Intravitreal Dobesilate Treatment of Dry Age-Related Macular Degeneration: 12-Months Results

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Abstract: *Purpose*: To evaluate the 12-month efficacy and safety of intravitreal Dobesilate in dry age-related macular degeneration (ARMD). *Patients and Methods*: Thirty patients with visual impairment due to dry ARMD received a single intravitreal injection of Dobesilate in the study eye. Ophthalmic evaluation included fundoscopy, spectral-domain optical coherence tomography (SD-OCT) and best-corrected visual acuity (BCVA) prior to therapy and 1 week, 1 and 12-months after treatment. *Main Outcome Measures*: Mean change in BCVA. Retinal anatomy. Incidence of ocular and non-ocular adverse events. *Results*: There was a statistically significant increase in mean BCVA at 12 months compared with baseline (0.30±0.04 *vs*. 0.49±0.06 SEM) (p<0.001). BCVA increased in 26 of 30 eyes (86.7%) and only 4 eyes (13.3%) didn't show any change. Intravitreal Dobesilate injection resulted in a significant improvement of outer retinal anatomy. Visual improvement was not correlated with age. No ocular or systemic events were reported during the follow-up period. *Conclusions*: This study confirms the safety of Dobesilate intravitreally injected, as well as the improvement in visual acuity and retinal anatomy at 12 months follow-up. Intravitreal Dobesilate may be a promising therapeutic strategy targeting the inflammatory component of dry ARMD.

Keywords: Dry age-related macular degeneration, Fibroblast Growth Factor (FGF), Intravitreal Dobesilate.

INTRODUCTION

Between 30 and 60 million people worldwide are estimated to be affected of age-related macular degeneration (ARMD), which is the most common cause of legal blindness in industrialized countries [1]. Clinically and histologically, ARMD is generally classified into two major subtypes: dry or non-exudative ARMD and wet or exudative ARMD. Dry ARMD accounts for approximately 90% of all cases of ARMD, including as clinical features drusen, retinal pigment epithelium (RPE) alterations and geographic atrophy (GA) [2]. Drusen are described as focal deposits of extracellular debris between the basal lamina of the RPE monolayer and the inner collagenous layer of the Bruch's membrane [3]. Drusen, particularly large, are a distinguishing feature and a characteristic physical sign of dry ARMD [4]. Over a few years patients develop a gradual visual loss with central visual scotomas slowly leading to complete loss.

Actually wet ARMD is treated with intravitreal repeated injections of anti-vascular endothelial growth factor (VEGF), with an elevated risk of ocular and nonocular adverse events [5-8]. However, dry ARMD still remains a challenge, for which the only approved treatment is the use of Age-Related Eye Disease Study (AREDS)-based vitamin supplements, which however do not halt the vision loss although they lower the risk of developing advanced stages of ARMD (either GA or wet ARMD). In addition, the AREDS formula does not prevent GA from forming or progressing [9]. Inflammation, oxidative stress, high-fat diet, light exposure and genetic factors all contribute to the pathogenesis of dry ARMD [10-16].

Fibroblast growth factor (FGF) is a pro-inflammatory and pro-angiogenic protein that plays an important role in ARMD pathophysiology [15,16]. Observational clinical studies have established the short-term efficacy of intravitreal Dobesilate, a synthetic FGF inhibitor for the treatment of dry ARMD [17-19]. Herein, we evaluate the 12-months follow-up data from patients with dry ARMD treated with a single intravitreal injection of Dobesilate, including the effect on vision and anatomic outcomes.

METHODS

Study Design

This is an observational study of 12-months follow-up conducted in an ophthalmologic clinic. Patients with dry ARMD received a single intravitreal administration

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of Dobesilate. This study was approved by the local institutional review board and performed in compliance with the ethical principles of the Declaration of Helsinki. All participating patients provided written informed consent before treatment.

Participants

Baseline data for all patients is shown in Table **1**.

Table 1: Baseline Characteristics of the Patients

Age	74.4±1.7
Age groups	
< 65 years	4
65-75 years	12
> 75 years	14
Gender	
Male	11
Female	19
Ethnic group	Caucasian (100%)
Total study eyes	30
Right	18
Left	12
BCVA	0.30±0.04 SEM

Inclusion/Exclusion Criteria

Inclusion criteria were the presence of early, intermediate or late stages of dry ARMD. Eyes that met any of the following criteria were excluded from enrolment: 1) Patients with visual acuity <0.20: 2) 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); 3) had vision loss from other coexisting ocular disease and 4) had undergone ocular surgical intervention within 6 months prior to study entry. Only one eye per patient was treated.

