CASE REPORT

Case Report: Resolution of submacular haemorrhage secondary to exudative age-related macular degeneration after a single intravitreal dobesilate injection [version 1; referees: 1 approved]

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Abstract

Introduction: Submacular haemorrhage is not an unusual cause of acute central vision loss, particularly in older people. It may be caused by a number of conditions, most common of which is exudative age-related madular degeneration. In patients affected by this type of macular degeneration, choroidal neovascularization extends into the subretinal space, producing substantial bleeding in approximately 17% of cases, resulting in large haemorrhages in the subretinal space that detach the neurosensory retina from the supporting retinal pigment epithelial (RPE) layer. This leads to substantial vision loss because of a relatively fast process of extensive photoreceptor atrophy in the overlying neuroretina and formation of macular scars
Case presentation: We describe a patient with submacular haemorrhage secondary to exudative age-related macular degeneration, treated with intravitreal injection of dobesilate. Two months later, visual acuity in the treated eye reached 0.50 with a significant improvement of the distortion and an anatomical resolution of the haemorrhage, as confirmed by optical coherence tomography.
Conclusions: Submacular haemorrhage secondary to exudative age-related macular degeneration can be successfully treated with intravitreal dobesilate. To our knowledge, this is the first case reporting a resolution of submacular haemorrhage after a single dobesilate injection.

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Case description

A 75 year-old Caucasian man with a history of exudative age-related macular degeneration (AMD) in both eyes developed a sudden vision decrease in the right eye. The best corrected visual acuity (BCVA) on presentation was 0.05. Fundus examination showed a recent medium-sized submacular haemorrhage (SMH) (Figure 1A), and spectral-domain optical coherence tomography (SD-OCT) depicted a remarkable anomalous architecture of the retina and serious disturbances under the retinal pigment epithelium (RPE) without significant accumulation of intraretinal fluid (Figure 1D). The haemorrhage also seemed to have resulted in RPE detachment at some points (Figure 1D, asterisk). Treatment with dobesilate was recommended. After approval of our Institution Ethical Committee, the patient signed an informed consent form, which included a comprehensive description of dobesilate and the proposed procedure. Using a standard protocol, the patient received an intravitreal solution of dobesilate (150 µl) in his right eye under sterile conditions, following the International Guidelines for intravitreal injections[1]. Dobesilate was administered as a 12.5% solution of diethylammonium 2.5-dihydroxybenzenesulfonate (etamsylate; Dicynone® Sanofi-Aventis, Paris, France). No ocular side effects were observed upon the administration of dobesilate or during the following days. Over two months follow-up the haemorrhage signs gradually disappeared (Figure 1B,C), and the SD-OCT scans showed a progressive normalization of the retinal architecture with the disappearance of the RPE detachment (Figure 1E,F). At the end of this period of two months, the patient's BCVA had reached a value of 0.50.

Discussion

Patients with exudative AMD and SMH on initial presentation have more than a 50% chance of developing recurrent submacular bleeding within the first subsequent three years[2]. Retinal diseases characterized by an excess of vessel proliferation are sometimes treated with antibodies that inhibit vascular endothelial growth factor (VEGF). Recently, anti-VEGF antibodies have been also proposed for the management of SMH[3,4]. However, this therapy needs repeated injections in some patients and takes several months to clear SMH[5]. In addition, SMH may occur following the injection of intravitreal anti-VEGF agents[6,7]. As subretinal haemorrhages are, so far, inadequately addressed with the use of the current anti-angiogenic therapies, many different treatments have been used to physically remove or displace them, with inconclusive results[8]. Thus, safe and efficient therapy for SMH is needed. Here we present a patient with SMH secondary to exudative AMD who was successfully treated with a single intravitreal dobesilate injection, a synthetic inhibitor of fibroblast growth factor.

Using a murine model of subretinal haemorrhage it has been shown that, like other central nervous system locations such as the cerebral cortex, inactive microglia, which reside in the inner retina under quiescent conditions, acquire the reactive phenotype and rapidly migrate to the site of the haemorrhage[8]. Once there, microglia participate in the phagocytosis of blood products and promote inflammation at the injury site, together with leukocytes and monocytes of the extravasated blood, by secreting cytokines, chemokines and other immunomolecules. In these studies it was also shown that inhibition of microglial activation reduced microglial infiltration and photoreceptor cell loss caused by SMH[8].

Microglial cells are activated by fibroblast growth factor (FGF) synthesized by astrocytes in the case of the central nervous system[9]. In the case of hemorrhages, extravasated blood cells like monocyte-derived macrophages also synthesize FGF[10], which also acts as chemoattractant of microglial cells. Furthermore, microglia also synthesize FGF and other cytokines, once they have been activated. Since activated microglia also expresses FGF receptors

