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Review Article

Safety Profile of Ocriplasmin Pharmacologic Vitreolysis for Vitreomacular Traction Release

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Abstract

Purpose: To determine the safety of intravitreal ocriplasmin for Vitreomacular traction (VMT) resolution.

Methods: To evaluate the above mentioned item based on recently published data.

Results: Although a safer alternative as compared to vitrectomy, yet many adverse events , mostly transient, were reported.

Conclusion: Fortunately, several Phase 4 evaluations of ocriplasmin are ongoing and should provide us with additional safety information. We believe that ocriplasmin should be used with caution pending further study results about the mechanism, incidence, and reversibility of its harmful effects on the eye.

Keywords: *Ocriplasmin; Adverse Events; Vitreomacular Adhesion; Vitreomacular Traction; Macular Hole*

Introduction

The Vitreomacular interface is a complex formed by the vitreous cortex, extracellular matrix, and the basal laminae of adjacent cells; all of them firmly attached to each other with some collagen fibers inserted to the basal laminae in a vertical fashion, and other fibers running parallel to the internal limiting membrane [1]. This area is rich in fibronectin, laminin, chondroitin sulfate, and other molecules, and is the target of new drugs aiming to treat pathologies that can distort the normal anatomy of the area resulting in visual complaints [2].

Posterior vitreous detachment (PVD) is a normal physiologic process of aging and results from the simultaneous weakening of the adhesion between the posterior vitreous cortex and the interior limiting lamina of the retina, combined with liquefaction of the vitreous [3-6]. Posterior vitreous detachment normally progresses to spontaneous separation of the vitreous from the retinal surface without complication [7].

Incomplete separation of the posterior hyaloid at the macula is termed vitreomacular adhesion (VMA). However, continued traction on the macula without vitreous release can lead to pathologic VMA manifesting either as vitreomacular traction (VMT) or macular hole (MH) formation.

Classification of vitreomacular interface disease

According to the International Vitreomacular Traction Group Classification, VMA is defined as perifoveal vitreous separation with remaining vitreomacular attachment and unperturbed foveal morphologic features; however, this can result in VMT characterized by anatomical distortion of the fovea, which may include pseudocysts, macular schisis, cystoid macular edema, and subretinal fluid. Vitreomacular traction is classified as focal when the area of vitreous attachment to the retina is 1,500 µm or less, or as broad when more than 1,500 µm is adherent to the retina. When associated with other macular diseases, it is classified as concurrent [8].

Full-thickness macular hole (FTMH) was defined as a foveal lesion including all retinal layers from the internal limiting membrane to the retinal pigment epithelium. Size of the FTMH, measured at the narrowest width, was defined as small (_250 µm), medium (> 250 and

_400 μm), or large (> 400 μm). FTMH was further classified as primary (due to VMT) or secondary (associated trauma or other cause) [9].

Management options of vitreomacular traction

The goal of therapy for symptomatic VMA/VMT is to relieve vitreous traction on the macula, thereby resolving the underlying condition before structural retinal damage has occurred, hence allowing a greater likelihood of clinically meaningful vision improvement [10].

Before January 2013, observation and vitrectomy were the only available approaches to patients with VMT [11,12]. Currently, intravitreal ocriplasmin (IVO) is another available option in the management of VMT [13].

Observation

May be an effective initial treatment strategy in patients with mild VMT and good presenting visual acuity [9].

Factors Predictive Of Spontaneous Vitreomacular Traction Release

Three studies sought to identify factors predictive of spontaneous VMT release. Reported factors were the following:

A. Adhesion diameter less than 400 μm [14].
B. Wide angle between the vitreous surface and nasal and temporal macula (vitreomacular angle) 14
C. Isolated inner retinal layer distortion [15].
D. Treatment of concurrent retinal diseases with intravitreal injections [15].
E. 'Vitreomacular interface area' value less than 101 002 μm^2 as calculated by optical coherence tomography [16].

Pars Plana Vitrectomy (PPV)

PPV remains the mainstay of VMT treatment when observation and/or medical therapy are either unsuccessful or not indicated [17].

