European **Rev**iew for **Med**ical and **Pharmacol**ogical **Sci**ences 2002; 6: 1-8

Deflazacort treatment of cystoid macular edema in patients affected by Retinitis Pigmentosa: a pilot study

C. GIUSTI, R. FORTE, E.M. VINGOLO

Institute of Ophthalmology, "La Sapienza" University – Rome (Italy)

Abstract. – ***Background.*** **To investigate the efficacy of a long-term treatment with Deflazacort (DFZ), a third generation synthetic glucocorticoid, in patients affected by Retinitis Pigmentosa (RP) complicated by Cystoid Macular Edema (CME).**

Methods. **A randomized group of 10 RP subjects were selected for this pilot study and treated with DFZ for one year according to a standard protocol. Far and near Best Corrected Visual Acuity (BCVA), fluorescein angiography (Heidelberg Retina Angiograph) and computerized perimetry (Humphrey Visual Field Analyzer) were statistically assessed.**

Results. **Near visual acuities, fluorescein angiographic findings and perimetric data improved significantly ($p < 0.01$) while far BCVA varied only slightly ($p < 0.05$). No ocular or systemic side effects were recorded.**

Conclusions. **Further case-control studies, also involving a larger number of patients, are required to confirm these preliminary results. However, the present investigation seem to suggest that DFZ could be effective in reducing fluorescein angiographic findings and improving perimetric data and near visual acuities in RP patients, even though the pathogenesis of CME remains poorly understood.**

Key Words:

Cystoid macular edema, Deflazacort, Heidelberg retina angiograph, Humphrey visual field analyzer, retina, Retinitis Pigmentosa.

Introduction

Retinitis Pigmentosa (RP) is one of the most common forms of hereditary retinal degeneration, occurring in about 1 in 5.000 individuals worldwide[1,2]. Patients affected by the typical form of RP often complain of faulty adaptation to light or darkness, photophobia, nightblindness as well as peripheral and midperipheral field defects; central vision is usually preserved in the early stages of the disease. The symptoms tend to appear at about 20 years of age but can occur later or even earlier, depending on the genetic defect and/or the pedigree. As the disease progresses, not only visual filed narrows but also central vision deteriorates, mainly due to the onset of posterior subcapsular cataract and Cystoid Macular Edema (CME). In particular, the persistence of CME over prolonged periods of time may lead to a legal blindness due to chronic foveal cysts, Retinal Pigment Epithelium (RPE) atrophy and lamellar macular holes[1,2].

Carbonic anhydrase inhibitors have been found to be helpful in reducing CME and improving visual acuity in RP patients[3,4]. Although a rebound of macular edema with a prolonged use of methazolamide has been observed[5], acetazolamide and methazolamide, orally taken, are the only drugs that have a proven beneficial effect at this time. On the contrary, no measurable improvement in visual acuity was observed with the topical use of dorzolamide hydrochloride[6].

Given the main role played by autoimmunity and apoptosis in RP, already postulated by several studies[7-10], we decided some years ago to test the efficacy of Deflazacort (DFZ) as a novel therapy of macular edema in RP patients[11]. This drug, an oxazolinic derivative of prednisolone with fewer side effects and a prolonged immunomodulating and anti-inflammatory activity, has already been used, with excellent results, in the treatment of chronic affections characterized by an impairment of the immune system: e.g., Duchenne muscular dystrophy[12], renal transplantation in childhood[13], autoimmune hepatitis[14].

However, despite the positive clinical effects on CME that we found in our first preclinical trial[11], no other studies are, to our knowledge, available in the ophthalmic literature at this time. It was therefore the purpose of this paper to present the final results of a one-year DFZ treatment of macular edema in patients affected by RP.

Subjects and Methods

10 RP subjects (4 M and 6 F; mean age: 42.7 ± 12.6 years) were randomly selected from our patient population in order to avoid interference by selection bias and, thereafter, studied during a one-year period.

