European Journal of Ophthalmology / Vol. 18 no. 1, 2008 / pp. 99-103

Octreotide acetate in dominant cystoid macular dystrophy

B.F. HOGEWIND, G. PIETERS, C.B. HOYNG

University Medical Centre St Radboud, Nijmegen, Gelderland - The Netherlands

PURPOSE. *Dominant cystoid macular degeneration (DCMD) is an autosomal dominant trait of cystoid macular edema with poor visual prognosis. Until now, no efficient treatments for DCMD have been reported. The authors evaluated a somatostatin-analogue (octreotide acetate) as treatment for DCMD.*

METHODS. *The authors treated four patients with early DCMD by intramuscular longacting octreotide acetate, 20 mg every 4 weeks for 1 year. In addition to general ophthalmologic examination the authors performed fluorescein angiography (FA) before and after treatment.*

RESULTS. *Seven out of eight eyes showed improvement on FA and stabilization of visual acuity.*

CONCLUSIONS. *Somatostatin-analogues may reduce cystoid edema in DCMD and may thus prevent disease-related visual loss. (Eur J Ophthalmol 2008; 18: 99-103)*

KEY WORDS. *Cystoid macular edema, Humans, Octreotide, Dominant cystoid macular dystrophy*

Accepted: August 30, 2007

INTRODUCTION

In 1976, a large pedigree of patients with an autosomal dominant trait of cystoid macular edema (CME) was reported. This disease entity has been called dominant cystoid macula degeneration (DCMD) (1). The gene for DCMD has been localized on chromosome 7p (2). The phenotype was elaborately described in 1983 (3). The disease develops from distinct macular edema in the early stage to a more diffuse edema of the posterior pole. The end stage of this disease is characterized by extensive chorioretinal atrophy with poor visual acuity. So far, no therapies (like the CME drugs acetazolamide, intravitreal triamcinolone acetonide, bevacizumab, or steroids) have been reported to cure DCMD or stop the progression.

Pathophysiology of CME in DCMD

The genetic background of DCMD shows similarities with retinitis pigmentosa (2), and the CME in DCMD is possibly induced by dysfunction of the retinal pigment epithelial (RPE) layer like the CME that occurs in retinitis pigmentosa (4). It has been suggested that the dysfunctioning RPE layer in hereditary retinal diseases results in abnormal permeability of the barrier between choroid and neurosensory retina. As fluid dissects into the nerve fiber layer, it may elevate the inner limiting membrane and displace the nerve fibers to create large accumulations of fluid. The macula becomes thickened and cystic spaces containing a transudate are present in the outer and inner plexiform layer and the inner nuclear layer (5). Longstanding CME leads to coalescence of the fluid-filled microcysts into large cystoid spaces and subsequent lamellar hole formation at the fovea with irreversible damage to central vision (6, 7).

Octreotide for CME

In 1998, Kuijpers et al described a beneficial effect of octreotide in a patient with non-inherited CME (8). Octreotide is a somatostatin analogue and the reduction of macular edema by a somatostatin analogue has been confirmed in patients with exudative diabetic retinopathy (9), uveitis (10), hereditary retinal dystrophies (11), and

Part of this paper was presented as a poster at ARVO Annual Meeting, Fort Landerdale, FL, USA, May 1-5, 2005

© Wichtig Editore, 2008

1120-6721/099-05$15.00/0

Irvine Gass syndrome (12). Notably, all intervention studies so far aim at an edema reducing effect, but no prevention studies have been performed (13).
Little is known on the effect of somatostatin-analogues on macular edema in general. Differential expression of somatostatin and its receptors have been assessed in neuroretina, RPE, and uvea. Somatostatin has proven immunosuppressive properties by modifying cytokine (e.g., IFN-γ) and immunoglobulin production (13). It may also act through inhibition of growth hormone and of insulin-like growth factor I, or through direct antiproliferative and apoptotic effects on endothelial cells mediated by specific receptor subtypes (14, 15).

Octreotide for CME in hereditary retinal diseases

Van Hagen et al postulated a mechanism through which somastatin analogues may decrease the CME in hereditary retinal diseases: octreotide acts directly on the ion transport systems of the dysfunctioning RPE, resulting in a rebalance of the fluid and ion transport (5). These premises are enhanced by the finding that activation of apical membrane somatostatin receptors results in an increase of fluid absorption across the RPE (16). The postulation suggests that somatostatin promotes also drainage of intraretinal edema across the RPE in DCMD.
We hypothesized that the somatostatin-analogue octreotide has a positive effect on the early stages of DCMD.

MATERIALS AND METHODS

This study was done in accordance with the principles of the Declaration of Helsinki. Before inclusion in the study informed consent of all study participants was obtained. For patients younger than 18 years, informed consent was given by the parents as well. We included affected subjects from the large pedigree of DCMD described earlier (1) with distinct cystoid macula edema on fluorescein angiography (FA). Exclusion criteria were lack of willingness to cooperate, other causes of CME in history, at examination, or on FA (e.g., previous cataract surgery, retinal vein occlusion uveitis, or idiopathic juxtafoveal telangiectasia), DCMD with atrophic changes, and systemic contraindications for somatostatin therapy like hyperglycemia or diabetes mellitus. The study period was 12 months for all patients. All study participants underwent a comprehensive ophthalmologic examination, including slit-lamp biomicroscopy, best-corrected visual acuity (BCVA), and FA. A complete general physical examination was performed and levels of serum glucose and growth hormone were assessed. In addition, optical coherence tomography (OCT) was performed in one patient. Each patient received an intramuscular injection of 20 mg somatostatin-analogue (long-acting octreotide acetate) once every 4 weeks during a period of 12 months. Ophthalmologic examination was performed after 1, 3, and 12 months. FA was performed after 4 and 12 months. In addition, all participants were monitored for drug-related adverse affects. Statistical analysis was performed using SPSS 12.0.1

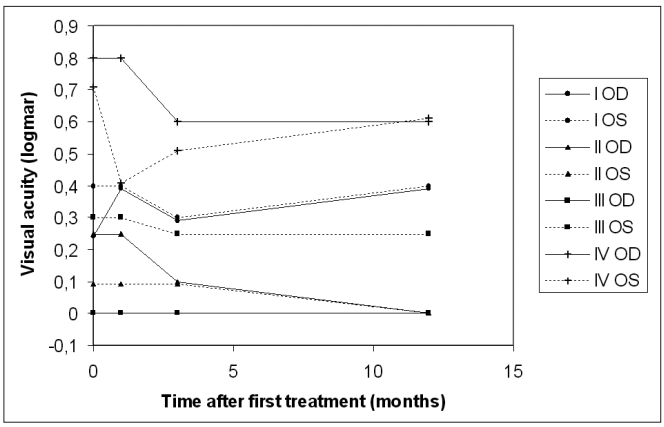

Fig. 1 - *Best-corrected visual acuity during treatment of dominant cystoid macular dystrophy with long-acting octreotide acetate. Both eyes of each patient (I through IV) are depicted (right and left).*

TABLE I - CHARACTERISTICS OF THE FOUR PATIENTS WITH DOMINANT CYSTOID MACULA DEGENERATION WHO WERE TREATED WITH LONG-ACTING OCTREOTIDE ACETATE

Patient	Age, yr	Duration of CME prior to treatment, y	BCVA at diagnosis, right/left logMAR
I	17	10	0.2/0.4
II	38	3	0.1/0.1
III	57	11	0.0/0.3
IV	33	25	0.6/0.3

For each patient the following are depicted: the age at inclusion in the study, the duration of cystoid macula edema prior to treatment, and previous treatments for the macular edema and the best-corrected visual acuity (right/left in logMAR) at the time of the diagnosis of dominant cystoid macula degeneration. No patient had undergone previous treatment

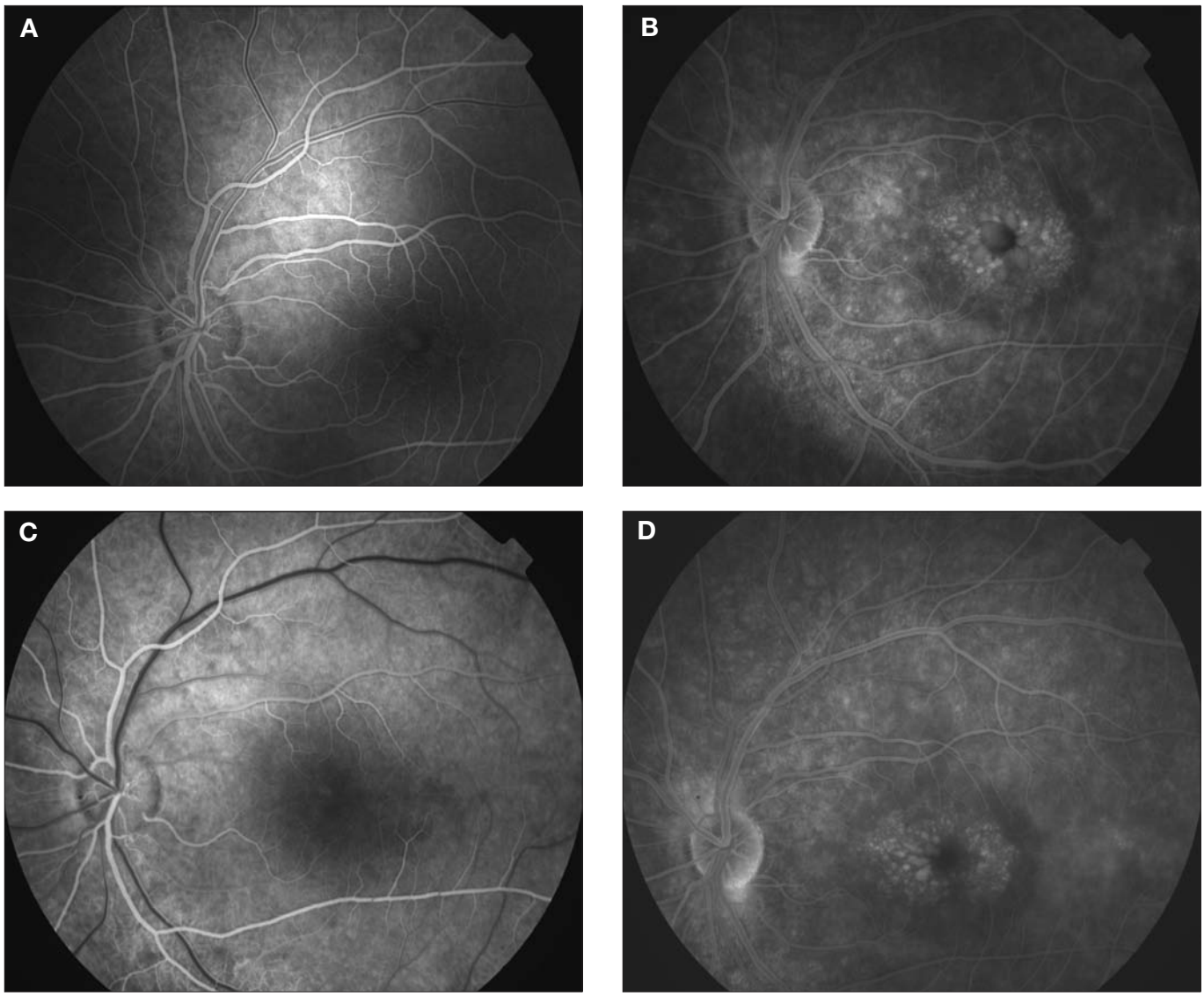

Fig. 2 - *Baseline fluorescein angiography of untreated dominant cystoid macula degeneration of the left eye of Patient 1.* **(A, B)** *The arteriovenous and late phase.* **(C, D)** *The same phases of the eye after 4 months of somatostatin therapy. Note the remission of the leakage and the decrease of amount and size of the cysts.*

software for Windows (SPSS Inc., Chicago, IL, USA). Intra-individual visual acuity changes during treatment and gender differences were put through the paired *t*-test for groups. A p value < 0.05 was considered to be statistically significant.

RESULTS

We included eight eyes of four patients (one male, three female) with a mean age of 36 years (Tab. I). In all patients a 12-month follow-up was available.

The mean BCVA (± standard deviation) was 0.35 logMAR (±0.28) before treatment and 0.33±0.24, 0.27±0.21, and 0.28±0.26 logMAR after 1, 3, and 12 months treatment respectively. The individual course of BCVA of all eyes is illustrated in Figure 1. The changes in BCVA and gender differences were not statistically significant (p value < 0.05). Within the follow-up period all eyes except the right eye of Individual I showed remission of the edema on FA (i.e., the cystoid lesions persisted but the surrounding leakage decreased on the

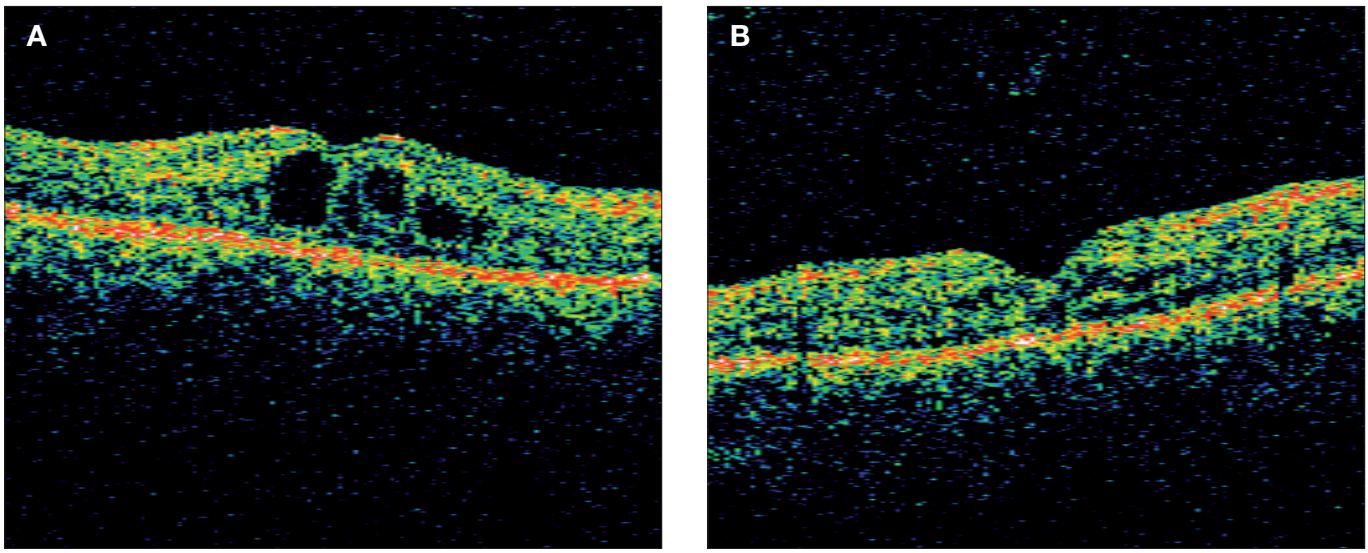

Fig. 3 - *Baseline optical coherence tomography (OCT)* **(A)** *of untreated dominant cystoid macula degeneration of the left eye of Patient 1, and OCT* **(B)** *of the same eye after 4 months of somatostatin-analogue therapy. The thickness of the central macula is clearly decreased.*

two FAs after start of the treatment). Figure 2 is representative for the seven good reacting eyes. Note that the right eye of Patient III shows macular edema on the pretreatment FA but has a visual acuity of logMAR 0. The BCVA was stabilized in all study eyes except for the right eye of Individual I; the macular edema in this eye increased on FA (in contrary to the left eye which gained visual acuity with improvement of the edema). The left eye of Patient IV gained visual acuity in the first month, but lost most of the gain in the subsequent 11 months; this initial gain and subsequent deterioration were synchronous with the macular edema on the 4- and 12-month follow-up FAs.

OCT was performed in one patient (Patient I) before treatment and 1 month after treatment. There was a substantial remission of the intraretinal fluid seen on OCT (Fig. 3). One patient had an episode of diarrhea after long-acting octreotide acetate treatment.

DISCUSSION

DCMD is a progressive disease that develops from distinct CME in the early stage to a more diffuse edema of the posterior pole. The end stage of the condition is characterized by extensive chorioretinal atrophy with poor visual acuity. No effective therapy has been reported so far. In this study long-acting octreotide acetate has been used as an original treatment in four patients with early stages of DCMD. BCVA could be stabilized and the angiographically visible edema was (partially) reduced in all eyes except one and there was a synchronous correlation between FA effect and BCVA changes. There was a substantial remission of the intraretinal fluid seen on the OCTs that were performed. The remission of the CME was even more pronounced on OCT than on the FA that was obtained on the same day.

One study eye did not react on the treatment whereas the other eye of the same patient did react. We cannot postulate a plausible explanation for the difference in reaction between the two eyes. A minor side effect of somatostatin-analogues occurred in one patient (13).

The follow-up period in this study is relatively short, since the disease may progress slowly in selected patients. To define more clearly if the results are induced by the treatment and not the result of the normal changing disease course a longer follow-up is suggested, also in order to define whether the treatment effect may only be transient, what the influence is of the age of the patient, and what the influence is of the duration of the disease at the start of the treatment. After the study Patients I, II, and III continued using the octreotide acetate treatment on their own request for more than 2.5 years until submission of this article and their BCVA did not decrease since the end of the follow-up. Patient 4 discontinued the medication after the follow-up period of 12 months and has changing BC-

VAs since then, but on average lost 0.1 logMAR in the 3.5 years since the end of the study.