Pharmacologic Vitreolysis with Ocriplasmin

Plasmin and its derivative ocriplasmin (Jetrea; Thrombo Genics, Inc., Iselin, New Jersey, USA) are nonspecific serine proteases that cleave peptide bonds located after a lysine or an arginine residue [18]. The potential advantages of pharmacologic Vitreolysis over surgical vitrectomy include the induction of vitreous detachment without vitreoschisis, greater ease, lower cost, avoidance of surgical risk, and faster visual rehabilitation, possibly with better visual outcomes. After the 2012 approval by the US Food and Drug Administration of intravitreal ocriplasmin for treatment of symptomatic VMT, many retina specialists were hopeful that ocriplasmin was the long-awaited silver bullet-a safe and effective vitreolytic agent that would fulfill the promise of this new treatment approach. Real-life experience with the drug, however, has raised serious safety concerns [19].

Adverse events (AEs) associated with ocriplasmin intravitreal injections

Adverse Events (AES) Related to Intravitreal Injection Procedures.

The incidence of AEs known to be associated with the intravitreal injection procedure is presented in Table 1 No clinically meaningful differences were observed between treatment groups for AEs of intraocular hemorrhage or increased intraocular pressure.

These events were of mild or moderate intensity. Adverse events of increased intraocular anterior chamber inflammation were reported in a higher proportion of patients in the ocriplasmin versus placebo group (Table 1). Two cases of vitreous chamber inflammation (deemed by the investigator as unrelated to study drug) required intravitreal steroid injections for vitritis. All other cases of anterior chamber or vitreous chamber inflammation resolved spontaneously. Two cases of self-limiting intraocular hemorrhage, which were peripheral in nature and not associated with any sequelae, were reported in the ocriplasmin group. Both cases spontaneously resolved within weeks. No intraocular hemorrhage cases were reported in the placebo group. No cases of intraocular infections, including endophthalmitis, were reported in any patient treated with ocriplasmin [7].

	Studies 006 and 007	
System Organ Class Preffed Term Category	Placebo (n = 187), n (%)	Ocriplasmin 125 µg (n = 465), n (%)
Number of patents (%)		
Intraocular hemorrhage	7 (3.7)	11 (2.4)
Retinal hemorrhage	4 (2.1)	8 (1.7)
Vitreous hemorrhage	2 (1.1)	3 (0.6)
Hyphema	0	1 (0.2)
Optic nerve sheath	1(0.5)	0
Hemorrhage		
Optic disk hemorrhage	0	0
Intraocular inflammation	7 (3.7)	33 (7.1)
Anterior chamber cell	5 (2.7)	17 (3.7)
Anterior chamber flare	2 (1.1)	6 (1.3)
Iritis	0	12 (2.6)
Vitritis	0	2 (0.4)
Iridocyclitis	0	1 (0.2)
Vitreal cells	0	1 (0.2)
Anterior chamber	0	1 (0.2)
Inflammation		
Iris adhesions	1 (0.5)	0
Increase in	10 (5.3)	19 (4.1)
Intraocular pressure		
Increased Intraocular	10 (5.3)	18 (3.9)
Pressure		
Ocular hypertension	0	1 (0.2)

Table 1: *Summary of AEs Known to Be Associated With the Intravitreal Injection Procedure; AEs in the Study Eye During the @Phase 3 Placebo-Controlled Studies (Safety Population).*

Suspected adverse drug reactions (sADRs)

In one recent article periodic aggregate safety reports consisting of premarketing, or clinical trial, data (n = 999 injections) and post marketing reports through July 16, 2013 (n = 4,387 injections), were retrospectively analyzed by the American Society of Retina Specialists Therapeutic Surveillance Committee (TSC). The aggregate data were analyzed to classify adverse events, and the post marketing safety data for each event type were compared with the premarketing data 20.

As recently noted by Beebe, 18 plasmin and its derivative ocriplasmin are nonspecific serine proteases that cleave peptide bonds located after a lysine or an arginine residue. Although their intended targets for pharmacologic vitreolysis are laminin and fibronectin at the vitreoretinal interface, they are capable of cleaving dozens of other proteins [18].

Furthermore, intra vitreous ocriplasmin, a relatively small protein with a molecular weight of 27 kDa, has been shown to penetrate all layers of the retina in rat eyes, causing degradation of laminin and fibronectin in outer retinal layers and at the vitreoretinal junction [21].

