Unilateral Transient Vision Loss Following Bilateral Intravitreal Ocriplasmin – Case Report With Two Years Follow Up

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ABSTRACT

Background: Ocriplasmin is a serine protease approved for the treatment of symptomatic vitreomacular traction (VMT). Post-marketing experience has revealed safety concerns.

Materials and Methods: Retrospective case report. Clinical and surgical data were analyzed.

Results: We report a case of intraindividual response to bilateral ocriplasmin injection in a 70 year-old female patient with symptomatic vitreomacular traction syndrome. A single surgeon injected the same patient twice, two years appart, following the same protocol. In the first eye we observed the commonest side effects and no VMT release while in the second eye we documented the rarer and severe ocriplasmin's adverse events nevertheless with successful VMT release.

Conclusions: Ocriplasmin's severe adverse events are unpredictable and underreported. The noticeable difference in adverse events is not accounted by patient, surgeon or tecnique's variability. This case raises the question of whether the degree of enzymatic cleavage necessary for drug efficacy and VMT release may coexist with more retinal toxicity.

Keywords: vitreomacular traction, vitreolysis, ocriplasmin, adverse events, safety

RESUMO

Introdução: A ocriplasmina é uma enzima proteolítica aprovada para o tratamento da tração vítreo-macular (TVM) sintomática. Após comercialização têm sido relatados alguns efeitos adversos raros mas graves.

Materiais e Métodos: Caso clínico retrospetivo. Análise dos registos clínicos e cirúrgicos.

Resultados: Relato de caso de injeção bilateral de ocriplasmina numa doente do sexo feminino de 70 anos com TVM sintomática. Um único cirurgião efetuou o procedimento, seguindo igual protocolo, no mesmo doente, com intervalo de dois anos. No primeiro olho não foram registados eventos adversos relevantes, tendo a TVM persistido. Todavia, no olho adelfo, foi

documentado um dos efeitos adversos raros mas graves da ocriplasmina: diminuição da acuidade visual marcada para vultos no primerio dia pós-injeção e alterações nos exames tomográfico e electrofisiológicos, não obstante a libertação da TVM.

Conclusões: Os efeitos adversos graves da ocriplasmina são imprevisíveis e estão subreportados. A ocorrência de efeitos adversos diferentes não pode, neste caso, ser explicada por variabilidade do doente, da técnica ou do cirurgião.
Este caso levanta a questão da existência de eventual relação entre o grau de clivagem enzimática necessária para a eficácia do fármaco e maior toxidade.

Palavras-chave: tração vítreo-macular, vitreólise, ocriplasmina, efeitos adversos, segurança

BACKGROUND

Ocriplasmin is a recombinant truncated form of plasmin with proteolytic activity against fibronectin and laminin approved by EMA in 2013 for the treatment of symptomatic vitreomacular traction (VMT).[3] The MIVI-Trust Study Group[9] reported resolution of VMT in 26.5% of cases reaching 56.6% in carefully selected cases[4]. Post-marketing analysis has revealed safety concerns related to ocriplasmin use[8]. A comprehensive study detected floaters, photopsia, and transient vision loss as the most common adverse events (AE).[2] Uncommonly, there have been descriptions of panretinal structural and functional abnormalities with severe vision loss.[1,5-8,10]

We aim to report the intraindividual response to bilateral ocriplasmin in a patient with VMT, emphasizing the dramatic difference in severe AE.

CASE PRESENTATION

A 70-year-old phakic woman presented with bilateral VMT, symptomatic in the right eye (OD). Corrected visual acuity (VA) was 20/32 OD and 20/20 left (OS). Clinical examination and spectral-domain optical coherence tomography (SD-OCT) confirmed the diagnosis of focal VMT (Fig. 1a) and she underwent intravitreal ocriplasmin injection (0.125 mg) OD. Twenty-four hours later the patient reported floaters and observation revealed moderate visual loss to 20/63 with no ellipsoid disruption on SD-OCT (Fig. 1b). The symptoms were resolved within a week and at 1-month VA was 20/25, althought the VMT remained unchanged (Fig. 1c). Observation was decided.

On repeated examinations, VA OS was stable for 2 years, when VA decreased to 20/32 along with an increase in macular thickness (Fig. 1d). Uneventful intravitreal ocriplasmin (0.125 mg) OS was performed. The next day patient complained of white photopsia on a black background and vision loss. Observation revealed hand motion vision, relative afferent pupillary defect (RAPD) and fundoscopy was negative for optic nerve edema, cherry red spot and abnormal vessel caliber. SD-OCT (Fig. 1e) and electrophysiology (Fig. 2a and b) demonstrated acute retinal changes. VA increased to counting fingers and 20/80, respectively 3 and 6 days post-treatment without RAPD. At 3 weeks follow-up, VA was 20/50 and there was improvement in both SD-OCT (Fig. 1f) and electrophysiology studies (Fig. 2c and d). VA recovered to 20/25 with VMT release at the 2 months visit (Fig. 1g) remaining stable at 6 months (Fig. 1h). Electrophysiology at 6 months was improved (Fig. 2e and f).