The diagnosis of RP was based on the clinical, genetic and instrumental criteria established some years ago by Marmor et al.[15]. Only patients whose inheritance pattern was clearly identified were selected for this study: autosomal dominant, autosomal recessive or X-linked forms were considered. In all patients, electroretinographic and clinical data were consistent with a typical rod-cone degenerative disorder (inclusion criteria). Patients who showed a definite cone-rod pattern or were affected by RP syndromic forms (i.e., Usher or Laurence-Moon-Bardet-Biedl) were not included in this study (exclusion criteria). Other therapies in progress (e.g. systemic corticosteroids, thiazide diuretics, digitalis, nonsteroidal anti-inflammatory agents, anticoagulants) as well as age-related macular degeneration, diabetes, amblyopia, smoking (> 10 cigarettes daily), pregnancy, cataract, aphakia or pseudophakia, intraocular pressure > 22 mmHg, refractive error > ± 4 D, history of vitreoretinal surgery, previous retinal occlusive disorders or other systemic diseases (e.g., tyroid pathologies; cancer; vasculitis; obliterating peripheral arteriopathies) were also exclusion criteria.

All necessary ethical approvals were obtained by the University Commitee and the study itself was conducted in compliance with the Declaration of Helsinki. The drugs used for this pilot study were supplied by the University of Rome "La Sapienza" (Azienda Policlinico "Umberto I") and were prescribed in accordance with the manufacturer's instructions. Regarding to this matter, the authors wish to clarify that they had no financial interests in this research.

Before starting the therapeutic protocol, all patients were fully informed about DFZ's risks and benefits and, thereafter, undersigned their consent. The chance to stop therapy was guaranteed to any subject at any time. After a baseline examination (T0), repeated thereafter at every modification of therapy, patients were orally treated with DFZ (FLANTADIN® – Gruppo Lepetit SpA, Lainate (MI), Italy) for one year as follows: 30 mg/die for a week (T1); 15 mg/die for two weeks (T2); 6 mg/die for one month (T3); 6 mg every other day for two months (T4); 6 mg/die every three days for four months (T5); 6 mg/die every three days for four more months (T6). This schedule was assessed some years ago in a preclinical trial in which the better treatment interval, in order to avoid both DFZ's adverse effects and decrease in retinal activity due to long-term suspension of therapy, was assessed[11].

Far and near best corrected visual acuity (BCVA), Amsler grid test, color vision testing (Ishihara pseudoisochromatic plates) and retinal biomicroscopy, using high positive power precorneal lenses (Super Field and +78D Volk Lenses), were performed at baseline (T0) and before any modification of therapy was made (T1 → T6). As previously done by Fishman et al.[3-5], the Early Treatment Diabetic Retinopathy Study (ETDRS) chart was used for assessing far BCVA whereas near BCVA was measured by means of a special chart following ICAO (International Civil Aviation Organization) recommendations. Fluorescein angiography (Heidelberg Retina Angiograph) and computerized perimetry (Humphrey Visual Field Analyzer, 10-2 threshold program), on the contrary, were performed at baseline (T0) and, thereafter, every four months only. In order to determine the correct area of CME to be graded, we decided to follow the ETDRS classification of clinically significant macular edema[16]: therefore, the area considered was that within one disc diameter (DD) from the center of the fovea, i.e., within a circle two DD in diameter concentric with the macula. Inside this area, all angiograms were graded by one examiner only (E.M.V.) according to the previously published Fishman's classification of

macular edema in RP[3]. Any leakage from radial peripapillary vessels seen along the temporal vascular arcades was not included in the grading.

At all visits, subjects were also asked if there was any subjective difference in vision between their current visual acuity and that at baseline and/or that at the previous visit. The response was graded as a large, moderate or small improvement; no change; worse; unsure.

Data were expressed as mean ± standard deviation (SD) and statistically analyzed by means of Student *t* test (Apple Macintosh, StatView II program). Statistical significance was expressed in terms of *p* values at 0.01 or less.

