

Pharmacologic vitreolysis: New strategy for treatment of anomalous vitreo-macular adhesion

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Author contributions: Koleva-Georgieva DN solely contributed to this paper.

Conflict-of-interest statement: None.

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Received: January 29, 2015
 Peer-review started: January 29, 2015
 First decision: March 6, 2015
 Revised: April 30, 2015
 Accepted: July 16, 2015
 Article in press: July 17, 2015
 Published online: August 12, 2015

Abstract

Persistent anomalous vitreo-macular adhesion (VMA) is a well-known factor, associated with a variety of sight threatening diseases - including macular hole, vitreo-macular traction syndrome, cystoid and diabetic

macular edema, exudative age-related macular degeneration, myopic traction maculopathy and others. With the advent of optical coherence tomography our understanding of these pathologies and the ability of their early diagnosis has gone much far in the past two decades. The release of macular traction has been of exclusive surgical capability. Notwithstanding good results, vitrectomy is hampered by the inability of complete vitreo-retinal separation (*i.e.*, smooth, bare internal limiting membrane), compulsory postoperative positioning in macular hole cases, surgical complications, and high costs. With aim to offer less invasive and safe treatment modality for anomalous VMA, investigators have made enormous progress in the past decade. Leading among the studied nonsurgical measures is the intravitreal application of pharmacologic agents for the induction of vitreo-retinal separation and vitreous liquefaction, a method termed pharmacologic vitreolysis. Several vitreolytic agents have been studied to date, the most potent among them proved to be plasmin. Recently, ocriplasmin (formerly known as microplasmin) - a more stable than plasmin recombinant product, proved to be safe and efficient in releasing VMA in large studies, and consequently received FDA approval. Its role in clinical practice is now in the process of being determined. This paper aims to review and summarize the current knowledge and status of investigation on this new approach for the treatment of VMA.

Key words: Pharmacologic vitreolysis; Vitreo-macular adhesion; Posterior vitreous detachment; Macular hole; Microplasmin

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Core tip: Persistent anomalous vitreo-macular adhesion (VMA) is a well-known factor, associated with a variety of sight threatening diseases (macular hole, vitreo-macular traction syndrome, macular edema, exudative age-related macular degeneration). The release of

traction has been of exclusive surgical capability. Notwithstanding good results, vitrectomy is hampered by the inability of complete vitreo-retinal separation and surgical complications. With aim to overcome limitations of surgery, investigators have made enormous progress with the advent of pharmacologic vitreolysis - a method for releasing VMA by intravitreal drug delivery. This paper aims to summarize the current knowledge and status of investigation on this new treatment approach.

Koleva-Georgieva DN. Pharmacologic vitreolysis: New strategy for treatment of anomalous vitreo-macular adhesion. *World J Ophthalmol* 2015; 5(3): 99-105 Available from: URL: <http://www.wjgnet.com/2218-6239/full/v5/i3/99.htm> DOI: <http://dx.doi.org/10.5318/wjo.v5.i3.99>

INTRODUCTION

With the advent of optical coherence tomography (OCT) - a sophisticated modality for retinal imaging, ophthalmologists obtained more knowledge on the important role of the posterior vitreous in a variety of retinal diseases. In the development of physiologic, or age-related, posterior vitreous detachment (PVD) two processes (liquefaction - synchysis, and fibrillar collapse - syneresis) take place simultaneously and interact, thus resulting in vitreo-retinal separation^[1-3]. With time areas of liquefaction increase, the collagen meshwork fibrils form thick fibers (synergetic debris), and after separation from the internal limiting membrane (ILM) the posterior hyaloid collapses anteriorly^[1-3]. While previously we believed the process of PVD to be an acute one, recent OCT studies have shown that it is a gradual one and may take years. Usually PVD starts as a shallow separation of the hyaloid from the retina in the perifoveal area and expands gradually until the last detachment from the optic disc margin. The results of this last separation are acute symptoms and the sign of Weiss ring (complete PVD)^[4,5]. In some subset of eyes this physiologic process of complete PVD is hampered by firm vitreo-retinal adhesions to different sites - optic disc margin, fovea, or focal areas in retinal periphery. If this is the case, the dynamic traction of the posterior hyaloid exerted upon retina at points of adhesion gives rise to various complications, such as vitreous hemorrhages, macular hole, vitreo-macular traction syndrome (VMT), vitreo-papillary traction syndrome, retinal tears and retinal detachment. It has been documented that persistent vitreo-macular adhesion (VMA) may aggravate macular edema and retinal pathology in various conditions such as diabetic retinopathy (DR), retinal vein occlusions, neovascular age-related macular degeneration (AMD), uveitis, myopic maculopathy, and others^[6-8]. Persistent vitreo-retinal adhesions may serve as scaffold for vitreo-retinal neovascular proliferations in DR and retinal vein occlusions. Sebag and associates have revealed the role

of vitreoschisis (vitreous cleavage with residual vitreous cortical layer on retinal surface) for the pathogenesis of macular holes and epiretinal membranes (ERM)^[3].

