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Dobesilate for dry age-related macular degeneration*

Pedro Cuevas[1#], Luis A. Outeiriño[2], Carlos Azanza[2], Javier Angulo[1], Guillermo Giménez-Gallego[3]

[1]Departamento de Investigación, IRYCIS, Hospital Universitario Ramón y Cajal, Madrid, Spain
[2]Departamento de Oftalmología, Hospital de Día Pío XII, Madrid, Spain
[3]Departamento de Estructura y Función de Proteínas, Centro de Investigaciones Biológicas, CSIC, Madrid, Spain
Email: #pedro.cuevas@hrc.es

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ABSTRACT

We have evaluated the effects of intravitreal dobesilate, a synthetic fibroblast growth factor inhibitor, in patients with dry age-related macular degeneration, an inflammatory-related retinal disease without available treatment up to date. 36 eyes from 36 patients with dry age-related macular degeneration were treated with a single intravitreal dobesilate injection. The end points were the improvement from baseline visual acuity and normalization of retinal histology at one month. Intravitreal dobesilate injection resulted in a significant improvement in functional and anatomical outcomes at one month after injection. Our results suggest that intravitreal dobesilate may increase the chance of visual acuity gain in dry age-related macular degeneration, even in cases with initial low vision. This study supports the findings of previously published case reports, regarding the short-term improvement in visual acuity by intravitreal dobesilate injection in different degenerative retinal diseases.

Keywords: Dry Age-Related Macular Degeneration; Fibroblast Growth Factor Inhibition; Intravitreal Dobesilate

1. INTRODUCTION

Age-related macular degeneration (AMD) is the primary cause of blindness and visual disability in people aged over 50 and its prevalence increases exponentially after the age of 70 [1,2]. AMD is diagnosed as either wet (neovascular) or dry (atrophic). Wet AMD is characterized by choroidal nevoascularization (CNV): the formation of hyperpermeable new blood vessels beneath the retinas that leak plasma and often bleed, leading to the formation of scar tissue which can severely and irreversibly compromise visual acuity. Although it constitutes only 10% - 15% of all cases, wet AMD accounts for almost 80% of AMD-related blindness [3].

Dry AMD, in contrast, does not involve leaking vessels from choroidal vasculature. Dry AMD is characterized by a well-defined constellation of clinical features, including drusen, pigment abnormalities/focal hyper- or hypo-pigmentation of the retinal pigment epithelium (RPE), and geographic atrophy (GA) of the macula. GA represents the atrophic late stage of dry AMD [1,2]. GA is characterized by roughly oval areas of hypopigmentation and is usually the consequence of RPE cell loss. Loss of RPE cells, responsible for the overlying photoreceptors surviving, leads to the gradual degeneration of nearly photoreceptors, resulting in thinning of the retina. RPE degeneration leads to the death of photoreceptor cells causing irreversible vision loss. Since the natural evolution of dry AMD is toward a wet AMD condition, the holy grail of therapy for AMD is to avoid the development of CNV. Today, there are no approved treatments for dry AMD.

Considering the significant medical, personal, social and economic costs of AMD, the need for novel therapeutic and preventive strategies for AMD is pressing. Innovation in AMD pharmacotherapy, in turn, depends largely upon a thorough understanding of the molecular mechanisms underlying AMD pathogenesis. There is ample evidence that inflammation plays an important role in both dry and wet AMD [4-9]. Several studies have documented a significant association between inflammatory diseases and upregulation of fibroblast growth factor (FGF) [10-16]. Recently, it has been posited the importance of FGF in neuroinflammatory diseases such as AMD where inflammation is one of the main components of disease progression and FGF and its receptors (FGF/FGFR) are prominently expressed [17].

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#Corresponding author.

This study supports an important clinical interest for searching safe and efficient inhibitors of FGF/FGFR axis to treat retinal inflammatory diseases, including AMD. The aim of this study was to analyze treatment with a single dose of intravitreal dobesilate in patients who were diagnosed with dry age-related macular degeneration.

