events reporting is that postmarket analyses were based on voluntary reporting, and sometimes the incidence of adverse events is underreported. Further studies are needed to shed light to the exact activity of ocriplasmin and the mechanism of development of adverse events.

A potential limitation of this meta-analysis pertains to the fact that there was no standardized OCT scanning protocol in all studies. In addition, the MH size measurement method was not referred to in the majority of the included studies, while the status of the vitreous (i.e., the stage of PVD, if evident) was not clearly defined in each study. As a result, we should take into account the possible diagnostic variations among the treating physicians and the variability of methodology between the various studies. Selection bias and limited follow-up period also remain important factors, limiting the conclusions and the

level of evidence in "real-world" studies. Therefore, further observation is needed to support the present findings.

In conclusion, ocriplasmin injection is a relatively new treatment modality for the treatment of VMT and MH. The results of this meta-analysis/review showed that ocriplasmin seems to be effective in resolving VMT and closing macular hole, since VMT release rate was about 46 % and MH closure rate 33 %, with consequent reduction in PPV need, provided that the treated patients fulfilled specific criteria [63]. Noticeably, the patients who benefit more are female, patients aged <65 years and those with phakic lens status, absence of ERM, VMA <1500 μm and MH size <250 μm. As far as safety is concerned, ocriplasmin is generally well tolerated. Adverse events have been reported, but were mainly transient and mild/moderate in severity. In any case, careful selection of patients is of significant value, so as to obtain the optimal therapeutic outcome. In addition, it is very important to select between the various treatment alternatives for VMT (observation, surgical or pharmacological treatment) [63, 64], based on the different predictive factors.

Compliance with ethical standards

Conflict of interest Irini Chatziralli, George Theodossiadis, Paraskevi Xanthopoulou, Michael Miligkos and Panagiotis Theodossiadis certify that they have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria, educational grants, or other equity interest), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript. Sobha Sivaprasad has received research grants, and attended Advisory Board meetings of Allergan, Bayer and Novartis.

Funding No funding was received for this research.

Ethical approval For this type of study, formal consent is not required.

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