CASE REPORT

Neurosensory Macular Retinal Detachment after Intravitreal Ocriplasmin Treated Successfully with Oral Carbonic Anhydrase Inhibitor

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Abstract
Ocriplasmin is an enzymatic drug used intravitreally to lyse focal vitreomacular adhesion and traction. We present a 45-year-old Bahraini female who developed a neurosensory macular retinal detachment from subfoveal fluid collection four weeks after its successful release following an ocriplasmin intravitreal injection. Subfoveal fluid is a well-known side effect of intravitreal ocriplasmin, mostly resolving spontaneously and completely over a period of few months. In order to reduce the attendant visual disability, rather than waiting for its natural recovery, we chose to treat it with oral carbonic anhydrase inhibitor, acetazolamide with an encouraging outcome. This drug is known to help in resorption of subfoveal fluid in the condition of central serous chorioretinopathy. However, to the best of our knowledge, its role is not explored in post-ocriplasmin setting. The purpose of this case presentation is to highlight the possible beneficial role of carbonic anhydrase inhibitors in ocriplasmin-related subfoveal neurosensory detachment.

Keywords: Neurosensory retinal detachment, Subfoveal fluid, Ocriplasmin, Vitreomacular adhesion, Vitreomacular traction, Carbonic anhydrase inhibitor

Introduction
Ocriplasmin is a low-molecular-weight recombinant molecule consisting of the catalytic domain of the human serine protease, plasmin.1 The United States Food and Drug Administration approved its intravitreal use for the treatment of vitreomacular adhesion (VMA) and vitreomacular traction (VMT) in October 2012.2 Until recent years, the mainstay of treatment for VMA/VMT with or without macular hole was pars plana vitrectomy (PPV).

Ocriplasmin previously known as micro-plasmin achieves the release of the vitreomacular adhesion and/or traction by its enzymatic activity by lysing the glycoproteins namely laminin and fibronectin at the anterior retina and inducing pharmacologic posterior vitreous detachment (PVD) resulting in separation of the posterior hyaloid from the retinal surface.3

Common ocriplasmin side effects and adverse events reported are: acute reduction in visual acuity, electroretinogram changes, dyschromatopsia, retinal tears and detachments, and retinal vascular changes.4 Transient short term subfoveal fluid, although not mentioned in the drug information leaflet is also a relatively commonly occurring adverse event in real life,5 The resulting neurosensory detachment resolves spontaneously over a period of few months in the majority of the patients. However longer persistence with only partial recovery is also described.6
The use of oral carbonic anhydrase inhibitor is well described modality of treatment in helping resolution of neurosensory detachment in central serous chorioretinopathy. The aim is to reduce the duration of accompanying visual disability while awaiting the natural resolution. To the best of our knowledge, no such exploits have been reported in the literature for its use in a post-ocriplasmin setting. We describe a case of VMT treated with intravitreal ocriplasmin that presented with neurosensory macular retinal detachment four weeks later. We used oral carbonic anhydrase inhibitor- acetazolamide successfully with complete resolution of the condition in the period of just four weeks.

Case Presentation

A 45-year-old Bahraini female initially presented to our on-call ophthalmology clinic with a complaint of painless sudden central blurring of right eye vision. There was no history of trauma to the eye. Her past medical and ocular histories were also unremarkable. Her best-corrected visual acuity (BCVA) was 6/9 in the right eye and 6/6 in the left eye. Anterior segment examination and intraocular pressure were within normal limits. Extra-ocular eye movements (EOM) were intact and painless. Pupillary reactions and red colour desaturation test were within normal limits. Fundus examination including optic disc and vitreous was unremarkable except for the loss of foveal reflex in the right eye. Spectral-domain (SD) - optical coherence tomography (OCT) (Spectralis Heidelberg Engineering, Heidelberg Germany) showed a focal vitreomacular adhesion (270µm) with minimal traction, and no macular hole (Figure 1).

![Figure 1: Right eye SD-OCT showing focal Vitreomacular adhesion (270µm) and minimal foveal traction.](image1)

For the treatment of VMA and VMT, she received an intravitreal injection of ocriplasmin in the right eye at the standard recommended dose of 0.125 mg in 0.1 mL. Her follow up at four weeks post injection showed a BCVA of 6/6 in the right eye and successful VMT release with normal underlying retinal architecture (Figure 2). One week later, that is, five weeks post injection, she presented again complaining of painless marked blurring of central vision in the right eye of four days duration. On clinical examination her BCVA were 6/20 in the right eye and 6/6 in the left eye. Intraocular pressures were within normal limits. The eye was quiet and white. Ocular movements were full and painless. Anterior segment assessment was unremarkable with normal anterior chamber depth and no signs of inflammation. The vitreous was clear and the fundus examination suggested a macular elevation with no breaks in the peripheral retina or the macula. OCT examination confirmed macular neurosensory detachment with subfoveal fluid collection in the right eye (Figure 3). Contralateral eye examination including OCT of macula was completely normal.

![Figure 2: Right eye SD-OCT four weeks post treatment with intravitreal injection of Ocriplasmin (Jetrea™) showing a complete release of VMA and VMT with a normal retinal structure.](image2)

With a view to enhance absorption of the subfoveal fluid, we started the patient on oral acetazolamide 250 mg q 8-hourly for four weeks, following which she recovered her visual acuity to 6/6 with complete
resolution of the neurosensory detachment and resumption of normal retinal architecture as shown on SD-OCT (Figure 4). She continued to maintain her normal visual acuity and the normal OCT findings at her further follow up six months later.