The therapeutic option in all these pathologic vitreo-retinal entities for many years has been vitreo-retinal surgery. Notwithstanding good results^[9,10], vitrectomy is hampered by the inability of complete vitreo-retinal separation (*i.e.*, "smooth", "cell-free" ILM, ILM)^[11], compulsory postoperative positioning for macular hole cases, surgical complications, and high costs. Some studies draw our attention that after vitrectomy, despite meticulous PVD induction and thorough aspiration, or posterior hyaloid peeling, some cortical vitreous fibers may still remain and adhere to the retinal surface, and thus give rise to fibrocellular proliferation and formation of postoperative ERM^[12]. Gandorfer and coauthors have documented by electron microscopy and immunocytochemistry that in 2/3 of vitrectomy cases with ERM removal, cortical vitreous cells remain on the ILM, which subsequently lead to recurrence of ERM^[11]. To achieve a "cleaner" retinal surface, surgeons may peel the ILM in every case, but this increases the risks of some complications, such as nerve fiber layer damage, retinal haemorrhages or breaks, and paracentral scotomas. With aim to overcome limitations of vitrectomy, investigators have explored as alternative different methods for achieving complete PVD and "smooth" ILM. Leading among the studied nonsurgical techniques is the application of different pharmacologic agents in the vitreous for inducing vitreo-retinal separation and vitreous liquefaction. This method was termed pharmacologic vitreolysis by Sebag^[13]. As a result of a huge work in this field of ophthalmology by many investigators, such as Sebag, Gandorfer, de Smet, Stalmans and others, we have now a better understanding of vitreo-macular pathology and recently obtained pharmacologic vitreolysis in the treatment armamentarium for anomalous VMA in our clinical practice. The early interest of vitreolysis was concentrated on the use of vitreolytic agents in difficult cases for obtaining cleaner vitreo-retinal separation (pharmacology assisted vitrectomy)^[13,14]. Realizing the potential of vitreolysis, investigators have then begun to explore the use of vitreolytic substances as stand-alone drug delivery therapy for the treatment of anomalous VMA related diseases^[15,16]. This paper aims to review and summarize the current knowledge and status of investigation on this new treatment approach.

VITREOLYTIC AGENTS

Pharmacologic vitreolytic substances can be categorized according to the mechanism of action as "enzymatic" (plasmin, microplasmin, tissue plasminogen activator, nattokinase, chondroitinase, dispase, and hyaluronidase) and "non-enzymatic" (Vitreosolve and RGD peptides - arginine-glycine-aspartate peptides). Sebag^[17,18] offers a more useful classification, based on their biological effect - "liquefactants" (able to induce liquefaction),

"interfactants" (able to disrupt vitreo-retinal adhesions) or having both effects. Sole liquefactants are collagenase and hyaluronidase, sole interfactants are RDG peptides and dispase, and having both effects - chondroitinase, nattokinase, plasmin, microplasmin, tissue plasminogen activator, and Vitreosolve.

It must be stressed, that for the induction of safe PVD with complete vitreo-retinal separation, it's fundamental to achieve both effects. If liquefaction occurs without adequate vitreo-retinal interface disruption, this will result in worsening of the existent tractional pathology^[17,18].

Collagenase

Collagenase is a bacterial protease, purified from *Clostridium histolyticum* and it selectively cleaves collagen type II which comprises the fibrillar meshwork of the vitreous body^[19]. It acts as a sole liquefactant. In animal models collagenase succeeded to liquefy the vitreous, but was noted to have adverse effects - ILM damage, disruption of retinal architecture, and retinal toxicity proved by histological and electrophysiological examination^[20]. In recent studies of collagenase-assisted pars plana vitrectomy some complications have been noted - vascular digestion of proliferative membranes and retinal hemorrhages^[21].