In addition to its distribution in vitreous gel and lens zonules [22] laminin is found in multiple retinal layers, including the internal limiting membrane, the outer plexiform layer (where it localizes to synapses between photoreceptor and bipolar cells), the external limiting membrane, and the interphotoreceptor matrix [23,24]. The specific adverse effects of ocriplasmin seem to correlate with the anatomical distribution of laminin within the retina and zonules [25,26]. For example, laminin degradation in synapses of the outer plexiform layer may explain ERG B-wave suppression, while cleavage of laminin in the interphoto receptor matrix and photoreceptor cell layer is consistent with such findings as visual acuity loss, dyschromatopsia, nyctalopia, afferent pupillary defect, visual field constriction, ERG A-wave suppression, disruption of ellipsoid and interdigitation lines, and macular detachment [25-27].

Acute reduction in visual acuity (progression of pathology or onset of subfoveal lucency)	Premarketing	Postmarketing
Rate, % (n)	7.7 (36)	1.3 (58)
Mean visual acuity loss, letters	13.6	~35
Significant vision loss (≤ 20/200), %	0.65	0.50
Time to onset, days	≤ 7	1
Time to resolution, days	14	10
% resolution	83%	40%
ERG Changes		
Number of reports*	10	2
Isoelectric responses?	No	Yes
Time to onset	1 week	3 days
Time to resolution	6 Months	ongoing
% resolution	60%	Ongoing
Dyschromatopsia (yellowish or black/white vision)		
Rate, % (n)	1.6 (16)	0.5 (9)
Time to onset, days	1	1
Time to resolution	3 Months	Not reported
% resolution	88%	30%
Retinal tear/detachment		
Rate, % (n)	1.9 (9)	0.4 (17)
Lens subluxation/phacodonesis		
Rate, % (n)	0.2 (2)	0.02 (1)
Impaired pupillary reflex (APD or sluggish respone)		
Rate, % (n)	0.5 (5)	0.3 (11)
Time to onset, days	1	1
Time to resolution	3 Days	Not responding
% resolution	100%	27%
EZ findings (loss or disruption of EZ)		
Rate, % (n)	NA†	0.18 (8)
Time to onset, days	NA†	5
Time to resolution, days	NA†	29
% resolution	NA†	75%

Retinal vessel findings (vascular attenuation or vasoconstriction)		
Rate, % (n)	0.1 (1)	0.05 (2)
Time to onset, days	7	2-7
Time to resolution	6 Month	Ongoing
% resolution	100%	Ongoing

**Reported as number of cases and not rate, because ERG8 were not consistently obtalned.*

†EZ findings were not observed in the premarketing program, whose imaging was limited to time domain optical coherence tomography.

APD, afferent pupillary defect; EZ ellipsoid zone.

Table 2: *Ocriplasmin related premarketing and post marketing adverse events [20].*

The observations that subretinal fluid developing after ocriplasmin injection strongly correlates with ellipsoid zone changes [28,29] and can persist for over 6 months 20 have led previous authors [27-31] to suggest that ocriplasmin causes weakening of retinal adhesion by degrading laminin and possibly other constituents of the interphoto receptor matrix, which is known to mediate retinal pigment epithelium–photoreceptor adhesion in primate eyes [32,33] Figure 1,2 & 3.

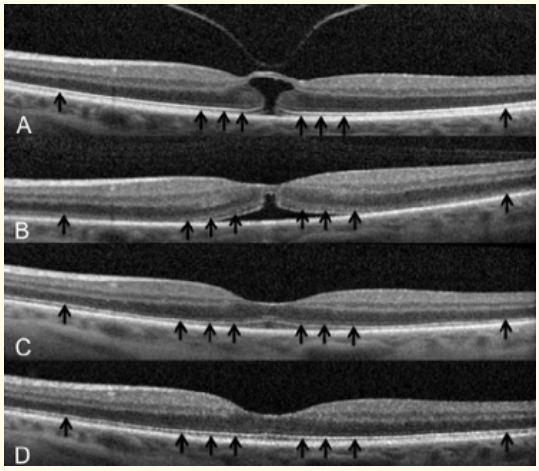

Figure 1: *Spectral domain optical coherence tomography scans of a patient with VMT release and transient outer band hyporeflectivity after ocriplasmin. A. Scan showing basal outer band reflectivity and loss of foveal depression the day of injection. B. Day 1 after IVO showing VMT release and decreased reflectivity of the outer bands, note that the "hyporeflectivity" is diffuse and not only restricted to the central area. C. Twenty-one days after IVO showing increase reflectivity of the outer bands. D. "Basal" reflectivity of the outer bands 116 days after the injection [33].*

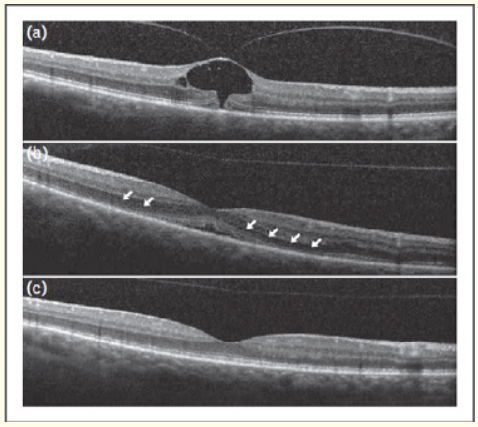

Figure 2: *Spectral domain optical coherence tomography immediately before (a), 10 days following (b), and 4 weeks following intravitreal injection of ocriplasmin (c) in a 63-year old female. (a) Prior to treatment, visual acuity was 20/40 with symptomatic visual distortion. SD-OCT reveals significant vitreomacular traction (VMT) with near fullthickness macular hole, inner layers remain intact). (b) Ten days following treatment, release of VMT, presence of submacular fluid, and disruption of the ellipsoid layer (arrows) are noted. Visual acuity was 20/30. (c) Four weeks later, integrity of the ellipsoid layer is improved with resolution of submacular fluid with subsequent improvement of visual acuity to 20/25. Final visual acuity 177 days postocriplasmin injection was 20/20 [9].*

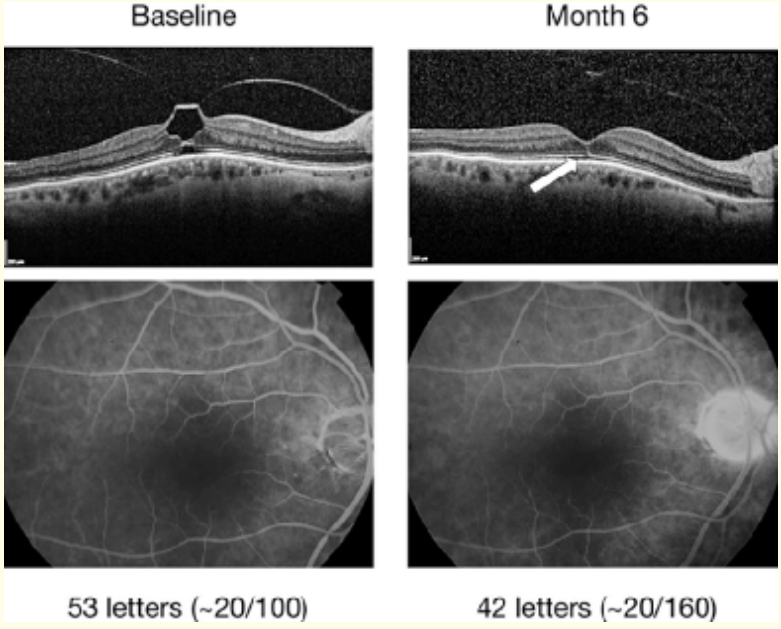

Figure 3: *Phase 3 ocriplasmin treated patient with persistent vision decrease at Month 6, white arrow indicates disruption of IS/OS junction because of the presence of subretinal fluid [7].*

Another possible mechanism could be a mechanical effect as IVO-induced vitreous collapse could result in a transient increase in traction, resulting in a temporary separation/misalignment between cells in the outer retinal bands [33].