Figure 4: Right eye SD-OCT four weeks post treatment with Diamox® (Acetazolamide) showing the disappearance of neurosensory retinal detachment with a normal retinal structure.

Discussion
Ocriplasmin has been used since 2012 in the treatment of VMA and VMT with or without macular hole due to its proven efficacy in achieving a resolution of posterior vitreous detachment (PVD). Earlier such cases were treated surgically solely by pars plana vitrectomy (PPV). Ocriplasmin (Jetrea™) insert package lists commonly reported adverse reactions as follows: vitreous floaters, blurred vision, macular hole, reduced visual acuity, visual impairment and retinal edema. The MIVI-TRUST trial reported blurred vision in 8.6% of ocriplasmin patients but the majority of these events were reported as transient. Paul et al in 2015 listed the following adverse events from both pre-marketing and post marketing experiences: acute reduction in visual acuity, electroretinogram changes, dyschromatopsia, retinal tears and detachments, lens subluxation and retinal vasoconstriction. Also, ellipsoid zone segment disruption was reported in 50% of treated eyes for focal VMA/VMT. Recent studies suggest that the disruption of the ellipsoid layer may be associated with transient visual loss and accumulation of subretinal fluid. Post-ocriplasmin subretinal fluid in foveal region is a well-known occurrence with an onset as early as 24 hours after the ocriplasmin injection or weeks to months later. Although short term subfoveal fluid collection after ocriplasmin injection has been shown to be a common side effect in real life usage, it does not find any mention in the drug leaflet. Longer-term persistence of subfoveal fluid following ocriplasmin treatment is also described.

The enzymatic activity of ocriplasmin includes its action on the protein components (e.g. laminin, fibronectin and collagen) of the vitreous and vitreoretinal interface, thereby facilitating vitreous liquefaction and separation of vitreous from retina. Laminin is prominent in Bruch’s membrane, the inter-photoreceptor matrix, the external limiting membrane, the outer plexiform layer, the inner plexiform layer and the internal limiting membrane. In the outer plexiform layer, laminin localizes the synaptic ribbon at synapses between photoreceptors and bipolar cells.

Possible causes for subfoveal fluid following ocriplasmin injection include enzymatic lysis of the matrix between the outer segments of the photoreceptors and the microvilli of the RPE-cells, or barrier disturbances in the RPE through lysis of the zonulae occludens. The fluid usually resorbs spontaneously over a few months, generally without permanent structural or functional damage. VMT resolution and ellipsoid zone degeneration are known associations and risk factors for development of subretinal fluid post ocriplasmin. Factors favoring their occurrence include age less than 65, female gender, vitreomacular adhesion diameter of less than 1500 micrometer, absence of epiretinal membrane and phakic lens status. Incidence of subretinal fluid is 73% in the eyes that have VMA release and 19% in eye that did not show release. Also, the size of the subretinal fluid was smaller in the absence of the VMA release.

Regarding the natural course of subretinal fluid absorption after ocriplasmin injection, Eric Nudleman, in his serial SD-OCT imaging study showed that partial resolution was noticeable at one month and complete resolution by six months in most patients. However, in a few patients it could last much beyond that time. Out of 36 patients, the subretinal fluid was still present at six months in three patients, improved thereafter in all, but was still persistent in two patients at one year. In view of such eventualities of longer persistence, it is only...
reasonable to consider some sort of therapeutic intervention to reduce the period of attendant handicap of visual blurring.

Carbonic Anhydrase Inhibitors (CAI) are known to be helpful in the management of central serous chorioretinopathy due to their action of inhibiting the enzyme in retinal pigment epithelium, thereby aiding in subretinal fluid absorption. In a prospective non-randomized trial, on fifteen CAI-treated patients and seven controls, Pikkel et al found that oral acetazolamide shortened the time for subjective and clinical improvement, without altering final visual outcome. We envisage a similar role for CAI in facilitating absorption of ocriplasmin related subfoveal fluid collection. We used oral acetazolamide in the dosage of 250 mg q 8 hourly in the index case. Complete regression of fluid and restoration of the normal retinal architecture on OCT was documented in just four weeks of the treatment. This correspondingly shortened the visual handicap for the patient, which probably could have been much longer had it been left to follow a natural course. As this is a single case observational study, further larger scale observations and controlled trials may explore the potential role of oral acetazolamide in helping management of neurosensory detachment following intravitreal ocriplasmin.

Conclusion
We present a case of a neurosensory macular retinal detachment from subfoveal fluid collection occurring after the injection of intravitreal ocriplasmin. Although this side effect is known to occur widely, it lacks any mention in the manufacturer’s drug information leaflet. Therefore, we suggest that the pre-treatment patient counseling should include appropriately elaborate discussion of this complication which has a significant potential to cause temporary or even long-lasting visual disability. Our case also uniquely suggests a role for carbonic anhydrase inhibitor in facilitating the resolution of post-ocriplasmin subfoveal fluid, a possibility hitherto not discussed in the literature, to the best of our knowledge.

Conflict of Interest
The authors have no financial or proprietary interests in any material or method mentioned.

References:


