Novel treatment (new drug/intervention; established drug/procedure in new situation)

Intravitreal dobesilate in the treatment of choroidal neovascularisation associated with age-related macular degeneration: report of two cases

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Summary

This case report presents the effectiveness of intravitreal administration of dobesilate, a synthetic fibroblast growth factor inhibitor, in two patients showing neovascular age-related macular degeneration of the classic, and of the occult choroidal neovascularisation types, respectively. Our study demonstrates that the treatment induces the regression of both forms of this pathology, as assessed by spectral optical coherence tomography. Improvement of the lesions was accompanied of visual acuity improvement.

CASE PRESENTATION

Hitherto, 48 patients, all Caucasian, affected of age-related macular degeneration (AMD) have been treated in our institution, following the protocol described below, with the same results as the two that were chosen as representative and presented in detail herein. The most common AMD risk factors are represented in the whole group of patients treated (age, family history, smoking, high blood pressure, obesity, prolonged sun exposure, etc). The first patients were treated 9 months ago and the improvements have been stable since then; no side effects have been observed over this time period.

After the approval of our Institution Ethical Committee, patients signed an informed consent form, which included a comprehensive description of dobesilate and the proposed procedure. Two patients, with classic and occult choroidal neovascularisation (CNV) associated with AMD, received 18.75 mg of dobesilate in a single intravitreal injection of 150 µl of a solution of diethylammonium 2,5-dihydroxybenzenesulfonate (etamsylate; Dicynone; Sanofi-Aventis, Paris, France) according to the International Guidelines.¹ No ocular side effects were observed during treatment. Intraocular pressure increase occurs transiently after dobesilate injection, although it returns to baseline within 2 h. The macula was studied by best-corrected visual acuity (BCVA) (Snellen chart test) and spectral optical coherence tomography (OCT), before and after treatment.

Patient 1 (classic CNV)

A 78-year-old woman presented at the clinic showing the three most commonly reported symptoms among individuals with neovascular AMD in her left eye (blurred vision, metamorphosis—distorsion of an image—and scotoma—a visual field defect). At presentation, visual acuity was 0.05, and OCT scan showed the typical features of classic CNV (intraretinal fluid and intense

fibrovascular signals at the foveal level; figure 1A). Fibrovascular lesion regularly includes aberrant blood vessels, fibrous tissue, serous fluid and other exudative material.² Two weeks after treatment, visual acuity improved to 0.4 and was accompanied by a decrease in macular thickness on respect to baseline (314 vs 539 µm) and disappearance of intraretinal fluid leakage (figure 1A, B). Furthermore, the highly reflective subretinal lesion showed a significant reduction, to become nearly unappreciable after 2 weeks of treatment. The patient is clinically stable over a 3-month follow-up period.

Patient 2 (occult CNV)

In 2009, a 77-year-old female patient presented at the clinic with symptoms of mild bilateral distorsion, specially of the left eye, and reading difficulties. The diagnosis of occult CNV associated to AMD was established. The patient was treated with three consecutive intravitreal injections of bevacizumab (Avastin) and two of ranibizumab (Lucentis) on both eyes without satisfactory visual benefit.

In 2011, the patient returned to the clinic complaining of blurred vision more accentuated in the left eye. On examination, BCVA was 0.05 and OCT revealed the presence of an active occult subfoveal CNV (figure 1C). A decision was made to treat the left eye of the patient with intravitreal dobesilate following the procedure described for the first patient. After 2 weeks of treatment there was significant improvement of the patient's vision associated with an important reduction of CNV on OCT scans (figure 1D). BCVA improved from 0.05 to 0.2. The patient is still clinically stable over a 2-month follow-up period.