2. METHODS

2.1. Participants

In this consecutive study, more than 200 patients with age-related macular degeneration who visited the Clínica Oftalmológica Hospital Pío XII of Madrid (Spain) between January 2012 and October 2012, were screened, and 36 eyes from 36 patients with dry age-related macular degeneration were included. Baseline data for all study patients is shown in **Table 1**. The study was approved by the local institutional review board and informed consent was obtained from every patient for the intravitreal injection. The subjects were also provided information about the off-label use of dobesilate.

2.2. Inclusion/Exclusion Criteria

Inclusion criteria were the presence of early, intermediate or late stages of dry AMD. Eyes that met any of the following criteria were excluded from enrolment: 1) had severe disease that was judged by the treating investigator as being unlikely to benefit from further therapy (such as those with central ischemia or macular scarring); 2) had vision loss from other coexisting ocular disease and 3) had undergone ocular surgical interventions within 6 months prior to study entry.

2.3. Procedures

Examination at baseline included best corrected visual acuity (BCVA) with a Snellen chart at a distance of 20 feet, slit lamp biomicroscopy of the anterior segment and fundus, and spectral domain optical coherence tomography (SD-OCT). The data recorded included complains as scotoma, blurred vision and metamorphopsia.

Table 1. Baseline characteristics of the patients.

Sex	
Male	16
Female	20
Age	
Mean	70 ± 7
Intermediate phase of dry AMD	
Male	14
Female	16
Late phase of dry AMD (geographic atrophy)	
Male	2
Female	4

The intravitreal injection of dobesilate was performed in accordance with the guidelines for intravitreal injections [18]. Before injection administration, the eye was washed with povidone-iodine (5%) and the eyelashes and lid region were then wiped, also with povidone-iodine (5%). Then, each patient received 18.75 mg of dobesilate in a single intravitreal injection of 150 µl of a solution of diethylamonium 2,5-dihydroxybenzesulfonate (etamsylate; dycinone®, Sanofi-Aventis, Paris, France). Antibiotic eye drops were then applied. Patients returned to the outpatient clinic for routine postinjection follow-up at day one and day three after injection; a slit lamp examination and pressure measurements were performed to rule out intraocular inflammation or elevated intraocular pressure (IOP). BCVA, slit lamp biomicroscopy of the anterior segment and fundus, and SDCOT were conducted again at 1 month postinjection. The ocular symptoms, such as scotoma, metamorphopsia and blurred vision were examined by questioning each patient before and after treatment. Scotoma and metamorphopsia on the Amsler grid were scored according to Verma *et al*. [19]. Accordingly, scotoma and metamorphopsia were graded numerically from 0 to IV, where a grade 0 indicates absence of scotoma and metamorhopsia, and a grade IV indicates very severe scotoma and metamorphopsia. Blurred vision was scored from 0 to 4, where a score of 0 indicates no vision disturbance and a score of 4 indicates very severe blurred vision.

2.4. Endpoints

The primary endpoint was the improvement of visual acuity at 1 month compared with baseline. The second endpoint was the effect of treatment in the normalization of retinal structure at the same time after treatment.

2.5. Statistics

The paired *t*-test was used to statistically evaluate changes in visual acuity at baseline and one month after treatment. A p value < 0.05 was considered to be statistically significant. Graphic representation of the data is expressed as mean ± standard error of the mean (SEM).

3. RESULTS

3.1. Visual Outcomes

In the current study, 36 eyes of 36 patients of both sexes were enrolled. All patients tolerated well the injection. The mean BCVA at baseline was 0.44 ± 0.03. At one

month examination, 32 eyes (89%) showed visual acuity improvement and only 4 eyes (11%) experienced visual acuity worsening. Individual patient BCVA values before and after treatment are shown in **Table 2**. The mean BCVA after treatment was 0.59 ± 0.03 ($p < 0.001$). Changes in BCVA after intravitreal injection of dobesilate appear in **Figure 1**. As the **Table 3** shows, scotoma, metamorphopsia and blurred vision were consistently reduced, inducing the improvement of quality of vision in all 32 cases.