Hyaluronidase

Hyaluronidase represents an endoglycosidase which is able to dissolve hyaluronan - a molecule that comprises the glycosaminoglycan meshwork of the vitreous body. Hyaluronidase is a pure liquefactant and its' effect was demonstrated *in vitro*^[22] and *in vivo*^[23], and recently in a phase III trial (Vitrace) in the management of hemophthalmus^[24]. As it has no effect on vitreo-retinal adhesions, if applied alone may worsen existing VMA-related pathologies.

Dispase

Dispase represents a protease molecule which cleaves collagen IV and fibronectin, and thus attenuates attachments between the hyaloid and the ILM. In experimental *in vivo* animal studies some harmful effects were reported - retinal toxicity with disruption of ganglion cells and photoreceptor layers, retinal and vitreous hemorrhages, cataract and lens subluxation^[23].

RGD peptides

Integrins are receptor molecules on the cell surface which take part in the cellular - extracellular matrix signaling and adhesion. They are bound to the ILM by a specific sequence of amino acids - RGD (arginine-glycine-aspartate). Synthetic RDG peptides compete for integrin-binding sites and thus disrupt the integrin-extracellular matrix interaction and loose vitreo-retinal adhesions^[25]. RGD peptides are non-enzymatic and are considered as pure interfactants. In a rabbit model RGD peptides facilitated the induction of PVD during

vitrectomy, and no toxicity was noted^[26]. No further investigations are reported.

Vitreosolve®

Vitreosolve® (Vitreoretinal Technologies Inc, United States) is a non-enzymatic urea-based molecule that is considered to have both liquefactant and interfactant vitreolytic effects. It currently undergoes Phase II / III study in patients with non-proliferative DR without PVD. Preliminary results demonstrate good ability at achieving complete PVD. Final results are being expected.

Chondroitinase

Chondroitinase is a protease which catalyzes depolymerization of chondroitin sulfate, hyaluronan, and dermatan sulfate. It has both liquefactant and interfactant properties. The results from pre-clinical studies are mixed. One group found no significant effect on inducing PVD^[20], while another group reported complete vitreo-retinal disinsertion in a monkey model^[27]. High doses demonstrate some toxicity, while lower doses were unable to achieve significant rates of spontaneous PVD, or bare ILM after vitreo-retinal separation^[28].

Nattokinase

Nattokinase is a serine protease produced by *Bacillus subtilis* and is derived from fermented soybean. It is known to have fibrinolytic effect and is under investigation in cardiovascular and thrombotic therapy. It is considered to enhance the activation of plasmin by increasing the synthesis of tissue plasminogen activator (tPA), thus it has both liquefactant and interfactant properties^[29]. In a rabbit model nattokinase showed good vitreolytic property with leaving smooth ILM, but only in the highest intravitreal doses tested. These doses, however showed also adverse actions, such as alterations in retinal structure, intraretinal hemorrhages, and toxicity confirmed by electroretinography^[30].

Plasmin

Plasmin represents a serine protease which lyses laminin, fibrin, and fibronectin, and also acts through increasing the levels of other proteases that disrupt extracellular matrix structures. Its' primary action is to weaken vitreo-retinal adhesion, and to a less extent provoke liquefaction^[31,32]. Plasmin was the most widely studied vitreolytic agent, and in many pre-clinical studies has shown good properties in achieving complete PVD with bare ILM (in a dose-dependent manner), and its' safety profile was excellent^[33-37].

However, plasmin is extremely unstable. The application of plasmin in clinical practice requires activation of plasminogen (its' proenzyme) with plasminogen activators immediately prior to use. As there is no commercially available plasminogen, investigators rely on a very expensive and time-consuming process of generation of autologous human plasminogen derived

from patients' own plasma and purified *via* affinity chromatography^[37]. Numerous studies using the described technique in difficult vitrectomy cases with plasmin-assisted PVD, such as retinopathy of prematurity (stage 5)^[38], tractional DME, complicated proliferative DR^[39], complicated X-linked retinoschisis^[40] report ease in PVD induction, improved final anatomic outcomes, and no enzyme-related complications^[37-40]. However, this method is quite expensive, time-consuming and inapplicable in daily clinical setting.

