Treatment chronic macular edema in Vogt-Koyanagi Harada syndrome with dexamethasone intravitreal implant: Description of Three Case

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Abstract

Purpose: To report our experience with dexamethasone intravitreal implant (Ozurdex, DEX implant) in the chronic cystic macular edema (ME)with Vogt-Koyanagi-Harada (VKH) Syndrome.
Method: A retrospective chart review of three patients with (VKH) treated with sustained-release dexamethasone 0.7 mg intravitreal implant was performed.Complete ophthalmic examination included: best corrected visual acuity; ocular tonometry, were also evaluated signs of inflammatory activity of the anterior segment with biomicroscopy slit-lamp, and posterior segment with fundus biomiocrosopy, fundus photography and fluorescein angiography; measurement of macular morphology and thickness, optical with coherence tomography; and tolerability of the implant. Mean follow-up time post-injection was 6 months. All three eyes received 1Ozurdex implants during the follow-up period. The duration of effect of the implant was 4 to 6 months. No serious ocular or systemic adverse events were noted during the follow-up period.
Results: In all three eyes, were observed a remarkable decrease ME, in angiographic and OCT , following placement intravitreal DEX implant
Conclusions: The DEX implant 0.7 mg may be an effective treatment option for reduction ME in VGT, met the primary efficacy endpoint for improvement in visual acuity (VA) and safety profile was also acceptable

Keywords: *Corticosteroids; dexamethasone implant; macular edema; Vogt-Koyanagi-Harada (VKH); visual acuity (VA).*

Introduction

VKH is often associated with neurological and dermatological manifestations and affects organs containing melanocytes, whose etiology is still uncertain [1]. It would appear that a viral antigen is involved, against which, in individuals with certain predisposing haplotypes, it would cause an autoimmune reaction [2]. The inflammatory reaction is directed against a stromal protein present in the melanocytes and against neuronal elements. The disease affects both eyes, although asymmetrically, and it has a progressive evolution. The symptomatology consists of: reduction of visual acuity, visual field reduction, metamorphopsia, floaters, alteration in color vision. In the acute phase, but more frequently in the convalescent phase and in the chronic phase [3].

It observed an involvement inflammatory of the anterior segment characterized by uveitis that cause redness, pain and further AV reduction [4].

Clinically it is possible to identify four stages of the disease: 1 prodromal: (3–5 days maximum) characterized by headaches, dizziness and nausea accompanied by a flu-like syndrome2 Acute exudative uveitis : appears with auditory and meningeal symptoms and can occur acutely

with severe iridocyclitis and ear involvement [5]. The acute exudative uveitis shows corneal precipitates in ram fat, cells and flare in the aqueous humor, irises nodules and synechiae. The severe manifestations charged to the posterior segment are: vitritis, edema and hyperemia of the optic disc, macular edema, chorioretinal scars, bleeding and choroiditis with exudative retinal detachment chronic: it may occur an increase of pigmentation or an albinotic depigmentation in those areas prior serous detachment, or even a fibrotic subretinal organization (typical appearance as "sunset flash") [3].

chronic with relapses: can be observed further complications such as cataracts, glaucoma, neovascularization and subretinal fibrosis. Relapses occur in 60% of cases in the first four years and involve mainly the anterior segment. The long-term prognosis is unfavorable, as there is a final loss of central vision through the direct

involvement retinal detachement and/or the maculopathy [2]. Daily administration of sistemical steroids, if established prematurely, can delay the progression of the disease [3].

Since some of the complications that are often connected with this disease, and which are able to further compromise the patient's vision, are susceptible to treatment, it is good to subject patients to regular follow-up with the aim of identifying any complications to treat them early.

The complications that manifest themselves most frequently include the cataract e glaucoma, (common in all forms of VKH ; these are treatable) and the more serious maculopathy, ME, subretinal neovascularization.

The latter may appear in atrophic form (cellophane maculopathy), or they may cause cystic macular edema, leading to the increased permeability of the perifoveal capillary network. For the latter form, good results can be obtained through systemic administration of steroids [6]

The steroids represent so far the first choice about the uveo-encephalitis therapy and it need to be set as soon as possible and in the long term [4]. Nevertheless its effectiveness is still controversial. ME is often refractory to oral administration, intravenous and / or topical steroid therapy [6].