3.2. Anatomical Outcomes

The effect of intravitreal dobesilate in retinal structural outcomes was assessed with SD-OCT. At baseline, inner retinal layer was normal, whereas the outer retinal layers showed structural alterations: 1) the integrity of photoreceptor inner segment and outer segment were not preserved; 2) retinal pigment epithelium (RPE) showed rarefactions and thinning. In contrast, normalization of outer retinal layers was achieved in 32 patients after dobesilate treatment. As an example of effectiveness of dobesilate, we show a SD-OCT scan of a patient with GA (**Figure 2**). GA is characterized by confluent areas of cell death of photoreceptors and RPE, is bilateral in more than half of patients, and is responsible for 10% of cases of legal blindness from AMD [20]. To date no effective treatment for progressive vision loss is available for GA.

Table 2. Change of BCVA from baseline to last observation.

P	Baseline	Treatment	P	Baseline	Treatment
		One month			One month
1	0.40	0.50	**19**	0.60	0.90
2	0.50	0.60	**20**	0.40	0.60
3	0.60	0.70	**21**	0.50	0.70
4	0.50	0.80	**22**	0.30	0.40
5	0.40	0.80	**23**	0.40	0.50
6	0.50	0.60	**24**	0.20	0.60
7	0.60	0.60	**25**	0.20	0.40
8	0.40	0.70	**26**	0.20	0.90
9	0.20	0.90	**27**	0.30	0.60
10	0.60	0.20	**28**	0.30	0.50
11	0.40	0.60	**29**	0.40	0.50
12	0.50	0.40	**30**	0.50	0.60
13	0.60	0.50	**31**	0.70	0.80
14	0.70	0.60	**32**	0.30	0.50
15	0.70	0.80	**33**	0.20	0.30
16	0.70	0.80	**34**	0.40	0.60
17	0.40	0.40	**35**	0.30	0.20
18	0.50	0.90	**36**	0.30	0.50

Intravitreal dobesilate injection improved BCVA in patients with dry age-related macular degeneration. P: Patient number (n = 36).

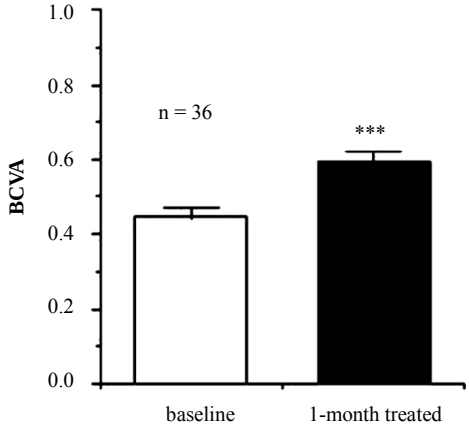


Figure 1. Visual acuity 1 month after an intravitreal injection of dobesilate showing statistically significant improvement.

3.3. Safety

There were no cases of treatment-associated complications such as retinal detachment, endophthalmitis or persistent elevated IOP.

4. DISCUSSION

Clinically and histologically, AMD is generally classified into two major subtypes: dry or non-exudative AMD, of which GA is a severe form, and wet or exudative AMD. Wet AMD is very debilitating and often develops after early dry AMD. The key feature of wet AMD is choroidal neovascularization (CNV), the growth of new hyperpermeable blood vessels from the choroids into the region underlying the RPE or extending into the subretinal space [21]. Dry AMD progresses more slowly and manifests RPE and photoreceptor cell dysfunction and degeneration [4]. Although the aetiology of AMD is not completely understood, it is indisputable that inflammation has a critical role in both dry and wet AMD [4-9]. Consequently, conventional therapies based on inhibiting choroidal neovascularization do not seem to be an appropriate strategy for dry AMD management. However, the aetiology of this disease suggests that the treatment of inflammation could be a suitable alternative to treat dry AMD.