PROCEDURES

Examination at baseline included BCVA with a Snellen chart at a distance of 20 feet, slit-lamp biomicroscopy of the anterior segment and fundus, and SD-OCT.

The intravitreal injection of Dobesilate was performed in accordance with the guidelines for intravitreal injections [20]. Before injection, the eye was washed with povidone-iodine (5%) and the eyelids and lid region wiped also with povidone-iodine (5%). Then, each patient received in the study eye 18.75 mg of Dobesilate in a single intravitreal injection of 150 µl of a solution of diethylamonium 2-5-dihydroxybenzene-sulfonate (Etamsylate, dycinone®, Sanofi-Aventis. Paris, France). Antibiotic eye drops were then applied. Patients returned to the clinic for routine post-injection follow-up at days one and 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 SD-OCT were conducted again at each visit post-injection (1 week, and 1 and 12 months postreatment).

Outcomes

The primary efficacy parameter was the mean BCVA and the secondary efficacy parameter was the retinal histology assessed by SD-OCT at each visit after treatment. Safety assessments were performed with BCVA, slit-lamp biomicroscopy observations, and tonometry through every visit. Slit-lamp biomicroscopy included examination of the cornea, lens, conjunctiva, iris and anterior chamber. Dilated fundus examination included examination of the vitreous, retina, macula and optic nerve.

Statistical Methods

BCVA data are expressed as mean ±SEM and baseline values were compared by paired *t*-test to those obtained at each time-point. The whole time-course evolution of BCVA was analyzed by one-factor ANOVA followed by Student-Newmann-Keuls post-test. A probability of less than 5% was considered significant.

RESULTS

Effect of Dobesilate on Visual Acuity

In the current study 30 eyes from 30 patients with dry ARMD were enrolled. Of the patients included in the study 19 were female and 11 were male. Their mean age was 74.4±1.7. The mean BCVA at baseline was 0.30±0.04. At 12 months examination, 26 eyes (86.7%) showed visual acuity improvement and only 4 eyes (13.3%) maintained the same vision than at baseline. Figure **1** depicts BCVA along with time and shows a progression improvement through the 12 months follow-up.

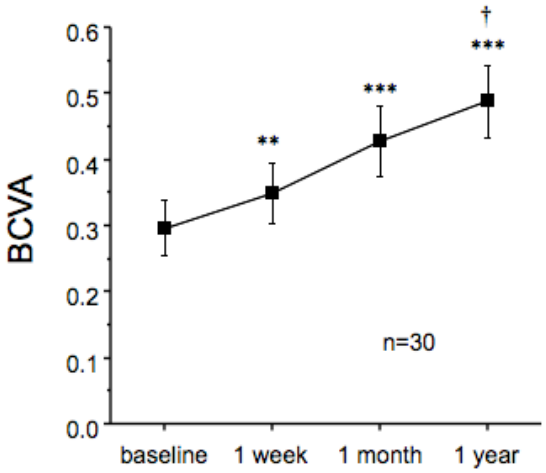

Figure 1: Evolution of best-corrected visual acuity (BCVA) after a single intravitreal injection of dobesilate (18.75 mg) in patients with dry ARMD. Data are expressed as mean ± SEM. n indicates the number of patients. *** $p < 0.001$ *vs.* baseline by paired t-test, † $p < 0.05$ *vs*. baseline by one-factor ANOVA followed by Student-Newmann-Keuls test.

Effect of Dobesilate on Macular Anatomy

The effect of intravitreal Dobesilate in retinal structural outcomes was assessed with SD-OCT. At baseline, inner retinal layers were normal, whereas the outer retinal layers showed structural alterations with drusen that disturb the RPE and the photoreceptors mosaic. In contrast, retinal anatomy improved at one month in eyes that responded to treatment and this improvement was maintained along the 12-months follow-up. As an example of effectiveness of intravitreal dobesilate, we show SD-OCT scans of a patient with dry ARMD at baseline and after 12 months of treatment (Figure **2**).