Unfortunately, corticosteroid may notoriously lead to the onset of severe side effects [5]. That is the reason why the frequent and important side effects of corticosteroid do not allow it to be administered for a prolonged period of time [6]. For this reason, it is necessary to find an alternative therapy that can be administered to these patients to prevent their visual acuity impairment, even before panuveitis, has run its course. Currently it seems that intravitreal injections of corticosteroids have shown to be effective in the treatment of chronic and relapsing forms of VKH [7].

For this reason, we describe three case reports of patients treated with dexamethasone intravitreal implant, to date, has not shown any systemic secondary effects. In accordance with literature [5] we defined the primary endpoint improvement BCVA and the secondary endpoint, significant improvement in the degree of ME, which was determined by measuring changes in the central foveal thickness and the foveal zone thickness on optical coherence tomography (OCT).

Materials and Methods

In this study, we report three cases of patients with VKH, successfully treated of DEX implant 0.7 mg (Ozurdex(®); Allergan, Inc, Irvine, CA) intravitreal [5]. This study was conducted in compliance with the Ethics Committee of the Department of Organs Senses of the University of Rome "Sapienza" , all patients provided written, informed consent. A systemic work-up included laboratory and radiographic imaging for infectious and noninfectious etiologies. Before initiating treatment, a baseline OCT scan was obtained on each patient with a Spectralis HRA-OCT produced by Heidelberg Engineering GmbH (Heidelberg, Germany) with a volumetric 512 × 49 scan for the measurement of macular thickness and morphology. The evaluation of vision was carried out pretherapy at baseline T0; best corrected VA was assessed using Early Treatment Diabetic Retinopathy Study (ETDRS) [8] tables placed at a distance of 4 meters, by slit-lamp biomicroscopy, ocular tonometry (using a Goldmann applanation tonometer), fundus biomiocroscopy, color fundus photography and fluorescein angiography. None of the patients in our study had additional ocular conditions or were on other medications that could potentially affect their visual acuity and/or retinal function. At subsequent follow-up visits, OCT images for all three patients were obtained. A central foveal thickness was calculated as an average of the measurements obtained. A change of more than 16% in foveal thickness and more than 11% in foveal zone thickness were considered significant. We compared all subsequent retinal thicknesses. It was performed fluorescein angiography (FA) and indocyanine green angiography (IGA) in order to highlight multiple sites of diffusion from the choroid into the subretinal space. After the first follow-up visit, each patient was seen several times (follow-up visits ranged from 2–6 months from the previous visit) to monitor the patient's response to treatment. At each visit, a repeat OCT measurement was obtained.

Results

Case 1.

A 52-year-old woman suffering from VKH disease, demonstrated microcystic macular edema on OCT, with a visual acuity of 4/10 in right eye (RE) and of 9/10 in left

eye (LE). She had a negative anamnesis of extraocular manifestations. The ocular anamnesis was negative for traumas, surgery and other diseases.

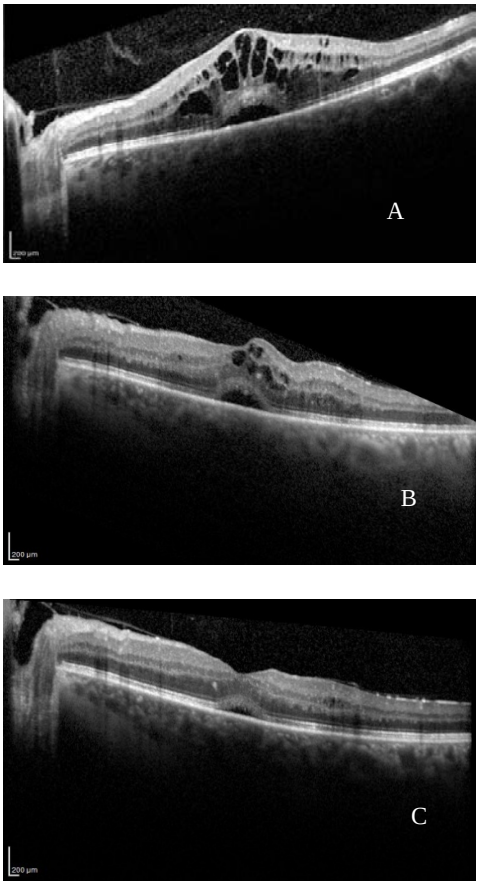

Figure 1. A) Baseline optical coherence tomography (OCT) RE (Right eye) with cystoids macular edema (CME). B) RE after 2 week following the 0.7 mg DEX implant intravitreal, OCT revealed a drastic reduction in CME. C) 6 months following implant placement OCT RE showed no recurrence of CME.

