Medical Case Reports
ISSN: 0976-8726 & E-ISSN: 0976-8734, Volume 5, Issue 1, 2014, pp.-063-067.
Available online at http://www.bioinfopublication.org/jouarchive.php?opt=&jouid=BPJ0000288

INTRAVITREAL DEXAMETHASONE IMPLANT IN THE TREATMENT OF A PATIENT WITH CYSTOID MACULAR OEDEMA SECONDARY TO LOWER BRANCH RETINAL VEIN OCCLUSION - A CASE REPORT

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Received: July 08, 2014; Accepted: October 09, 2014

Abstract- *Introduction*: Purpose of this study is to present the results of reimplantation of biodegradable intravitreal implant of dexamethasone (Ozurdex®) of patient with cystoid macular oedema secondary to temporal lower branch retinal vein occlusion. This article is the first documented case report of treatment with 2 intravitreal implants of dexamethasone.

Case Presentation: The patient with cystoids macular oedema secondary to temporal lower branch retinal vein occlusion. The diagnosis was based on examination of the eyes, extended by fluorescein angiography and optical coherence tomography. Implantations of Ozurdex® took place in the operating theatre, while respecting aseptic conditions and in accordance with the principles of intravitreal injections. From the onset of symptoms to the administration passed the time of 2 weeks. Patient controls were held on schedule: 2 weeks, 4 months, 7 months, 8 months and 10 months since the onset of symptoms and included measurements of visual acuity, intraocular pressure, optical coherence tomography of the retina. Before implantation as well as in postoperative period patients used topical antibiotic with an extended spectrum of action (Vigamox®).

Conclusions: In the presented patient with cystoids macular oedema secondary to branch retinal vein occlusion, the use of an intravitreal biodegradable implant containing dexamethasone (Ozurdex®) resulted in improved visual acuity and reduced retinal oedema. The first implantation of a biodegradable implant containing dexamethasone resulted in partial improvement of functional and morphological condition of central retina. A six-month follow-up after reimplantation of Ozurdex® showed functional and morphological stabilisation of central retina. Ozurdex® is an effective drug in the treatment of cystoid retinal edema resulting from retinal vein occlusion.

Keywords- retinal vein occlusion, cystoids macular oedema, dexamethason, intravitreal iniection, reimplantation

Citation: Kabiesz A., et al. (2014) Intravitreal Dexamethasone Implant in the Treatment of a Patient with Cystoid Macular Oedema Secondary to Lower Branch Retinal Vein Occlusion - a Case Report. Medical Case Reports, ISSN: 0976-8726 & E-ISSN: 0976-8734, Volume 5, Issue 1, pp.-063-067.

Introduction

This paper presents the results of using a biodegradable intravitreal implant of dexamethasone (Ozurdex®) in a patient with cystoid macular oedema (CMO) secondary to branch retinal vein occlusion (BRVO).

Of among abnormalities within the retinal vascular network, branch retinal vein occlusion is considered the second most common cause of visual acuity loss after diabetic retinopathy [1]. Central retinal vein occlusion (CRVO) and branch retinal vein occlusion (BRVO) are usually associated with advanced atherosclerosis, hyperlipidaemia, diabetes mellitus or other systemic diseases.

Cystoid macular oedema may be the most severe complication of venous occlusion, leading to reduced visual acuity and pathological neovascularisation. CMO is caused by many factors, the following being considered most important: interruption of the blood-retina barrier, hydrostatic effect resulting from increased venous blood pressure, presence of numerous pro-inflammatory cytokines and over-production of vascular endothelial growth factor (VEGF) induced by hypoxia [3]. The prognosis regarding visual acuity improvement and restoration of normal retinal function varies and is largely dependent on the factors responsible for vessel occlusion. Treatment options for CMO related with RVO include laser photocoagulation and therapy with corticosteroids and anti-VEGF agents [4,5].