Previously, we have reported the efficacy of dobesilate, a synthetic inhibitor of FGF/FGFR axis [22] in patients with retinal diseases [23-27]. FGF in spite of being an

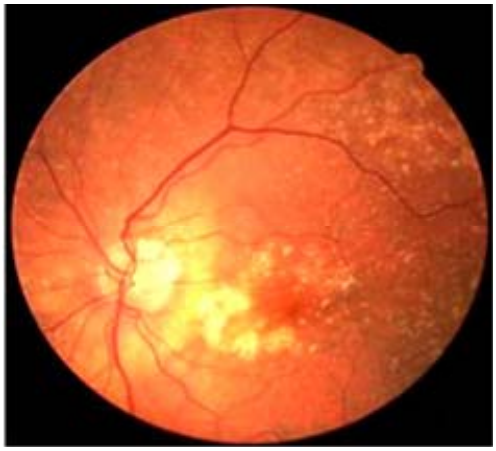
Table 3. Change in ocular symptoms score from baseline to last observation.

	P	B	T	P	B	T	P	B	T	P	B	T
S	**1**	II	I	**10**	II	II	**19**	III	0	**28**	II	0
M		II	I		I	0		II	0		III	I
BV		1	0		1	1		1	0		3	1
S	**2**	III	II	**11**	I	III	**20**	II	I	**29**	II	I
M		I	I		I	II		II	I		III	0
BV		1	0		1	2		2	1		2	0
S	**3**	I	0	**12**	I	0	**21**	I	0	**30**	II	I
M		I	0		II	0		I	I		I	0
BV		0	0		1	0		1	0		1	0
S	**4**	0	0	**13**	I	I	**22**	II	I	**31**	0	0
M		I	0		I	III		II	0		0	0
BV		1	0		0	1		1	0		1	0
S	**5**	I	0	**14**	II	II	**23**	I	0	**32**	0	0
M		0	0		I	0		I	I		0	0
BV		1	0		1	1		1	0		1	0
S	**6**	I	0	**15**	I	II	**24**	II	I	**33**	0	0
M		0	0		I	II		II	I		I	0
BV		0	0		1	1		1	0		1	0
S	**7**	I	0	**16**	II	I	**25**	III	I	**34**	III	II
M		0	0		I	I		II	0		III	II
BV		0	0		0	1		3	0		2	2
S	**8**	II	I	**17**	I	0	**26**	II	0	**35**	I	0
M		II	0		I	0		II	0		I	0
BV		1	0		1	0		1	0		1	1
S	**9**	III	0	**18**	I	I	**27**	III	I	**36**	II	III
M		II	0		II	II		III	I		II	II
BV		1	0		1	1		3	0		2	2

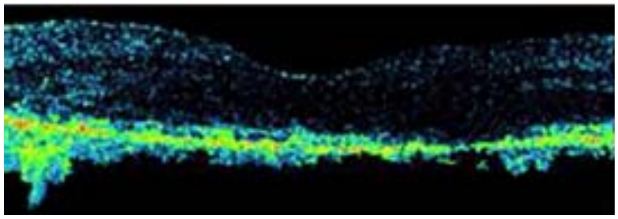
Dobesilate injection in the vitreous gel improved ocular symptoms associated to dry age-related macular degeneration. S: Scotoma; M: Metamorphopsia; BV: Blurred Vision; P: Patient number (n = 36); B: Baseline; T: after one month of Treatment.

angiogenesis promoter [28] is involved also in inflammation [10-16] and seems to play key roles in neurodegenerative diseases such as Alzheimer's and Parkinson's diseases as well as in AMD [17].