Plasminogen activators (tPA and urokinase)

Plasminogen activators have fibrinolytic properties and are approved for non-ophthalmic vascular disorders (stroke, symptomatic coronary artery). They exert their effect through plasmin, thus having potent vitreolytic properties. Their advantages are commercial availability, safety in terms of microbial contamination (recombinant molecule), established ocular safety in some other ophthalmological conditions (post-surgical fibrin lysis, submacular hemorrhage, acute retinal vein occlusion)^[41,42]. Pre-clinical studies on plasminogen activators for inducing PVD show promising efficacy and safety results^[43,44]. The difficulty in applying plasminogen activators in clinical practice comes from the inability to achieve sufficient quantities of intraocular plasminogen (which can be achieved by blood-retinal barrier brake down, *i.e.*, cryopexy), or exogenous administration. Thus dosing would be imprecise.

Ocriplasmin (microplasmin)

Ocriplasmin (formerly known as microplasmin) represents a recombinant protein which contains the catalytic domain of plasmin, and so having the properties of human plasmin^[45]. Microplasmin was developed for intravenous administration for the treatment of systemic thromboembolic disease. Its' effects after intravitreal application are specific for vitreous and less active on ocular structures, such as vessels, lens, lamina cribrosa, and ciliary body^[46]. It has numerous advantages over plasmin, autologous plasminogen, and tPA: it is more stable than plasmin, commercially available, allows accurate dosing, generated by recombinant technique it assures sterility, the smaller size (22 kDa of microplasmin versus 88 kDa of plasmin) facilitates its' permeability in tissues. Pre-clinical studies have demonstrated a dose- and time-dependant efficacy in achieving complete PVD with clean, bare ILM^[32,33,46]. It showed no histological or functional toxicity, except a- and b-wave depression in electroretinography in cases, treated with the highest dose (250 µg)^[47].

The most potent and safe vitreolytic agent among all tested proved to be microplasmin, thus it underwent exploration in a series of clinical trials sponsored by ThromboGenics and collectively entitled the Microplasmin Intravitreal Injections (MIVI) trials - 14 listed in the clinical trials registry. The majority has been completed and ocriplasmin (Jetrea, ThromboGenics Inc) received

FDA approval (on 17th October 2012) for nonsurgical treatment of symptomatic VMA.

MIVI I was an uncontrolled Phase I / II a clinical trial that aimed to assess the safety profile and efficacy of ocriplasmin, applied intravitreally in different concentrations (25, 50, 75, and 125 µg) and increasing exposure times (2 h, 24 h and 7 d). Subjects of the trial were patients scheduled for surgery (with DME, VMT syndrome, macular hole)^[48]. The incidence of spontaneous PVD as well as the ease of PVD induction during vitrectomy was found to be dependent on the dose and time exposure. However, less than 50% of eyes in every subgroup developed spontaneous PVD. Except one case of retinal detachment, there was no safety concern described^[48]. The results from this initial trial have demonstrated the good safety profile of ocriplasmin and confirmed that it's capable in inducing PVD in some cases.

MIVI II t (traction) was a prospective and sham-controlled Phase II clinical trial for assessment of the efficacy of ocriplasmin alone for the treatment of symptomatic VMA and macular holes. Four cohorts were examined in randomization 4:1 to ocriplasmin at doses 75, 125, 175 µg and sham^[49]. The primary endpoint of non-surgical release of VMA at day 28 after injection was reached in 8%, 25%, 44% and 27% of patients in the sham, 75, 125, 175 µg cohort, respectively. The greatest proportion of VMA release was noted until day 7, and repeated injections in eyes with unreleased VMA after day 28 in the 125 µg cohort did not increase the chance of PVD induction.

MIVI III was a larger multicenter prospective placebo-controlled study designed to evaluate three doses of ocriplasmin (25, 75, and 125 µg) compared to placebo for facilitating PVD before vitrectomy^[50]. The percentage of complete PVD were 10%, 14%, 21% and 31% for the placebo, 25, 75, and 125 µg ocriplasmin, respectively.

