CASE REPORT

Durable recovery of the macular architecture and functionality of a diagnosed age-related macular degeneration 1 year after a single intravitreal injection of dobesilate

P Cuevas,¹ L A Outeiriño,² C Azanza,² G Giménez-Gallego³

¹Departamento de Investigación, IRYCIS, Hospital Universitario Ramón y Cajal, Madrid, Spain

²Departamento de Oftalmología, Hospital de Día Pío XII, Madrid, Spain

³Departamento de Estructura y Función de Proteínas, Centro de Investigaciones Biológicas, CSIC, Madrid, Spain

Correspondence to

Professor P Cuevas,
pedro.cuevas@hrc.es

All authors contributed equally to this case report.

SUMMARY

Among the age-related diseases that affect vision, age-related macular degeneration is the most frequent cause of blindness in patients older than 60 years. In this communication, we report the full anatomical and functional recovery of a patient diagnosed with wet age-related macular degeneration 1 year after a single intravitreal injection of dobesilate.

CASE PRESENTATION

Intravitreal injection of antivascular endothelial growth factor (VEGF) agents has revolutionised the treatment and prognosis of neovascular age macular degeneration (AMD). However, the chronic use of intravitreal injections of anti-VEGF compounds can be associated in some patients with unexpected detrimental ocular effects,¹ suggesting that the development of alternative strategies might be necessary. Based on our experience, we used intravitreal dobesilate, a well characterised fibroblast growth factor (FGF) inhibitor with safe and efficient profiles, previously used in our institution in patients with neovascular AMD.²

A 68-year-old woman presented with a history of reduced vision in the left eye. Baseline colour fundus photography was performed. The best-corrected Snellen visual acuity (BCVA) and spectral-domain optical coherence tomography (SD-OCT) were obtained. BCVA at baseline was 0.35. SD-OCT revealed a subfoveal picture of classic choroidal neovascularisation (type 2 CNV; figure 1A). The macular thickness was 345 µm. The retinal layers showed severe structural alteration, characterised by a complete loss of defined boundaries with disappearance of fovea and obvious alteration of the retinal pigment epithelium (RPE; figure 1A). A neovascular AMD was diagnosed. The patient was provided with information about the off-label use of dobesilate and consent was obtained after the Ethical Committee approval of our Institution. Under sterile conditions and following the International Guidelines for intravitreal injection,³ the patient received an intravitreal solution of dobesilate (150 µL) in her left eye. Dobesilate was administered as 12.5% solution of diethylaminonium 2,5-dihydroxybenzenesulfonate (etamsylate, Dicynone Sanofi-Aventis, Paris, France). Antibiotic eye drops were then applied. After the treatment, the evolution of the AMD was monitored on a

bimonthly basis for 1 year. At the second month visit, BCVA was 0.60 and SD-OCT showed a more normal appearance and only vestiges of CNV were observed (figure 1B, asterisk). After 1 year, BCVA was 1 and the SD-OCT examination revealed a complete structural normalisation of the macular neurosensory retina as well of the RPE. As figure 1C shows, the presumed external limiting membrane, the presumed photoreceptor inner segment–outer segment junction and the presumed interdigitation between the photoreceptor outer segments and the RPE appeared normal along the horizontal meridian scan (cross-sectional scan) of the retina. Furthermore, SD-OCT also showed a normal Sattler's layer. The macular thickness was 200 µm. No signs of macular fibrosis were observed in SD-OCT scans. No ocular and systemic adverse effects associated with the treatment were observed during the follow-up period.

DISCUSSION

Among the age-related diseases that affect vision, AMD is the most frequent cause of blindness in patients older than 60 years.⁴ AMD presents two distinct forms (1) a slow progression non-neovascular, avascular, dry or atrophic form, and (2) a rapidly progressive blinding vascular form, wet or exudative. Wet AMD is characterised by the growth of new choroids blood vessels.⁵ AMD is caused by chronic inflammation of the RPE.^{6–7} In trying to explain the origin of this inflammation, the appearance of a characteristic sort of aggregate at the RPE, drusen deposits, should probably be taken into account. Indeed, drusen accumulation is a major pathological hallmark, common to dry and wet AMD, that has been proposed as biomarker of immune-mediated processes at the RPE-Bruch's membrane interface in AMD.^{8–9} Recently, the presence of amyloids in this sort of deposit have been described and the parallelism between the formation of drusen and the build up of Alzheimer's plaques proposed.^{10–11} Actually, AMD could be considered an Alzheimer's disease of the eye.¹² The inflammatory properties of the oligomers, precursors of the formation of the amyloid fibrils is today widely accepted,^{13–14} and has been proposed specifically for drusen in the case of AMD.¹⁰

An inflammation agent has been described to be closely associated with AMD, the protein known as fibroblast growth factor.¹⁵ This protein was the first

CrossMark

To cite: Cuevas P, Outeiriño LA, Azanza C, et al. *BMJ Case Rep*. Published online: [please include Day Month Year] doi:10.1136/bcr-2013-010203