Results

Far BCVA varied only slightly ($p < 0.05$) (Figure 1) while near visual acuity improved significantly during the whole follow-up period, even though DFZ showed a greater efficacy during the first three weeks of treatment ($p < 0.01$) (Figure 2). Amsler grid test demonstrated insufficient sensibility in detecting variations of CME, resulting statistically insignificant in this study ($p > 0.05$). Despite the clinically evident improvement of near vision, a slight degree of metamorphopsia and color vision impairement persisted in many subjects. A small subjective improvement from baseline examination was reported by most patients after the first three weeks of treatment only.

A remarkable angiographic reduction of macular edema (Figures 3-5) was observed during the study, even though a full and long lasting resorption of CME was not obtained (Figures 4-5). These data were more evident after the first four months of treatment, when all patients showed a significant reduction of fluorescein leakage compared to the baseline angiograms (Figure 3). Thereafter, as already reported in RP patients during methazolamide therapy[5], a slight rebound of macular edema was observed and persisted during the whole follow-up period. Nevertheless, at the end of the study, a reduction of fluorescein leakage, compared to the baseline angiograms, was still present in about 47% of subjects (Figure 3).

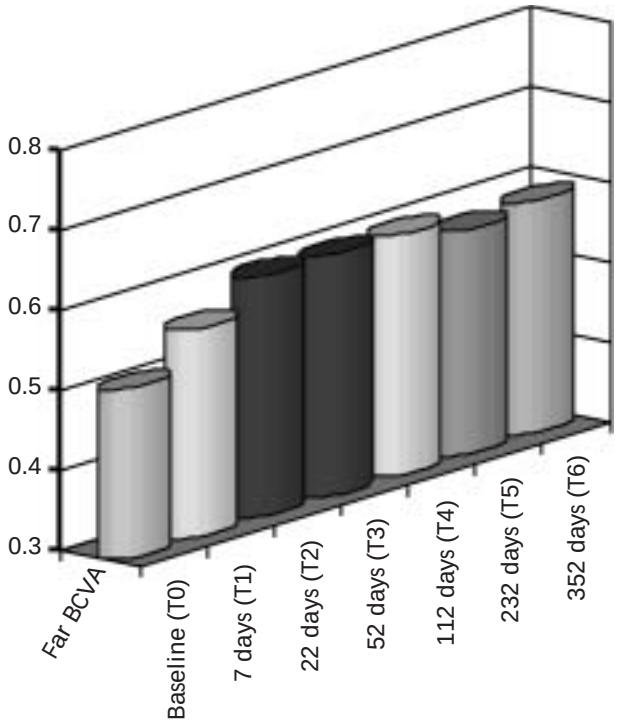

Figure 1. Modification of far best corrected visual acuity (BCVA) during the study (decimal values; *n* = mean).

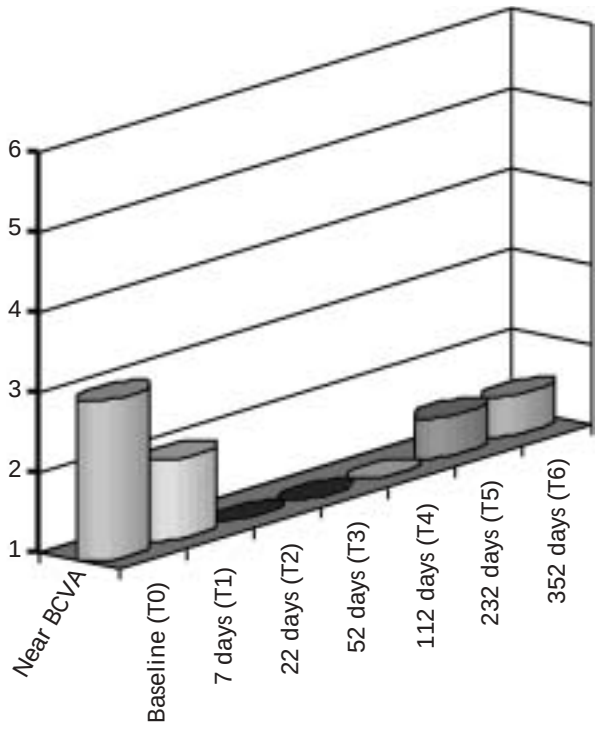

Figure 2. Modification of near best corrected visual acuity (BCVA) during the study (size print, being N1 the smallest and N6 the largest one; *n* = mean).