MIVI-TRUST comprises pooled data from two parallel multicenter, randomized Phase II clinical trials (MV 006 and MV007), which had same protocol except the ratio of randomization. The aim was to compare a single dose of 125 µg ocriplasmin with sham in patients with symptomatic VMA alone and in VMA associated with macular hole^[51]. The primary endpoint of VMA resolution at day 28 was achieved in 26.5% of ocriplasmin treated eyes and in 10% of placebo-injected eyes ($P < 0.001$). Non-surgical closure of macular holes resulted in 40.6% of ocriplasmin treated eyes compared to 10.6% of sham-injected eyes ($P < 0.001$). The subgroup analysis showed that resolution of VMA at day 28 was achieved more often in eyes without ERM, younger patients (< 65 years), eyes with full thickness macular hole, phakic eyes, and those with a focal VMA ≤ 1500 µm^[52]. Eyes with macular hole width ≤ 250 µm were more likely to achieve nonsurgical macular hole closure. As safety concerns, investigators reported: similar rates of retinal holes (0.9% vs 1.6%) and retinal detachment (1.1% vs 2.7%) in the ocriplasmin and vehicle

injected eyes, respectively; decrease in visual acuity with > 3 lines in 5.6% and 3.2% in the ocriplasmin and sham injected eyes (a condition of progression of the pathology, that requires proper monitoring and timely schedule for surgical treatment); mild transient intraocular inflammation in 7.1% and 3.7% of eyes injected with ocriplasmin and sham, respectively; 2% of ocriplasmin cases reported dyschromatopsia and accompanying a- and b-wave amplitude decrease in electroretinography; potential for lens subluxation^[51,52].

Studies for treatment of anomalous VMA in cases with DME (MIVI 11), ARMD (MIVI 5), as vitreolysis-assisted vitrectomy in children and infants scheduled for surgery (MIC), and in uveitic macular edema (MIME) are still undergoing and their results are being expected.

The use of ocriplasmin is now on its way of translation to the real world clinical practice. Ophthalmologists report comparable results to those in the clinical trials^[53,54], or even better in cohort of selected (best outcome expectancy) cases^[55]. Singh and coauthors report overall response rate of 47.1% (8/17 eyes), in patients meeting three of four positive predictors criteria (e.g., focal VMA \leq 1500 μ m, no ERM, and phakic lens status) they report successful VMA release in 50.0% (7/14 eyes), and patients meeting all four criteria (e.g., VMA diameter \leq 1500 μ m, no ERM, younger than 65, and phakic lens status) showed a response of 75.0% (3/4 eyes)^[55]. Other authors have published initial results of much lower macular hole closure rate - 12.5% (one of 8 eyes with stage 2 macular hole)^[56], unsuccessful resolution of VMA (none of 7 treated eyes)^[57], and enlargement of macular hole with worsening of visual acuity^[58]. With view of previous good results and the latter disappointing ones, a careful selection of candidates for ocriplasmin treatment as well as watchful observation after treatment should be done. It is important to discuss with the patient that in rare cases macular hole progression may result with worsening of the condition. On the whole, investigators that are involved in the development of ocriplasmin treatment, advise that candidates for ocriplasmin injections should be scheduled for surgery, thus if drug delivery does not succeed within 4 wk, surgery would be performed without delay.

In terms of adverse effects ophthalmologists report their clinical observations of vision loss^[59,60], dyschromatopsia, subretinal fluid accumulation predominantly in cases with release of VMA^[61], cystoid macular edema development^[62], spectral OCT detection of disturbances in the neuroreceptor ellipsoid zone^[60-64], as well as documented by electroretinography a decrease in the a- and b-waves^[63,64]. These effects seem to be short (months)^[59] or long lasting (years)^[60], but transient. These documented observations raise the concern about the enzymatic effect on photoreceptors and pigment epithelial cells. Further investigations are needed to elucidate the precise mechanisms by which ocriplasmin exerts these retinal microstructure alterations.

CONCLUSION

Though great progress has been done in the research process, the development of non-surgical treatment for anomalous VMA related diseases is very much an ongoing work. From the various agents, tested for the needs of pharmacologic vitreolysis, microplasmin has shown the greatest potential for safe and complete PVD. Randomized controlled clinical trials documented efficacy, but in less than 50% of cases. In selected cases (smaller than 250 μ m macular holes, without ERM, focal VMA \leq 1500 μ m, younger than 65, and phakic lens status) the prognosis is documented to be better, thus they represent best candidates for ocriplasmin treatment. Safety results seem satisfactory, though caution regarding some possible complications is advisable. The clinical role of ocriplasmin in cases with macular traction and persistent DME, uveitic edema, exudative AMD and others is still under investigation.

Future perspectives in this field of research would cover exploration of non-enzymatic agents that would offer vitreolysis without collateral damage of adjacent structures. Some investigators believe that the most promising concept would be to use a mixture of specific agents at much lower doses, previously found to have some toxicity, as a combination therapy may allow the use of lower and safer doses to increase the success rate of VMA release.

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