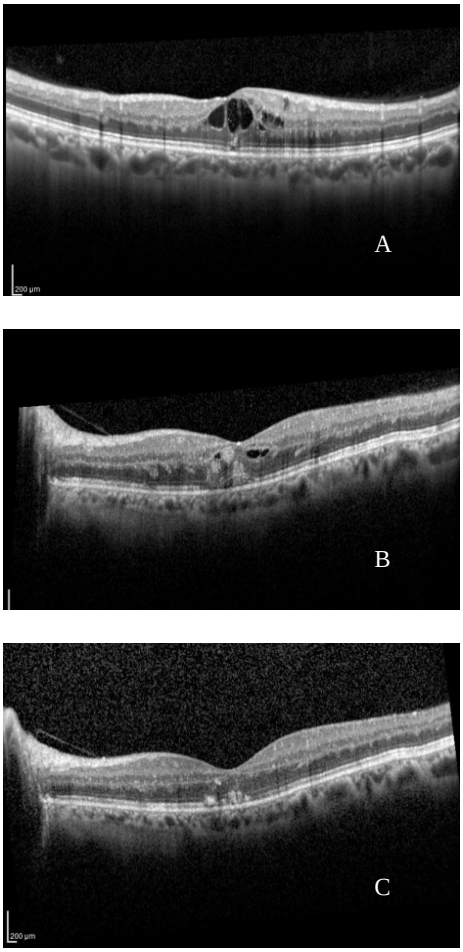

Figure 2. A) Baseline optical coherence tomography (OCT) LE (Left eye) with cystoids macular edema (CME).
B) LE after 2 week following the 0.7 mg DEX implant intravitreal, OCT revealed a drastic reduction in CME. C) 6 months following implant placement OCT LE showed no recurrence of CME.

She had a VA of 4/10 (29/65 ETDRS letters) in the RE and 9/10 (62/65 ETDRS letters) in the LE. There were no evident signs of anterior segment inflammation. The fundus oculi examination showed bilateral exudative retinal detachment and ME.

The OCT examination showed the presence of intra- and subretinal fluid in both eyes. (See figure)

The FA examination showed multiple leakage points and pooling areas. A 3-days intravenous methylprednisolone therapy (500 mg / day) was set; after that, improvements in visual acuity and retinal edema reduction occurred in both eyes. Subsequently, by switching from intravenous to oral therapy with prednisone (1 mg / kg for 4 weeks), a morpho-functional worsening occurred in both eyes.

Therefore , in order to keep the edema under control, a DEX was set up in the RE with worse BCVA. In further checkups, a progressive improvement in visual acuity and a tendential retinal edema reduction were observed; this led to a reduction and a subsequent suspension of the oral therapy.

During the follow-up, after six months from the injection, it was observed that the VA was corrected to 10/10 (65/65 ETDRS letters) in RE e 9/10 (62/65 lettere ETDRS) in LE and that there was absence of intra- and sub-retinal fluid on OCT examination (CMT RE 276 µm, CMT LE 355 micron). Furthermore, there weren't increases in intraocular pressure (IOP) (Fig.1).

Case 2.

A 35-year-old woman suffering from VKH presented with ME both eyes, as documented upon OCT, with a VA of 5/10 in RE and 3/10 in LE.

The medical history was positive for an episode of bilateral anterior uveitis about 6 months before successfully treated with topical dexamethasone 0.2% (LUXAZONE ®). The initial BCVA resulted of 3/10

(25/65 ETDRS letters) in RE and 5/10 (47/65 ETDRS letters) in LE. At the time of our assessment there were no signs of inflammation of the anterior segment. The ophthalmoscope examination of fundus highlighted a macular edema, more evident in RE.

The OCT examination confirmed the presence of cystoid macular edema (CME) (RE: CMT 455 µm, LE: 311 µm CMT). FA showed many leakage points and pooling areas. Therapy with oral prednisone (1 mg / kg for 4 weeks) does not show substantial improvement in terms nor morphological (evalued by OCT) nor functional.

It was therefore decided to make an intravitreal of DEX implant in the RE.