A marked perimetric increase of the retinal central sensitivity (10° around the fixation point) was found ($p < 0.01$) (Figure 6). In particular, it was characterized not only by a higher mean retinal sensitivity and a lower mean defect (compared to the baseline examinations), but also by a parallel reduction of the short fluctuation value, an important parameter that indicates a reduced and more stable defect after treatment. Similarly to what observed on fluorescein angiograms, also the improvement of perimetric data was particularly evident after the first four months of therapy, corresponding to the increase in far and near visual acuity. All patients were fully trained in computerized visual field testing and, therefore, the potential beneficial effect due to the so called "learning effect" is meaningless.

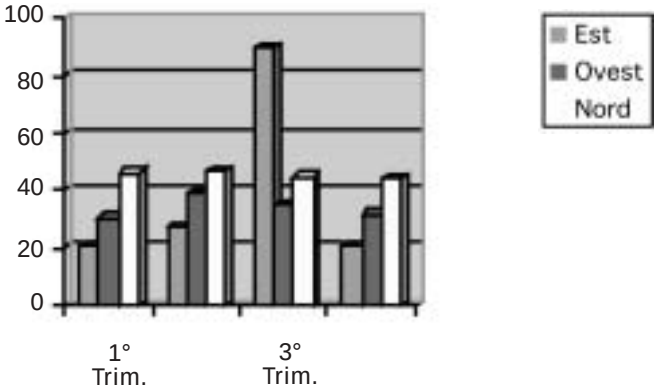

Figure 3. Modification of fluorescein leakage (FL) during the study compared to the baseline examination (percentages of patients).

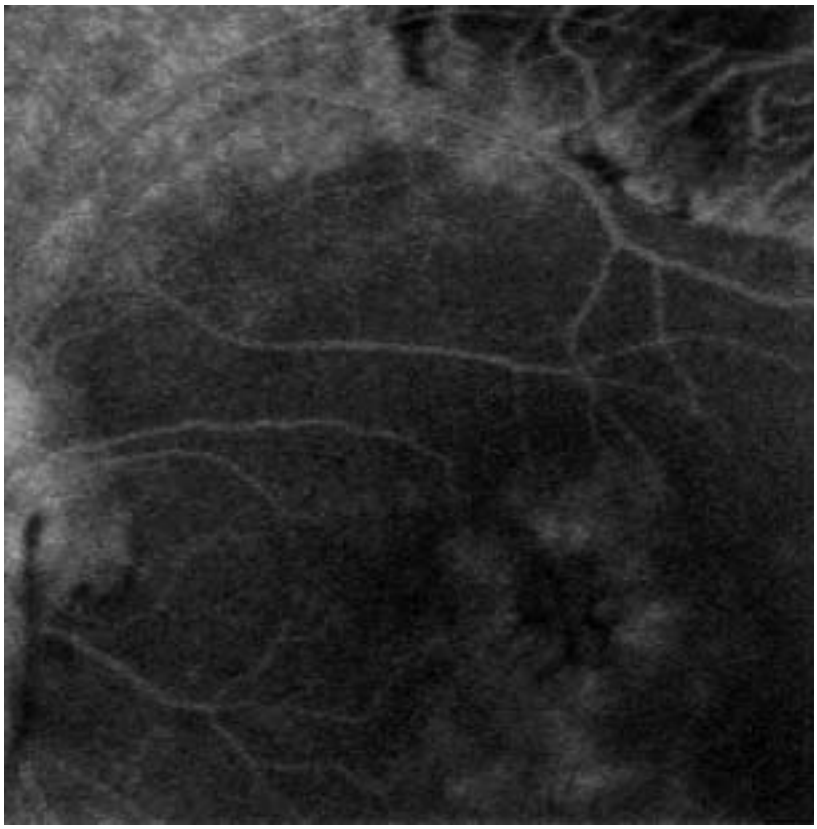

Figure 4. Case report: angiographic findings at baseline (T0) (late phase).