The best duration of treatment is not known, but when the therapy is discontinued, it should possibly be tapered down slowly, since the patient who quit the therapy had a BCVA decrease of 0.1 logMAR on the first control at 4 months after the study.

In conclusion, based on angiographic improvement and stabilization of BCVA in the studied patients, the results suggest that octreotide acetate may be beneficial as treatment in the early stages of DCMD.

The authors have no proprietary or financial interest. No grants or funds were received in support of the study.

Reprint requests to:
Barend Hogewind, MD
Department of Ophthalmology
University Medical Centre St Radboud
Philips van Leydenlaan 15
Nijmegen, Gelderland
The Netherlands
b.hogewind@ohk.umcn.nl

REFERENCES

1. Deutman AF, Pinckers AJ, Aan de Kerk AL. Dominantly inherited cystoid macular edema. Am J Ophthalmol 1976; 82: 540-8.
2. Kremer H, Pinckers AJ, van den Helm B, Deutman AF, Ropers HH, Mariman EC. Localization of the gene for dominant cystoid macular dystrophy on chromosome 7p. Hum Mol Genet 1994; 3: 299-302.
3. Pinckers A, Marre M. Basic phenomena in acquired colour vision deficiency. Doc Ophthalmol 1983; 55: 251-71.
4. Scorolli L, Morara M, Meduri A, et al. Treatment of cystoid macular edema in retinitis pigmentosa with intravitreal triamcinolone. Arch Ophthalmol 2007; 125: 759-64.
5. van Hagen PM, Baarsma GS, Mooy CM, et al. Somatostatin and somatostatin receptors in retinal diseases. Eur J Endocrinol 2000; 143: S43-51.
6. Funatsu H, Yamashita H, Ikeda T, Mimura T, Eguchi S, Hori S. Vitreous levels of interleukin-6 and vascular endothelial growth factor are related to diabetic macular edema. Ophthalmology 2003; 110: 1690-6.
7. Tranos PG, Wickremasinghe SS, Stangos NT, Topouzis F, Tsinopoulos I, Pavesio CE. Macular edema. Surv Ophthalmol 2004; 49: 470-90.
8. Kuijpers RW, Baarsma S, van Hagen PM. Treatment of cystoid macular edema with octreotide. N Engl J Med 1998; 338: 624-6.
9. Chantelau E, Frystyk J. Progression of diabetic retinopathy during improved metabolic control may be treated with reduced insulin dosage and/or somatostatin analogue administration—a case report. Growth Horm IGF Res 2005; 15: 130-5.
10. Kafkala C, Choi JY, Choopong P, Foster CS. Octreotide as a treatment for uveitic cystoid macular edema. ARVO 2005 abstract. Invest Ophthalmol Vis Sci 46: abstract 2850.
11. van Velthoven M, Verbraak F, Boxer A, Pedro J, de Smet M. Volumetric and topographic measurement in patients with cystoid macular edema using a combined SLO-OCT ophthalmoscope. ARVO 2003 abstract. Invest Ophthalmol Vis Sci 44: abstract 3623.
12. Shah SM, Haller JA, Campochiaro PA, Polito A, Nguyen QD, Vitale S. A randomised, prospective, controlled clinical trial of sandostatin LAR depot in patients with cystoid macular edema. ARVO 2003 abstract. Invest Ophthalmol Vis Sci 43: abstract 4310.
13. Missotten T, Baarsma GS, Kuijpers RW, et al. Somatostatin-related therapeutics in ophthalmology: a review. J Endocrinol Invest 2005; 28: 118-26.
14. Grant MB, Caballero S Jr. The potential role of octreotide in the treatment of diabetic retinopathy. Treat Endocrinol 2005; 4: 199-203.
15. Katz MD, Erstad BL. Octreotide, a new somatostatin analogue. Clin Pharm 1989; 8: 255-73.
16. Maminishkis A, Jalickee S, Miller SS. Somatostatin (SST14) enhances retinal reattachment of experimentally produced subretinal space (SRS) blebs in vivo. ARVO 2002 abstract. Invest Ophthalmol Vis Sci 43: abstract 4541.