DISCUSSION

AMD is a disease affecting the central region of the retina that can lead to irreversible central vision loss as consequence of photoreceptors degeneration. AMD is the

Figure 1 Dobesilate improves choroidal neovascularisation in age-related macular degeneration. The upper row depicts optical coherence tomography (OCT) scans from classic choroidal neovascularisation at baseline (A) and 2 weeks after treatment (B). Lower row shows OCT scans from occult choroidal neovascularisation before (C) and 2 weeks after treatment (D). Choroidal neovascularisation appears as a voluminous green reflection at the level/underneath retinal pigment epithelium (A/C). Arrows indicate the localisation of the performed OCT scans.

leading cause of permanent vision impairment and blindness among the elderly, affecting near 50 million individuals worldwide.³ Analyses of US medical claims data have estimated the total annual direct cost of AMD to be US\$575-733 million.⁴ AMD represents a chronic, progressive disease with various phenotypic manifestations, different diseases stages and different rates of progression over time. Taking into account clinical and pathological features, two subgroups of AMD are classically distinguished: atrophic (dry form) and exudative (wet form). The dry form (also known as geographic atrophy, central and/or non-central) is typically characterised by a progressing course leading to degeneration of retinal pigment epithelium (RPE) and photoreceptors. The neovascular (exudative or wet) form is caused by an abnormal CNV that leads to leakage of blood and fluid into and underneath the retina, with a devastating result for the patient central vision when it occurs at the macular region. Classic CNV exhibits a typical subretinal growth pattern, while in the case of the occult one the abnormal formations are mainly composed of fibrovascular tissue that apparently forms from subretinal RPE space.⁵

In the era of thermal laser photocoagulation, fluorescein angiography (FA) was used for accurate localisation of choroidal leakage in AMD. Nowadays, with the advent of monoclonal antibody-based therapies against CNV, and the development of new tomographic approaches, it seems that FA is a technique dispensable to obtain the required appropriate diagnostic in most cases, something very desirable by the significant decrease of risk/discomfort to patients that this entails. Furthermore, the assessment of leakage by FA is not always easy and reliable.⁶ In contrast, OCT is a rapid and non-invasive imaging technique, which is able to depict at micrometer resolution cross-sections of the macula that allow one to visualise abnormal choroidal neovessel growths and concomitant

fluid leakage (figure 1A,C).^{7 8} Furthermore, OCT has become fundamental in the diagnosis and follow-up of CNV associated to AMD.⁹

A decade ago, AMD was largely untreatable. However, new therapeutics based on the inhibition of vascular endothelial growth factor (VEGF) were introduced and caused great expectation.¹⁰ Although VEGF has been implicated in the development of a number of neovascular diseases of the eye, it should be taken into account that VEGF is an ocular parahormone that plays very relevant physiological functions: it maintains the correct perfusion of the retina and has a key role in the survival of retinal cells.^{11 12} Therefore, it does not result totally unexpected that blockade of VEGF in AMD caused in many patients RPE and photoreceptor injuries, simultaneous in some cases, which in turn aggravate the overall disease progress and its ultimate outcome.¹³ In addition, severe and sustained ocular hypertension following intravitreal anti-VEGF therapy has been recently shown.^{14 15} Furthermore, it has been reported that intravitreal Avastin (an anti-VEGF monoclonal antibody) injection in animals reduced fenestration of normal choriocapillaries, promoted circulatory disturbance in these vessels,^{16 17} and showed sometimes quite adverse general secondary effects.¹⁸ Finally, quite often, the treatments of AMD with antibodies that inhibit VEGF have a quite short-lived effect that requires of a periodic repetition of the treatment, which as it becomes progressively less effective cannot be maintained indefinitely.¹⁹ Therefore, there is an urgent need to develop new agents targeting other pathways involved in angiogenesis that could be translated into more safe and effective therapeutic outcomes to replace or complement existing therapies in AMD.

Both acidic and basic isoforms of fibroblast growth factor (FGF-1 and FGF-2, respectively) have been proposed to participate in the pathophysiology of neovascular

AMD.^{19–21} Drusen accumulation is a major pathological hallmark common to dry and wet AMD.²² Recently it has been reported that several protein aggregates of drusen activate both inflammatory²³ and angiogenesis responses in AMD retina.^{24–25} Particularly, a family of leucine-rich repeat (LRR) proteins,²⁶ that are implicated in FGF signalling are present in drusen.²³ Furthermore, platelet-activating factor (PAF) and signal transducer and activator of transcription-3 (STAT-3), are activated in AMD,^{27–28} and are mediators of the four interplayed key biological events in AMD: vascular hyperpermeability, inflammation, neovascularisation and neurodegeneration.^{27–29–30} PAF and STAT-3 are activated by FGF³¹ and inhibited by dobesilate.^{32–35}