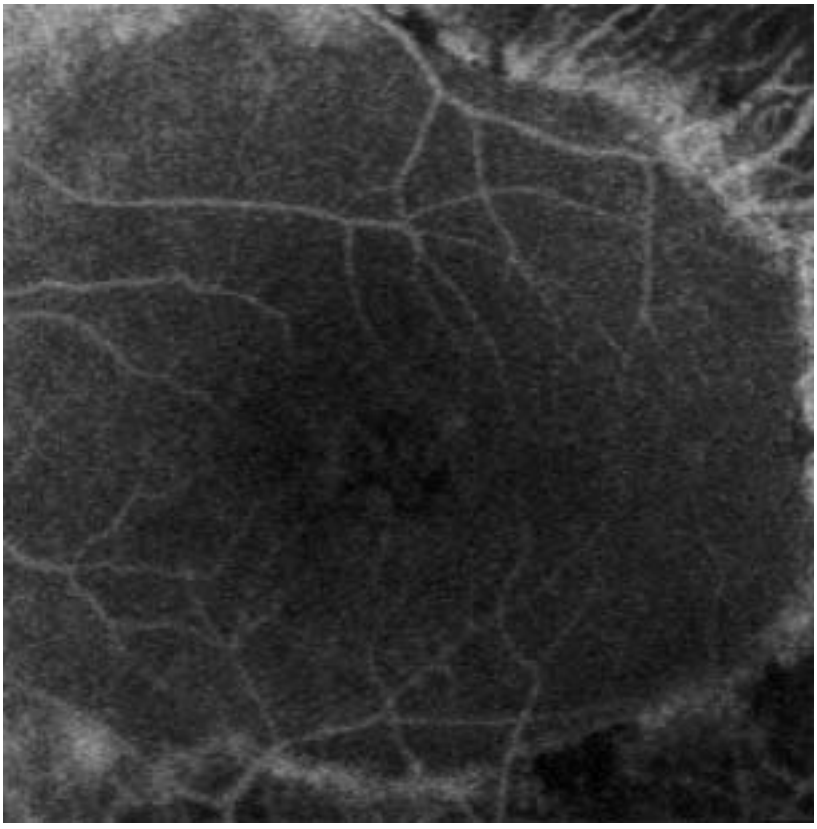

Figure 5. Case report: angiographic findings after therapy (T6) (late phase).