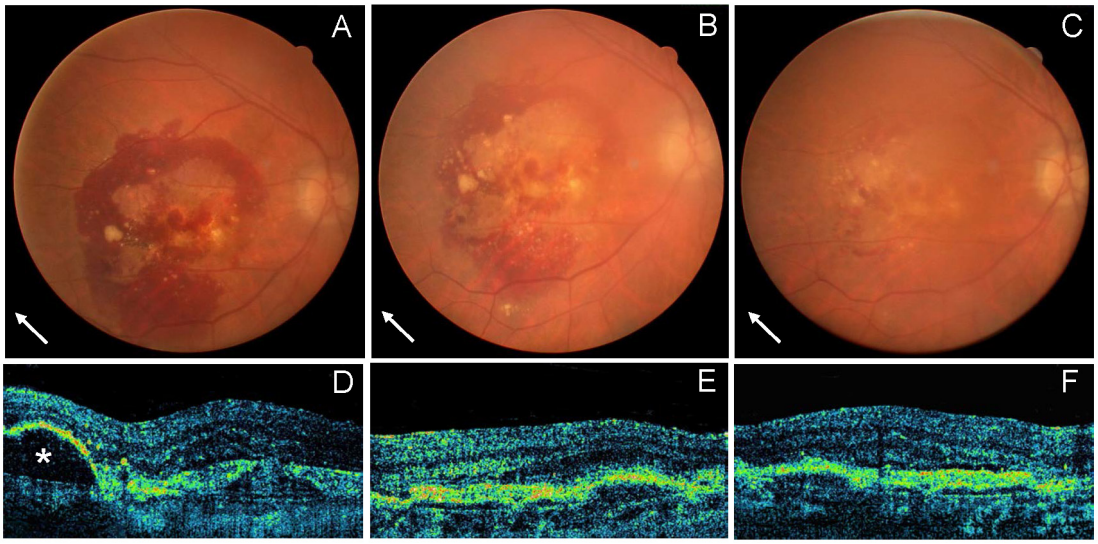

Figure 1. Sequence of fundus photographs (A–C) and spectral-domain optical coherence tomography (SD-OCT) scans (D–F) of a patient with a moderate-sized submacular haemorrhage at baseline (A,D), and at one (B,E) and two months (C,F) after a single intravitreal injection of dobesilate. The asterisk in D indicates retinal pigment epithelium (RPE) detachment.

(FGFRs), an autocrine loop could readily develop in the case of important lesions, which could sustain the appearance of chronic inflammation. In addition, recently published studies, point to the fundamental importance of activated microglia in re-shaping the vasculature during pathological insults[9,11–16]. This additional source of FGF may greatly contribute to the development and worsening of AMD.

FGF was the first inducer of vasculogenesis and proliferation of endothelial cells to be isolated[17]. Later on, it was shown that it is a broad-spectrum mitogen[18] and, recently, that FGF should be envisioned rather as an inflammation-triggering and -sustaining protein than as mere mitogen for mesoderm-derived cells[19,20]. These inflammatory activities are probably an important contributor to the sequelae of the brain and retinal haemorrhages, including development and worsening of AMD. FGF may further contribute to aggravate this scenario by directly promoting vascular permeability when it participates in neovessel formation[17,21,22]. We have shown that neovascular growth induced by FGF and the accompanying bleeding can be suppressed with inhibitors of FGF[23]. Consequently, it seems that inhibition of FGF could be an appropriate treatment to prevent retinal injuries in the aftermath of haemorrhages.

We have spent important efforts in the development of synthetic inhibitors of FGF. These studies led to the identification of a family of small-size chemical inhibitors, structurally similar to gentisic acid, the first member of the group that was identified. The most active of the family was a compound known in pharmacology as dobesilate, the active principle of Doxium, a drug that has been orally administered for more than 35 years for the treatment of diabetic retinopathy with a good safety profile, but inconclusive outcomes[25,26]. Contrarily, we have obtained clear positive results in different retinal pathologies[27–31] by administering, off-label, dobesilate through intraocular injection.

Our results may seem in contradiction with those of Haritoglou *et al.*[26], who carried out an accurate statistical study to assess the real clinical benefits of calcium dobesilate in the treatment of diabetic retinopathy. They concluded that the oral administration of dobesilate did not show statistically significant clinical benefits for treating this disease. Perhaps, as we discussed in detail in previous articles, the different administration procedures employed in the Haritoglou *et al.* study and in our treatments, respectively, may explain the differences in outcome, since the intestinal flora and relative instability of dobesilate above pH 5 may significantly hamper the ability of the inhibitor to reach adequate concentrations in the retina[27]. FGF is involved in the homeostasis of the tissues of mesodermal and neuroectodermal origin. A detailed discussion about the apparent paradox that constitutes that the administration of a FGF inhibitor does not cause considerable distortion in those tissues has been carried out in previous articles[27].

VEGF is a protein that enhances the permeability of blood vessels (actually, it was also isolated under the name of vascular permeability factor). It is also, apparently, a paradox that the treatments with antibodies against VEGF had not shown significant therapeutic effects in the treatment of SMH. To shed some light on this apparent contradiction one has probably to take into account the serious drawbacks of depleting VEGF for a long time, since it is a key component in the homeostasis of the retina. The clearance of those antibodies from the vitreous is about 10 days, although some believe it to be as long as 2.5 months[32–34]. In contrast, inhibition of FGF is not accompanied by a prolonged presence of dobesilate at the eye, as it readily decomposes at physiological pH[24]. We have also shown that dobesilate can also be used to suppress VEGF-induced angiogenesis, as expected from the necessary synergism between VEGF and FGF for promoting angiogenesis[35].

Consent

Written informed consent for publication of the clinical details and images was obtained from the patient.

Author contributions

PC and GGG wrote the paper. LO and CA were the physicians responsible for the patient in this case report. All authors have participated in the concept and design/analysis and interpretation of data, drafting and revising the manuscript, and they have given final approval for the manuscript.

Competing interests

No competing interests were disclosed.

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In my opinion the manuscript is well written and describes the effects of intravitreal dobesilate in the resolution of submacular haemmorrhage due to exudative AMD.

I think the authors could describe the findings of the angiogram and ICG and how they ruled out other causes of SMH as polipoidal or RAP. As we know, polipoidal is always a diagnostic hypothesis that must be thought when a patient has SMH.

Another point to be discussed is if the patient developed a new subretinal fluid and the possibility of a new dobesilate administration in refractory cases. Also something not clear is that the patient was or wasn't already submitted to intravitreal anti-VEGF injections before the dobesilate administration.

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Competing Interests: No competing interests were disclosed.