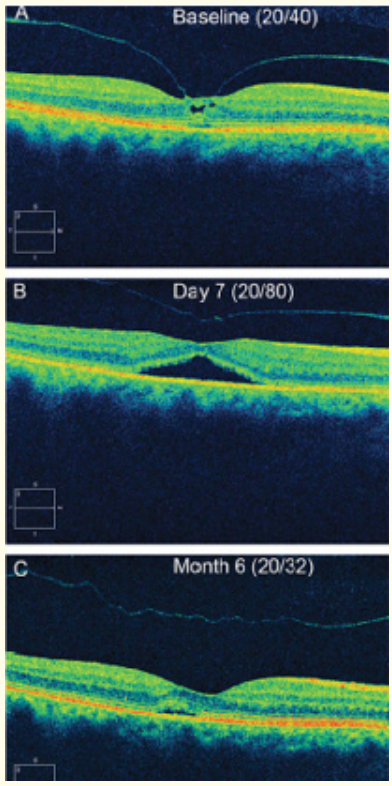

Figure 4: *Transient vision loss from development of subretinal fluid at the fovea. Vitreomacular adhesion at baseline (A) is resolved by Day 7 after ocriplasmin injection, but acute vision loss is reported accompanied by onset of localized subretinal fluid (B). At Month 6, visual acuity has improved but a small pocket of subretinal fluid remains (C) [20].*

Ellipsoid layer loss was correlated with vision loss, and both reached a significant nadir at 2 weeks after injection. Both ellipsoid layer loss and vision loss subsequently recovered. Recovery had begun by weeks 3 to 4, persistent defects still existed up to 3 months after injection. Analysis of Weeks 1 and 2, however, revealed an increase in macular thickness. Most of the change in macular thickness occurred within the inner retina with less change in the outer retina. The etiology of this change is not fully understood. Possible explanations include traction from the hyaloid on the inner retina or another toxic manifestation of ocriplasmin. Vision loss after ocriplasmin is therefore not only associated with changes in the ellipsoid layer but also may be associated with changes in macular thickness overall [34].

Significantly, different changes in the optic disk morphology were observed between the "VMT resolution" and the "no VMT resolution" subgroups. The type of changes included a decrease in cup/disk area ratio and an increase in mean peripapillary RNFL thickness, both greater for the "no VMT resolution" subgroup. In some patients, transient peripapillary SRF was observed.

There are several nonexclusive explanations for the observed optic disk changes. One hypothesis is a realignment of the vitreous traction over this area, as the vitreous is strongly attached to the optic disk margin. An alternative hypothesis for the optic disk changes is edema of the RNFL. Whether the observed swelling of the nerve fiber layer is due to a direct effect of ocriplasmin at the ganglion cell axons with or without a transient increase in traction over the posterior pole remains to be determined [35] Figure 5.

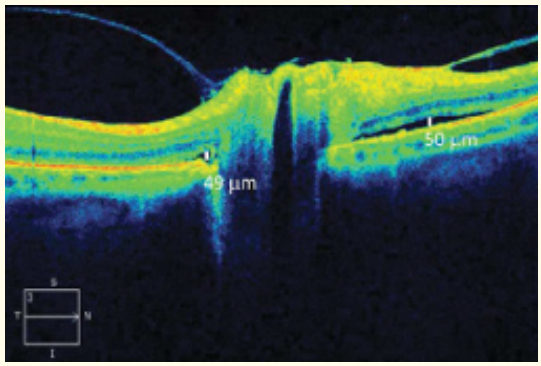

Figure 5: *Optical coherence tomography image of peripapillary SRF. Peripapillary line raster showing two peripapillary SRF collections (maximal height: temporal 49 µm, nasal 50 µm) [35].*

It is currently not understood why ocriplasmin produces clinically evident retinal damage in some patients but not in others. In humans, laminin comprises 5 alpha, 3 beta, and 3 gamma chains, which produce 15 different isoforms. It is therefore possible that genotype plays a role in determining vulnerability to ocriplasmin-induced vision loss. Other factors, such as variable dilution by the vitreous and variations in drug preparation and injection technique, might also influence drug safety [19].

Conclusion

Fortunately, several Phase 4 evaluations of ocriplasmin are ongoing and should provide us with additional safety information. We believe that ocriplasmin should be used with caution pending further study results about the mechanism, incidence, and reversibility of its harmful effects on the eye.

However, alternative therapies for VMT and macular hole, such as vitrectomy and pneumatic Vitreolysis, also have adverse effects, and comparative studies with long follow-up are needed to definitively establish preferred treatment paradigms.

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