Intravitreal injection is a method of administration of a therapeutic substance which allows achieving high concentration of the drug in the vitreous body without crossing the blood-retina barrier, minimizing the risk of systemic adverse effects. Steroids that are most commonly administered intravitreously include fluorinated derivatives of

dexamethasone and triamcinolone. Their binding to glucocorticosteroid receptors exerts much stronger effects compared with hydrocortisone [6]. Intravitreal injection is associated with interruption of the integrity of the ocular wall and needs to be performed under aseptic conditions. Complications of the injection can be classified as procedure-related and active ingredient-related. The former include vitreous haemorrhage, increased risk of endophthalmitis, retinal detachment and thrombosis of retinal vessels. The latter include accelerated cataract formation as the most severe complication and increased intraocular pressure [7]. The most common complaints reported by patients are burning, stinging and extravasation at the site of injection.

The therapeutic effect of dexamethasone is five times stronger compared with triamcinolone. However, its short half-life in the vitreous body does not allow achieving sustained high concentration. What proved to be a solution to this problem was developing a biodegradable intravitreous implant containing dexamethasone and ensuring sustained release of the drug from 4 to 6 months.

Ozurdex® (Allergan Inc., Irvine, CA, USA) contains 700 µg of dexamethasone and has been approved for the treatment of patients with central retinal vein occlusion or branch retinal vein occlusion and for the treatment of non-infectious uveitis [8]. The implant is administered to the eye with a special injector. It is made from substances which undergo degradation to H_2O and CO_2, thus do not cause allergic reactions. At the initial phase, after injection into the vitreous cavity, a large quantity of dexamethasone is released to rapidly achieve the therapeutic concentration. Subsequently gradual release of the steroid allows maintaining sustained effect [9].

Case Presentation

An Asian male patient, citizen of Vietnam, aged 42 years, treated for non-insulin dependent diabetes mellitus for the last 4 years, presented at the Emergency Department of Medical University of Silesia due to sudden deterioration of visual acuity in the left eye. A slit-lamp examination revealed intraretinal haemorrhages, blurred contours and swelling of the optic disc and retinal oedema in the region drained by the lower branch of central retinal vein in the left eye [Fig-1]. The patient received pharmacotherapy necessary to restore normal rheological state of the venous network. Platelet aggregation inhibitors (Vessel Due F) and vessel-sealing agents (Calcium dobesilate) were started. The patient was referred to the Hospital Ophthalmology Outpatient Clinic for further specialist diagnostic examinations necessary to confirm the diagnosis.

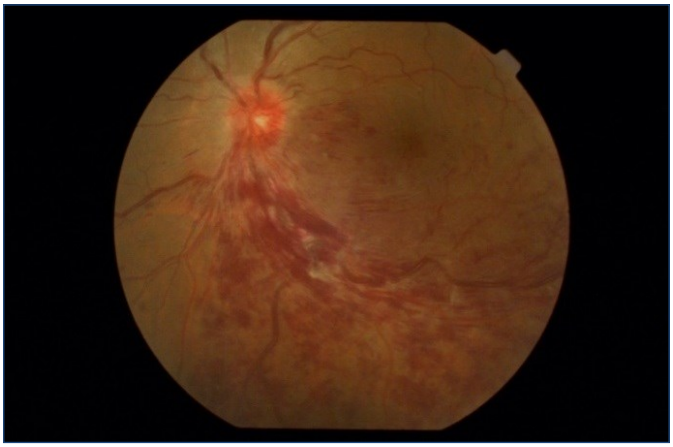

Fig. 1- Fundus of the left eye – at baseline

The results of ophthalmic examinations of the right eye performed throughout the entire observation period were normal. BCVA (best-corrected visual acuity) 1.0, RE NS (near sight in the right eye) = 0.5; RE IOP (intraocular pressure in the right eye) = 16 mmHg.