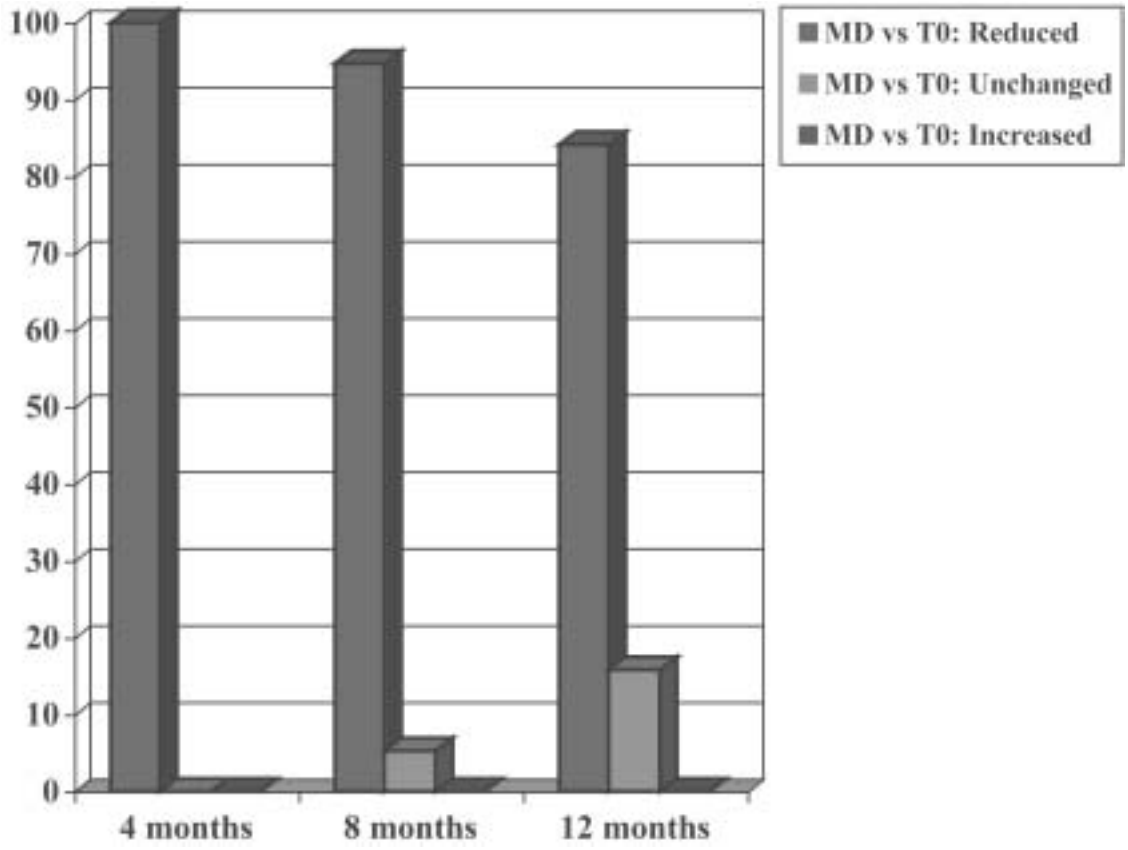

Figure 6. Modification of the visual field parameter "mean defect" (MD) during the study compared to the baseline examination (percentages of patients).

Regarding to the response to therapy, no ocular or systemic side effects were recorded and the patient compliance was good during the whole study.

Discussion

Despite the remarkable clinical impact on visual function of this frequent complication of RP (about 10%-15% of cases according to Gass[17] and Fishman[4] respectively), the exact pathogenesis of CME is still poorly understood.

There should be no doubts that a main role is probably played by a specific loss of the perifoveal capillary vascular integrity with the consequent pooling of fluid into the foveal region[1]. At the same time, however, a disruption of the constant transport of fluid outward from the retina to the choroid through a damaged RPE could also lead to a lack of the normal relative deturgescence of the outer retinal extracellular space and, consequently, to the characteristic "honeycombed" biomicroscopic appearance and the "flower-petal" angiographic pattern of the foveal retina (Figure 7)[2]. In fact, Gass already reported several years ago that the extravascular staining observed in the degenerative areas of the retina seemed to originate both from the retinal perifoveal vessels (inner retina) and the RPE-photoreceptor complex (outer retina)[17]. Moreover, as already hypothesized in the pathogenesis of diabetic maculopathy[18], the vitreous should also play some unknown role in determining CME, as vitreal alterations are a common feature in RP subjects[7].