An inhibitor of the FGF signalling system, dobesilate, with important anti-inflammatory and antivascular permeability activities *in vivo* has been recently described,^{36–38} features that suggest that its intravitreal application could be of potential clinical benefit in AMD patients management. Calcium dobesilate is the active principle of Doxium a drug used for more than 35 years. It has been orally administered for the treatment of diabetic retinopathy with a good safety profile.³⁹ Haritoglu *et al*⁴⁰ have carried out an accurate statistical study to assess the real clinical benefits of oral calcium dobesilate (Doxium) in the treatment of this disease. The study concluded that the oral administration of dobesilate did not show statistically significant clinical benefits. Although diabetic retinopathy and AMD are different diseases, the many common features they reciprocally share could suggest that our results are in contradiction with those of Haritoglu *et al*. Perhaps the different administration procedures employed in this last study and in the cases reported here are at the root of the outcome differences. Oral administration is not the best choice for dobesilate to reach the adequate concentration at the retina. Dobesilate has a very low product of solubility at the acidic pH of the stomach, and, further, readily oxidises at the duodenal pH. Accordingly, a local delivery seems a better choice in order to reach appropriate therapeutic concentrations of dobesilate in the case of well-delimited targets, as is the case of AMD. In addition, the recently described relevance of the intestinal flora in the efficiency of orally administered drugs should be taken into account, mainly in conditions in which they are not totally stable.⁴¹ Thus, the important differences observed between individuals at the level of their gut microbiome⁴² may introduce considerable statistical noise that blurs the significance of the differences in studies as that of Haritoglu *et al*. This gut microbiome effect is obviously avoided when the drug is directly directed to its target. It may result somehow surprising that an inhibitor of FGFs shows the good safety profile of dobesilate, given the broad spectrum of physiological activities, in which they are involved.^{36–39} FGFs have been detected in most adult tissues derived from the embryonic mesoderm and neuroectoderm, tightly bound to the sulphated glycosaminoglycans of the extracellular matrix, at times at very high levels.³⁶ Thus, under normal physiological conditions FGFs do not act as a signalling molecule in solution, but as a solid-phase growth factor. As far as FGFs remain part of the extracellular matrix, they cannot be inhibited by dobesilate, which has an affinity constant for FGF

approximately 3000 times lower than that of the sulphated glycosaminoglycans of the extracellular matrix that, furthermore, reach extraordinarily high concentrations. Nevertheless, the physiological FGF signalling system get sometimes subverted, causing very serious physiological disturbances, when high concentrations of free FGF accumulate, either through uncontrolled synthesis or mobilisation by heparanases and other specialised proteins. In contrast to when it is part of the extracellular matrix, dobesilate efficiently inhibits the free FGF.³⁶ Consequently, it inhibits mainly the pathological FGF, leaving relatively untouched the physiological FGF pool.

In these two representative case reports, we describe the rapid resolution of macular oedema and decreased CNV, documented with OCT, and the normalisation of retinal structure running paralleled to a considerable improvement of visual acuity (VA), after intravitreal administration of dobesilate. Intravitreal injection of dobesilate may, thus, constitute an alternative to the anti-VEGF treatments. This report adds some more valuable data to the recently published promising good results regarding the use of dobesilate in dry AMD.⁴³ To our best knowledge, this is the first report on the use of dobesilate in CNV related to AMD. However, longer follow-up time and higher number of patients with exudative AMD are needed in future studies.

Learning points

- ▶ Age-related macular degeneration is a chronic inflammatory and angiogenesis-dependent retinal disease.
- ▶ Choroidal neovascularisation is associated with wet age-macular degeneration.
- ▶ Fibroblast growth factor participates in the pathophysiology of age-related macular degeneration.
- ▶ Intravitreal injection of dobesilate, a synthetic fibroblast growth factor inhibitor, promotes clinical benefit in wet age-related macular degeneration.

Competing interests None.

Patient consent Obtained.

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