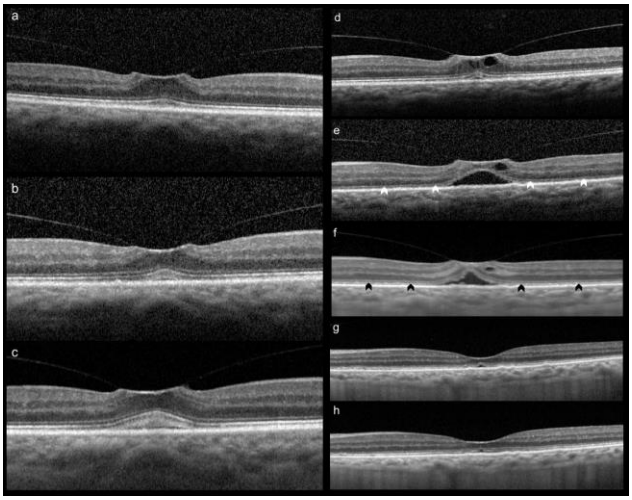

Figure 1 – Sequential optical coherence tomography (OCT) scans. Right eye - **(a)** Pretreatment OCT revealed a focal vitreomacular traction (VMT). **(b)** and **(c)**, respectively post 1 day and 1 month after ocriplasmin treatment demonstrated no relevant pathologic changes of the ellipsoid zone and the VMT remained unchanged. Left eye - **(d)** Pretreatment OCT showed a focal VMT. Day 1 OCT **(e)** showed outer retinal changes with a subfoveal neurossensorial detachment and generalized ellipsoid attenuation (arrowheads). Three weeks after treatment **(f)**, there was improvement with reorganization of the ellipsoid layer (arrowheads). VMT release, reappearance of the foveal depression and almost total reabsorption of the subretinal fluid was noted at 2 months **(g)**. These findings remained stable at 6 months (h).

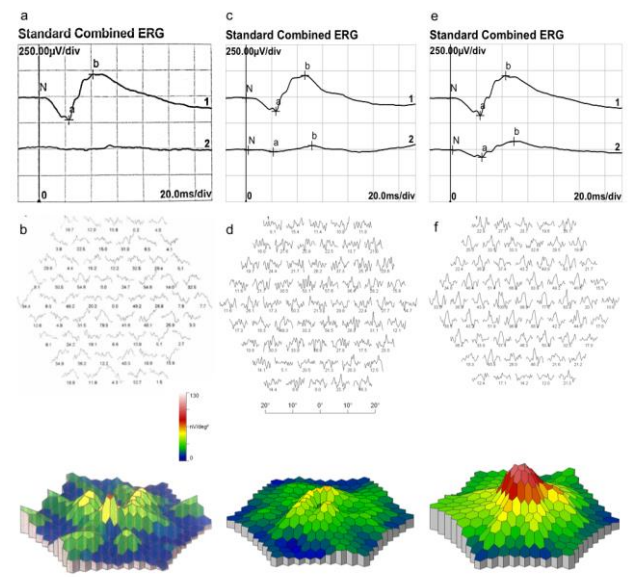

Figure 2 – Left eye electrodiagnostic testing. Acute phase standard combined electroretinogram (ERG) **(a)** showed a severe reduction in a- and b-wave amplitudes indicating both cone and rod dysfunction and multifocal ERG **(b)** revealed absent foveal peak and reduced P1 wave amplitude with increased implicit time. Three weeks standard combined electroretinogram **(c)** and multifocal ERG **(d)** showed a mild improvement. At the 6 months visit, there was partial reconstitution of the a- and b-wave morphology still indicating retinal dysfunction **(e)**, while the multifocal ERG **(f)** revealed foveal peak attenuation with borderline P1 wave amplitude.

DISCUSSION AND CONCLUSIONS

The relevance of this case relies on the assimetric response to bilateral ocriplasmin injection. The AEs observed in OD were the most common, transient and self-limited as described in previous reports.[2,4] The expectedness of these AEs did not discourage the administration of ocriplasmin in OS. In this eye, we documented severe AEs namely profound VA loss, RAPD, attenuation of outer retinal layers on SD-OCT and severely reduced ERG responses demonstrating acute panretinal disfunction.

Ocriplasmin's variable retinal AEs are still poorly understood. It has been hypothesized that genotype, variable dilution by the vitreous and variations in drug preparation and injection technique might influence drug safety.[7] However, the same surgeon injected the same patient twice. Therefore, it seems unlikely that only patient and surgical variability explains all cases of retinal damage. It may be that the degree of enzymatic cleavage necessary for drug efficacy and VMT release may coexist with more retinal toxicity.

Further studies are needed to ellucidate possible drug-inherent functional enzymatic dysfunction, to evaluate the reproductibility of ocriplasmin's proteolytic properties and possibly identify inhibitor or potentiator co-factors of cleavaging potencial.

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Authors' contributions

FP and HP reviewed the patient at first presentation. HP performed surgery and post-operative care. HP and SVP contributed to patient care after adverse event and FP and FC performed ancillary testing. HP and SVP collected and prepared the patient data. HP and SVP took the lead in writing the manuscript. All authors red and approved the final manuscript.

Competing interests

The authors declare that they have no competing interests.

Availability of data and materials

The data in the current case report are available from the Department of Ophthalmology, Centro Hospitalar Universitário Lisboa Norte, EPE – Hospital de Santa Maria medical records. The data is available from the corresponding author on reasonable request.

Consent for publication

Consent for publication was obtained.

Ethics approval and consent to participate

Ethics approval for this research was obtained by the Local Ethics Comitee. Consent for participation was obtained.

Funding

None