After 6 months the patient showed considerable edema reduction in RE; her VA increased to 8/10 (8/10; 55/65 lettere ETDRS) compared to the contralateral (5/10; 45/65 lettere ETDRS) with considerable reduction of macular thickness observed with OCT (RE: CMT 291 µm, LE: CMT 312 µm) (Fig. 2).

Case 3.

A 48-year-old woman suffering from VKH presented with ME in both eyes, as documented by OCT at the beginning, at the first examination, she presented chronic anterior bilateral granulomatous uveitis, emerged two years before and then remained quiescent throughout the period. Had a VA of 4/10 in OD (34/65 lettere ETDRS) e 3/10 (29/65 lettere ETDRS) in LE. The fundus examination was made difficult by endothelial precipitates.

In topical therapy with topical dexamethasone 0.2% (LUXAZONE®) 6 times a day for 6 weeks..

The not optimal VA was explained by the presence in both eyes of CME documented with OCT (RE: CMT 317 µm, LE: CMT 344 µm) and with FA and, furthermore, LE showed a cataract advanced (N3C3P1). It was decided to make an intravitreal implant of DEX in the LE with a VA worse. In the third month of follow-up the patient is subjected to phacoemulsification operation to the LE with IOL implantation in the capsular bag, reaching after seven days a VA of 9/10 (62/65 ETDRS letters).

This result coincided with the improvement of the CME documented by OCT (LE: CMT 292 µm). After 6 months of follow-up, the patient presented again a lowering of VA (7/10, 48/65 ETDRS letters) in LE, explained by a new increase in macular thickness (RE: CMT 319 µm , LE: CMT 322 µm) due to the presence of intraretinal fluid (CME).

However the value of CMT in LE, six months after intravitreal implant DEX, did not reach the values of basal In RE the VA remained almost constant (5/10, 31/65 ETDRS letters) (Fig.3).

Discussion

There are no codified, uniform guidelines for the treatment of clinically significant ME [9,11] Therefore, various therapeutic options have been considered [12-14].

ME is one of the most important clinical disabling manifestations of ocular and in patients with VKH syndrome [1-4].

Intravitreal treatment with corticosteroids undoubtedly plays a key role in the management of macular complications of an exudative nature [5].

Byon [9] highlighted as triamcinolone acetonide is a valid treatment of ME for patients suffering from VKH in the acute phases and in short duration relapses and as the need for repeated injections expose patients to a greater risk of endophthalmitis, increases in IOP and the onset of cataracts [15].

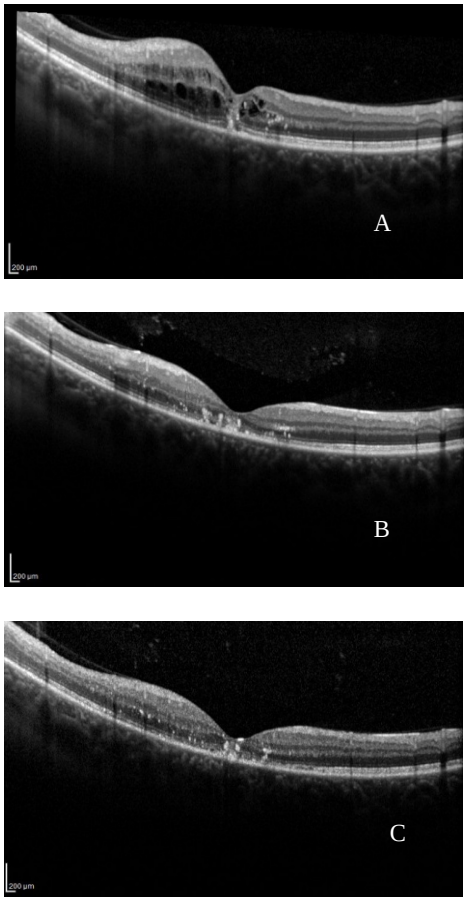

Figure 3. A) Baseline optical coherence tomography (OCT) LE (Left eye) with cystoids macular edema (CME). B) LE after 2 week following the 0.7 mg DEX implant intravitreal, OCT revealed a drastic reduction in CME. C) 6 months following implant placement OCT LE showed no recurrence of CME.

For this reason, a new intravitreal device with slow corticosteroid (dexamethasone) release has been developed, able to exercise a significant anti-edema action,

Table 1. Changes from baseline (T0) to the first follow-up visit within 3 months of starting therapy with DEX implant (T1) and follow-up visit at 6 months (T2) in central macular thickness (CMT).