Figure 1 Spectral-domain optical coherence tomography (SD-OCT) of a patient with neovascular macular degeneration in the left eye at different times, along a year. As shown in A, immediately before the start of treatment, the SD-OCT image showed obvious signs of subfoveal choroidal neovascularisation and of histological abnormalities in the retinal structure. Visual acuity was 0.35 at that time. Two months later (B), simultaneous with an enhancement of visual acuity that reached a value of 0.60, the SD-OCT image showed a normalisation of the structure of the retina that was accompanied by a significant decrease in choroidal neovascularisation (asterisk). One year after the treatment, visual acuity was 1 and normalisation, seemingly total, of the retinal histology became evident (C).

angiogenic growth factor that was isolated,¹⁶ although it was later shown that angiogenesis induced by FGF was rather the consequence or the triggering of an inflammatory phenotype in the endothelium than a merely direct angiogenesis induction.¹⁷ Inflammation elicited by FGF is prone to the consolidation of a positive inflammatory feedback loop, typical of chronic diseases, since it induces the upregulation of the synthesis of COX-2 and phospholipase A2, which reciprocally promote the expression of FGF.¹⁹ Inhibition of FGF obviously interrupts these loops, which probably explain the success of the clinical benefits of the inhibition of FGF in treating chronic inflammatory diseases,^{20–21} as seems also the case presented here of the 1-year lasting effects of a single punctual treatment of FGF inhibition.

We have spent important efforts of exploratory research to single out inhibitors of FGF. These studies led to the identification of the low molecular mass compound known in pharmacology as dobesilate. This compound is the active principle of doxium, a drug orally administered for more than 35 years for the treatment of diabetic retinopathy with a good safety profile, but dubious outcomes.^{22–23}

Our results may contradict those of Haritoglou *et al*²³ who did not find statistically significant clinical benefits for treating diabetic retinopathy with dobesilate. 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, could be the reason of the outcome differences.² A detailed discussion about the apparent paradox supporting that the administration of an FGF inhibitor does not cause considerable distortion in adult tissues of mesodermal and neuroectodermal origin, being FGF involved in their homeostasis, was also pointed in previous articles.²

Retinal diseases characterised by an excess of vessel proliferation are sometimes treated with antibodies that inhibit vascular endothelial growth.²⁴ We have shown that, as expected from the necessary synergism between VEGF and FGF for promoting angiogenesis, dobesilate also suppresses VEGF-induced angiogenesis.²⁵ Consequently, dobesilate could be sufficient to treat efficiently all the pathological conditions treated with anti-VEGF antibodies. In addition, treatment with dobesilate may help to overcome the serious concerns of the drawbacks that may follow a long-time depletion of VEGF, a key component of the homeostasis of the retina, being the half-time of clearance from the vitreous of the anti-VEGF antibodies of about 10 days, although some other estimate to be of even 2.5 months.²⁶ Oppositely, dobesilate not bound to FGF and its receptors readily decomposes at physiological pH.²²

The data here reported further stresses that a single treatment with dobesilate, a compound with a long history of safe use, may drive to a durable progressive correction of AMD.

Learning points

- ▶ Neovascular age-related macular degeneration is still the leading cause of blindness in people older than 60 years.
- ▶ Inflammatory and angiogenic activities of fibroblast growth factor have been implicated in the pathology of age-related macular degeneration.
- ▶ Single intravitreal dobesilate injection, an inhibitor of fibroblast growth factor, demonstrated long-term efficacy in the treatment of neovascular age-related macular degeneration with a favourable safety profile.