At present, still exists a genuine controversy regarding the precise location of the tissues from which the cystic spaces arise in CME. The "intracellular" theory holds that the cysts develop from edematous Müller cells, whereas the "extracellular" theory, accepted by most Authors, proposes that the

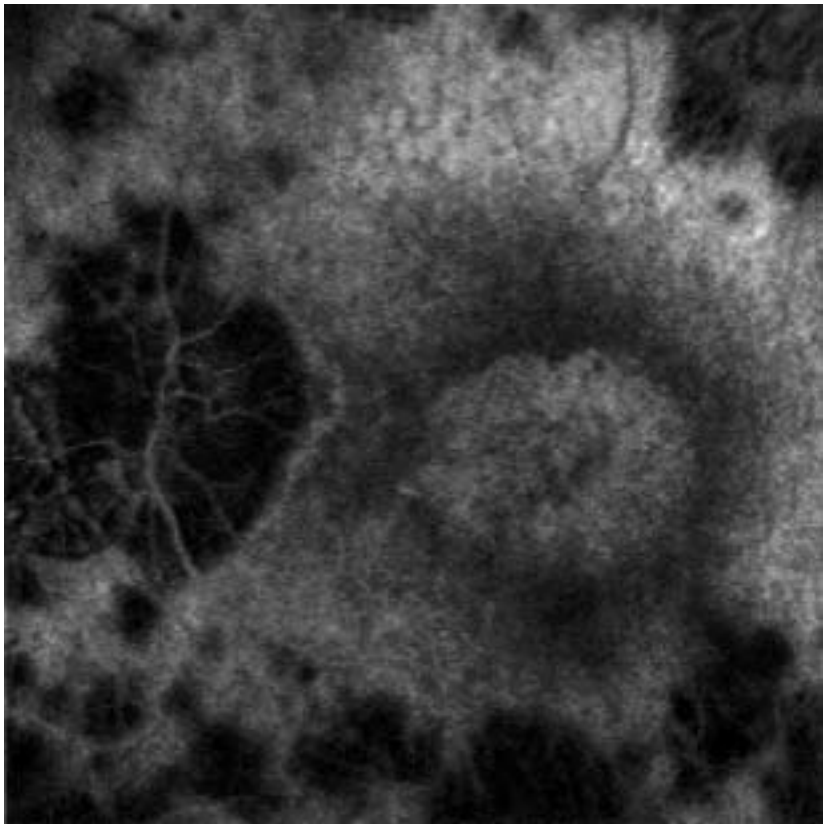

Figure 7. A typical example of cystoid macular edema in retinitis pigmentosa with the characteristic "flower-petal" angiographic pattern of the foveal retina.

cysts originate from spaces within the outer plexiform and inner nuclear layers of the macula[2].

The potential implication of autoimmunity and apoptosis in RP, in determining the immune-related RPE alterations and the correlated photoreceptor death, has already been postulated by several studies[7-10]. Given these experimental data as well as the reported DFZ therapeutical effects on RPE and blood cells (reduced expression of interleukin (IL) receptor and HLA-DR antigen by RPE; reduced chemoattractants plasma levels; increased monocyte-mediated expression of cytokines, IL, growth factors and activin by RPE; inhibited HLA class II antigen expression by activated T-cells and macrophages; inhibited antibody-dependent cellular cytotoxicity and natural killer activity; inhibited proliferation and response of T and B lymphocytes)[11-14], the novel therapy of CME proposed in this paper could successfully interfer, in theory, with the RP natural history, slowing the degenerative progress itself and improving the clinical impact of CME on visual function.

Observations from this pilot study seem to suggest that DFZ could be effective in the treatment of macular edema in RP patients, being able to determine a significant reduction of fluorescein leakage and an improvement of both perimetric data and near visual acuities compared to the baseline examinations. According to us, these positive clinical findings could not only be explained by an effective removal of the retinal edema across the RPE but also by a partially restored integrity of the RPE-photoreceptor complex itself that allows a better macular function.

In summary, our investigation may not be considered conclusive, because of the small number of patients involved, the open design with absence of a control group and the relatively short follow-up, but only as a personal contribution for finding a valid medical ap-

proach to CME. However, even though further studies are required to determine the exact mechanism of action of DFZ in RP subjects, these preliminary results seem to suggest that this drug could be useful in the treatment of these patients, even though the pathogenesis of CME remains poorly understood.