Patients Number	Gender	Age	T0 CMT (Central Macular Thickness; microns)		T1 CMT (Central Macular Thickness; microns)		T2 CMT (Central Macular Thickness; microns)		T3 CMT (Central Macular Thickness; microns)	
Eye			RE	LE	RE	LE	RE	LE	RE	LE
A	F	52	432	352	296	355	285	358	276	355
B	F	35	455	311	275	308	292	315	291	312
C	F	48	317	344	317	288	319	292	319	322

after being injected into the vitreous and able to maintain the integrity of the outer membrane, as well as of the inner one and outer segments of interface photoreceptors as documented by the OCT.

The reduction of CMT generally results in an improvement in VA [13,14].

In the three tested patients, DEX intravitreal implant, has caused a significant reduction in their ME, as shown in the OCT [16, 17].

This insert, for the edema treatment, could be used as maintenance therapy in the management of 'chronic ME. For this reason, the DEX intravitreal implant, approved by the FDA for treating macular post thrombotic edema [13,18] and macular noninfectious posterior uveitis edema , has undeniable advantages over other intravitreal corticosteroids, including: the biodegradability of the dexamethasone system compared to other implants, does not need to be removed, low cost [10] and less frequent giving with reduction of collateral effects [19] .

Table 2. Changes from baseline (T0) to the first follow-up visit within 3 and 6 months of starting therapy with DEX implant (T1) in Visual Acuity (ETDRS).

PatientsNumber	Gender	Age	T0 BCVA (ETDRSLETTERS)		T1 BCVA (ETDRSLETTERS)		T2 BCVA (ETDRSLETTERS)		T3 BCVA (ETDRSLETTERS)	
Eye			RE	LE	RE	LE	RE	LE	RE	LE
A	F	52	29	62	52	59	57	60	65	62
B	F	35	25	47	45	46	51	45	55	45
C	F	48	40	30	43	44	42	62	44	31

T0= PREOPERATIVE
EVALUATIONT1= 1 MONTH AFTER OZURDEX
T2=3 MONTHS AFTER OZURDEX
T3=6 MONTHS AFTER OZURDEX

Initial studies seem demonstrate the effectiveness of DEX intravitreal implant in controlling inflammation not only in the vitreous body but also at the level of the anterior segment. This result, in particular, has made it possible to suspend temporarily the topical and systemic treatment steroids that these patients had to perform. However, intravitreal corticosteroids could play a role as adjuvant therapy. The small number of randomized double-blind clinical trials do not establish absolutely the greater effectiveness of DEX implant than other corticosteroids.

However Hunter et al [12] reported greater efficacy of dexamethasone versus fluocinolone in terms of BCVA: the improvement of 15 ETDRS letters is achieved in 21% of patients treated with fluocinolone after 34 weeks and 38% after 26 weeks with dexamethasone. The randomized study carried out by Kupperman et [14] al using the implant of dexamethasone in the treatment of persistent ME detected a statistically significant improvement in VA after 90 days [12]. These data are in agreement with the result obtained in our cases, in which it is obtained a reduction of CMT resulting in improved VA after 6 months.

Except for the patient subjected to phacoemulsification, the significant improvement of VA is due to the significant decrease in ME, as shown by the OCT examination in the three cases.

The difference in half-life of dexamethasone compared to fluocinolone makes it difficult to compare the relative effectiveness in the absence of randomized clinical trials.

As regards the safety profile is currently difficult to assert the superiority of dexamethasone than other corticosteroids [13]. The greater efficacy and lower incidence of collateral effects lie in the lower dexamethasone lipophilicity compared to triamcinolone and fluocinolone. This data is in agreement with our observations during the follow-up. Furthermore, none of the three observed cases shows increases in IOP.

Conclusion

In the present series, Dex Implant was able to control and improve CME in 3 eyes of 3 patients of VKH syndrom [14-19]. The duration of effect of the implant was 4 to 6 months. No patients developed major systemic or ocular side effects, particularly ocular hypertension. In only one eye required surgical intervention, for cataract progression that was already present at baseline.

Despite the short follow-up and the small sample it could be considered a valid therapeutic approach in patients with refractory Vogt-Koyanagi-Harada disease and in the prevention of all the typical side effects of systemic corticosteroid therapy. Further prospective, controlled studies need to be performed to better determine efficacy, duration of effect, and side effects.

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