Competing interests None.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

- 1 Kurihara T, Westenskow PD, Bravo S, *et al*. Targeted deletion of VEGF-A in adult mice induces vision loss. *J Clin Invest* 2012;122:4213–17.
- 2 Cuevas P, Angulo J, Giménez-Gallego G. Long-term effectiveness of dobesilate in the treatment of papulopustular rosacea. *BMJ Case Rep* 2011;2011: pii: bcr0820114579.
- 3 Aiello LP, Brucker AJ, Chang S, *et al*. Evolving guidelines for intravitreal injections. *Retina* 2004;24(5Suppl):S3–19.
- 4 Clemons TE, Milton RC, Klein R II, *et al*. Age-related eye disease study research group. Risk factors for the incidence of advanced age-related macular degeneration in the Age-Related Eye Disease Study (AREDS) AREDS report no. 19. *Ophthalmology* 2005;112:533–9.
- 5 Ferris FL III, Fine SL, Hyman L. Age-related macular degeneration and blindness due to neovascular maculopathy. *Arch Ophthalmol* 1984;102:1640–2.
- 6 Strauss O. The retinal pigment epithelium in visual function. *Physiol Rev* 2005;85:845–81.
- 7 Cao S, Walker GB, Wang X, *et al*. Altered cytokine profiles of human retinal pigment epithelium: oxidant injury and replicative senescence. *Mol Vis* 2013;19:718–28.
- 8 Vinding T. Occurrence of drusen, pigmentary changes and exudative changes in the macula with reference to age-related macular degeneration. An epidemiological study of 1000 aged individuals. *Acta Ophthalmol (Copenh)* 1990;68:410–14.
- 9 Hageman GS, Luthert PJ, Victor Chong NH, *et al*. An integrated hypothesis that considers drusen as biomarkers of immune-mediated processes at the RPE-Bruch's membrane interface in aging and age-related macular degeneration. *Prog Retin Eye Res* 2001;20:705–32. Review.
- 10 Yoshida T, Ohno-Matsui K, Ichinose S, *et al*. The potential role of amyloid beta in the pathogenesis of age-related macular degeneration. *J Clin Invest* 2005;115:2793–800.
- 11 Isas JM, Luibl V, Johnson LV, *et al*. Soluble and mature amyloid fibrils in drusen deposits. *Invest Ophthalmol Vis Sci* 2010;51:1304–10.
- 12 Kaarniranta K, Salminen A, Haapasalo A, *et al*. Age-related macular degeneration (AMD): Alzheimer's disease in the eye? *J Alzheimers Dis* 2011;24: 615–31.
- 13 Bucciantini M, Giannoni E, Chiti F, *et al*. Inherent toxicity of aggregates implies a common mechanism for protein misfolding diseases. *Nature* 2002;416:507–11.
- 14 Chiti F, Dobson CM. Protein misfolding, functional amyloid, and human disease. *Annu Rev Biochem* 2006;75:333–66.
- 15 Amin R, Puklin JE, Frank RN. Growth factor localization in choroidal neovascular membranes of age-related macular degeneration. *Invest Ophthalmol Vis Sci* 1994;35:3178–88.
- 16 Thomas KA, Rios-Candelero M, Giménez-Gallego G, *et al*. Pure brain-derived acidic fibroblast growth factor is a potent angiogenic vascular endothelial cell mitogen with sequence homology to interleukin 1. *Proc Natl Acad Sci USA* 1985;82:6409–13.
- 17 Andrés G, Leali D, Mitola S, *et al*. A pro-inflammatory signature mediates FGF2-induced angiogenesis. *J Cell Mol Med* 2009;13:2083–108.
- 18 Presta M, Andrés G, Leali D, *et al*. Inflammatory cells and chemokines sustain FGF2-induced angiogenesis. *Eur Cytokine Netw* 2009;20:39–50.
- 19 Cha YI, Dubois RN. NSAIDs and cancer prevention: targets downstream of COX-2. *Annu Rev Med* 2007;58:239–52. Review.
- 20 Cuevas P, Angulo J, Giménez-Gallego G. Topical treatment of contact dermatitis by pine processionary caterpillar. *BMJ Case Rep* 2011;2011: pii: bcr0620114351.
- 21 Cuevas P, Outeiriño LA, Azanza C, *et al*. Intravitreal dobesilate in the treatment of choroidal neovascularization associated with age-related macular degeneration. Report of two cases. *BMJ Case Reports* 2012;2012: pii: bcr2012006619.
- 22 Fernández IS, Cuevas P, Angulo J, *et al*. Gentisic acid, a compound associated with plant defence and a metabolite of aspirin, heads a new class of in vivo FGF inhibitor. *J Biol Chem* 2010;285:11714–29.
- 23 Haritoglou C, Gerss J, Sauerland C, *et al*. CALDIRET study group. Effect of calcium dobesilate on occurrence of diabetic macular oedema (CALDIRET study): randomised, double-blind, placebo-controlled, multicentre trial. *Lancet* 2009;373:1364–71.
- 24 Stifter E, Michels S, Prager F, *et al*. Intravitreal bevacizumab therapy for neovascular age-related macular degeneration with large submacular hemorrhage. *Am J Ophthalmol* 2007;144:886–92.
- 25 Angulo J, Peiró C, Romacho T, *et al*. Inhibition of vascular endothelial growth factor (VEGF)-induced endothelial proliferation, arterial relaxation, vascular permeability and angiogenesis by dobesilate. *Eur J Pharmacol* 2011;667:153–9.
- 26 Stewart MW. Clinical and differential utility of VEGF inhibitors in wet age-related macular degeneration: focus on aflibercept. *Clin Ophthalmol* 2012;6:1175–86.

Copyright 2013 BMJ Publishing Group. All rights reserved. For permission to reuse any of this content visit <http://group.bmj.com/group/rights-licensing/permissions>.
BMJ Case Report Fellows may re-use this article for personal use and teaching without any further permission.

Become a Fellow of BMJ Case Reports today and you can:

- ▶ Submit as many cases as you like
- ▶ Enjoy fast sympathetic peer review and rapid publication of accepted articles
- ▶ Access all the published articles
- ▶ Re-use any of the published material for personal use and teaching without further permission

For information on Institutional Fellowships contact consortiasales@bmjgroup.com

Visit casereports.bmj.com for more articles like this and to become a Fellow