References

1) *Albert DM, Jakobiec FA.* Principles and practice of ophthalmology. Philadelphia: Saunders, 1994

2) *Federman JL, Gouras P, Schubert H, Slusher MM, Vrabec TR.* Retina and vitreous. Textbook of Ophthalmology, Vol. 9. London: Mosby, 1994

3) *Fishman GA, Gilbert LD, Fiscella RG, Kimura AE, Jampol LM*. Acetazolamide for treatment of chronic macular edema in Retinitis Pigmentosa. Arch Ophthalmol 1989; 107: 1445-1452.

4) *Fishman GA, Gilbert LD, Anderson RJ, Marmor MF, Weleberg RG, Viana MA*. Effect of methazolamide on chronic macular edema in patients with Retinitis Pigmentosa. Ophthalmology 1994; 101: 687-693.

5) *Fishman GA, Glenn AM, Gilbert LD.* Rebound of macular edema with continued use of methazolamide in patients with Retinitis Pigmentosa. Arch Ophthalmol 1993; 111: 1640-1646.

6) *Grover S, Fishman GA, Fiscella RG, Adelman AE.* Efficacy of dorzolamide hydrochloride in the management of chronic cystoid macular edema in patients with Retinitis Pigmentosa. Retina 1997; 17: 222-231.

7) *Vingolo EM, Giusti C, Forte R, Onori P.* Vitreal alterations in Retinitis Pigmentosa: biomicroscopic appearance and statistical evaluation. Ophthalmologica 1996; 210: 104-107.

8) *Portera-Cailliau C, Sung CH, Nathans J, Adler R.* Apoptosis photoreceptor cell death in mouse models of Retinitis Pigmentosa. Proc Natl Acad USA 1994; 91: 974-978.

9) *Dryja TP, Berson EL*. Retinitis Pigmentosa: the Friedenwald Lecture. Invest Ophthalmol Vis Sci 1995; 36: 1197-1200.

10) *Adler R.* Mechanisms of photoreceptor death in retinal degenerations. Arch Ophthalmol 1996; 114: 79-83.

11) *Forte R, Iacobelli L, Grenga P, Volante V, Vingolo EM*. Cystoid macular edema in Retinitis Pigmentosa: treatment with Deflazacort. Clinical and functional investigations [ARVO Abstract]. Invest Ophthalmol Vis Sci 1998; 39(4): S969. Abstract nr 4477.

12) *Biggar WD, Gingras M, Fehlings DL, Harris VA, Steele CA*. Deflazacort treatment of Duchenne muscular dystrophy. J Pediatr 2001; 138: 45-50.

13) *Ferraris JR, Pasqualini T, Legal S, et al.* Effect of Deflazacort versus methylprednisone on growth, body composition, lipid profile and bone mass after renal transplantation. The Deflazacort Study Group. Pediatr Nephrol 2000; 14: 682-688.

14) *Rebollo Bernardez J, Cifuentes Mimoso C, Pinar Moreno A, et al*. Deflazacort for long-term maintenance of remission in type 1 autoimmune hepatitis. Rev Esp Enferm Dig 1999; 91: 630-638.

15) *Marmor MF, Aguirre G, Arden G, Berson EL.* Retinitis Pigmentosa symposium on terminology and methods of examination. Ophthalmology 1983; 90: 126-131.

16) *Diabetic Retinopathy Study Research Group.* Report 7. A modification of the Airlie House classification of diabetic retinopathy. Invest Ophthalmol Vis Sci 1981; 21: 210-226.

17) *Gass JDM.* Stereoscopic atlas of macular diseases. Diagnosis and treatment. St. Louis: C.V. Mosby Company, 1987

18) *Nasrallah FP, Jalkh AE, Van Coppenolle F*. The role of the vitreous in diabetic macular edema. Ophthalmology 1988; 95: 1335-1339.