Dobesilate features suggest that its intravitreal application could be of potential clinical benefit in dry AMD management. In this report, we describe the rapid normalization of retinal structure, running parallel to a considerable improvement of visual acuity in patients with dry AMD after a single intravitreal administration of dobesilate. This study adds some more valuable data to the recently reported promising good results to the use of dobesilate in both dry and wet AMD and also in other retinal diseases [23-27].



(a)



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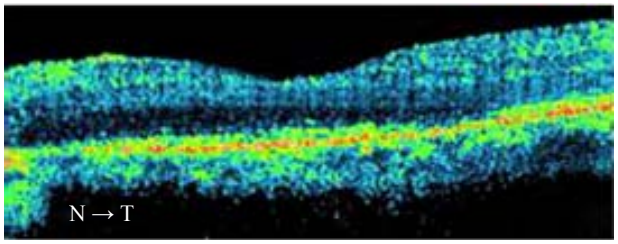

(c)

Figure 2. Fundus photographs of the left eye of an enrolled patient at baseline with peripheral areas of pigment accumulation, autofluorescence deposits and patches of geographic atrophy of the retinal pigment epithelium (a). Optical coherence tomography of the central macula before treatment with dobesilate (b), showing loss in some areas of both outer retinal layers and pigment epithelial cells, and one month after treatment (c), with improvement of vision from 0.20 to 0.60. Note the anatomical recovery of outer retinal layers and retinal pigment epithelium after a single intravitreal injection of dobesilate.

It may result somehow surprising that an inhibitor of FGF shows the good safety profile of dobesilate, given the broad spectrum of physiological activities in which FGF is involved [29-32]. In effect, FGF has been detected in most adult tissues tightly bound to the sulphated glycosaminoglycans (GAG) of the extracellular matrix

(ECM), at times at very high levels [22]. Thus, under normal physiological conditions, FGF does not act as a signalling molecule in solution, but as a solid phase growth factor. As far as FGF remains part of the ECM, it cannot be inhibited by dobesilate, which has an affinity constant for FGF approximately 3000 times lower than that of the sulphated GAG of the ECM; furthermore, it reaches extraordinarily high concentrations [22]. Nevertheless, the physiological FGF signalling system gets sometimes subverted, causing very serious physiological disturbances, when high concentrations of free FGF are accumulated, either through uncontrolled synthesis or mobilization by heparanases and other specialized proteins which could be upregulated in inflammatory conditions [33-35]. In contrast to ECM bounded FGF, dobesilate efficiently inhibits free FGF [22]. Consequently, it inhibits mainly pathological FGF, leaving the relatively untouched physiological FGF pool.

Several limitations are inherent in the current study. First, the design was prospective, the sample size was small and there was no control group. Second, this one time follow-up of patients does not describe visual acuity evolution over time and the results may be transient. However, this study shows for the first time the efficacy and safety of a new therapy for dry age-related macular degeneration that has been considered as an orphan disease. Furthermore, treatment with dobesilate increased visual acuity above the expected baseline decrease during the natural evolution of untreated dry AMD. In sum, dobesilate with a long history of use, and abundant preclinical data supporting its biological effects and its potential efficacy, is promising as a FGF targeted therapy for AMD. A large population cohort study is needed to establish the effectiveness of intravitreal dobesilate in treating dry AMD patients.

5. AUTHOR CONTRIBUTIONS

Conceived and designed the study: PC, GGG, LO. Performed the study LO, CA. Analyzed the data: LO, CA, JA, GGG, and PC. PC, GGG, wrote the paper. All authors read and approved the final manuscript.

6. ACKNOWLEDGEMENTS

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ABBREVIATIONS

BCVA: Best corrected visual acuity
SD-OCT: Spectral domain optical coherence tomography
FGF: Fibroblast growth factor
FGFR: Fibroblast growth factor receptors