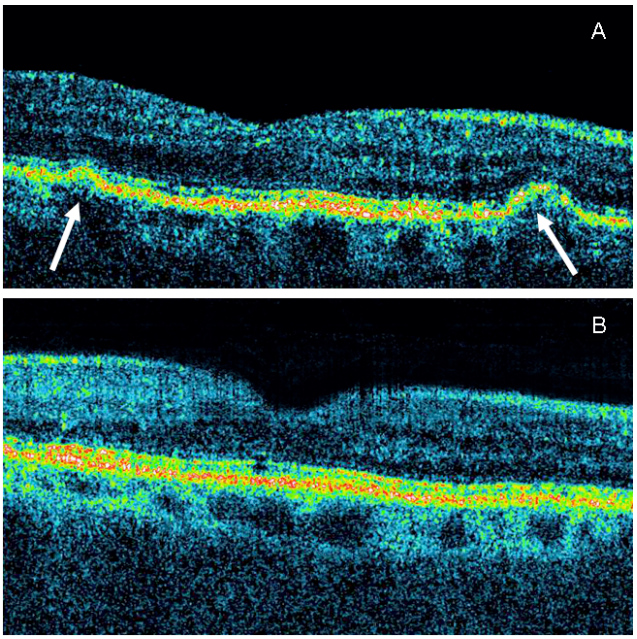

Figure 2: Comparison of representative SD-OCT scans before (**A**) and 12-months (**B**) following single intravitreal injection of dobesilate (18.75 mg) in a patient with dry ARMD. Arrows indicate large drusen. At baseline, visual acuity was 0.10. Drusen are resolved after treatment and visual acuity measures 0.50.

Safety

There were no cases of treatment-associated complications.

DISCUSSION

Each year millions of individuals lose their central vision, compromising their ability to distinguish faces, read and drive, that will increase the 15-20 millions people in the US who suffer from ARMD [21].

It has been reported that inflammation has a critical role in both dry and wet ARMD [10-16]. Since chronic retinal inflammation appears to represent a common pathway of macular degeneration, an appropriate mean of treating retinal degenerative diseases could be the local inhibition of the inflammatory process. Inflammation is present in drusen such as components of the complement system, lipofucsin, acute-phase proteins, proteins that modulate the immune response and dendritic cells [22-25]. Therefore, it seems that reducing inflammation would slow dry ARMD progression. This hypothesis is being investigated with a number of approaches, including corticosteroids [26] and complement inhibition system [27].

Fibroblast growth factor (FGF) is an important inflammatory protein that is involved in intraocular inflammation and proliferation reaction process [28, 29]. Because an increase of FGF is sufficient to cause cardinal features of both wet and dry ARMD, FGF can serve as a target for therapeutic intervention in retinal inflammatory diseases as ARMD.

Features of Dobesilate, a compound with a long history of safe use [30], suggest that its intravitreal application could be of potential clinical benefit in dry ARMD management. Recently, we have reported the short-term normalization of retinal structure, running parallel to a considerable improvement of visual acuity in patients with dry ARMD after a single intravitreal administration of Dobesilate [18, 19]. The present report shows the 12-months clinical improvement in patients with dry ARMD, after a single intravitreal injection of dobesilate.

Recently, it has been postulated that retinal microglia plays important roles in ARMD. Microglial cell activation in the outer retina has been proposed as part of the pathogenic mechanisms in some retinal diseases including ARMD with involvement in photoreceptor and RPE loss [31, 32]. Therefore, a new therapeutic strategy to treat ARMD should target the chemo-attractant molecules that regulate retinal microglia activation. Microglial cells synthesize FGF when they become activated. Since they also express FGF receptors, this growth factor should autocrinally contribute to sustain a chronic nervous system inflammation [33-35].

In healthy retina, microglial cells are located in inactivated conditions, mainly in the inner retina. However, under conditions of advanced age and photoreceptor injury, retinal microglia cells translocate from the inner retina into the outer retina and accumulate in the subretinal space where they acquire the morphological features of activation [36]. Activated microglia has been found in patients with ARMD [37]. FGF in spite of being an angiogenesis promoter [38] is involved also in inflammation [39-44], and seems to play key roles in neurodegenerative diseases such as Alzheimer's and Parkinson's diseases as well as ARMD, through activation of microglial cells [35]. However the implication of FGF in microglial cell migration from the inner retina to the outer retina, and its activation in this site in ARMD has not been specifically studied. The general [17] anti-inflammatory activities of Dobesilate [45-47] could explain its efficacy in dry ARMD.

Two limitations are inherent in the current study: first, the sample size is small and second, there is no control group. However, according to our study results, dry ARMD which is considered as an orphan disease, could be managed with intravitreal Dobesilate injection which has demonstrated to be safe and long-term efficient, as described for the first time in the present report.

COMPETING INTEREST

The authors report no conflicts of interest in this work.

AUTHOR CONTRIBUTIONS

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

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