Prior to implantation of Ozurdex to the left eye, the results of ophthalmologic examination were as follows: BCVA = 0.1, LE NS = does not read, LE IOP = 15 mmHg and central retinal thickness (CRT) = 1326 µm [Fig-2]. Before implantation as well as in postoperative period patients used topical antibiotic with an extended spectrum of action (Vigamox®). Fluorescein angiography revealed inferior branch retinal vein occlusion [Fig-3], and OCT of the posterior segment showed massive central retinal oedema. There were no intra-operative or peri-operative complications of the implantation.

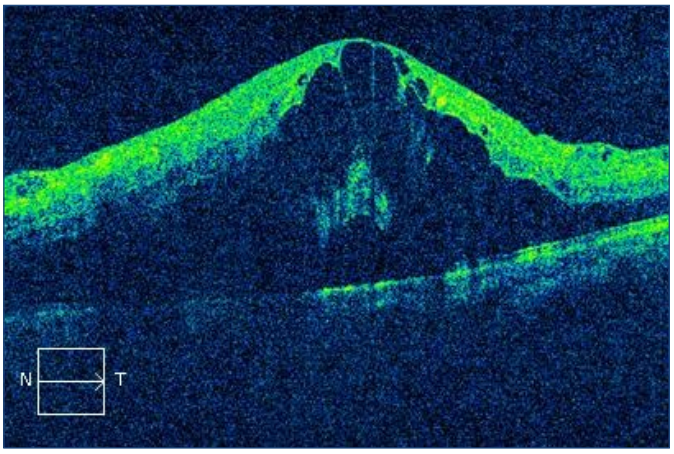

Fig. 2- OCT image of the left eye macula: CRT = 1326 µm

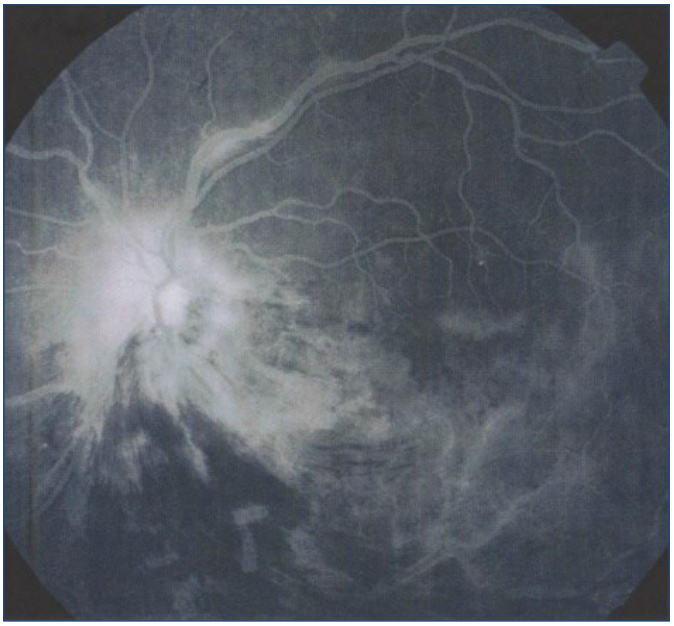

Fig. 3- Fluorescein angiography image of the left eye at baseline

At follow-up examination 14 days after the implantation, the patient did not report any adverse effects of the drug and improvement in visual acuity was 1 Snellen line. BCVA = 0.2, LE NS = does not read, LE IOP = 18 mm Hg. Repeated OCT showed reduced but persistent central retinal oedema [Fig-4]: CRT = 1061 µm [Fig-5] and numerous intraretinal haemorrhages. Then, for three months the patient did not respond to contact attempts made by medical staff. Only 114 days after the implantation, did he present at the

Hospital Outpatient Clinic. Ophthalmic examination of the Ozurdex-implanted eye revealed functional and morphological improvement in the retina. BCVA = 0.3, LE NS = D-3.0, LE IOP = 15 mmHg, CRT = 281 µm [Fig-6].

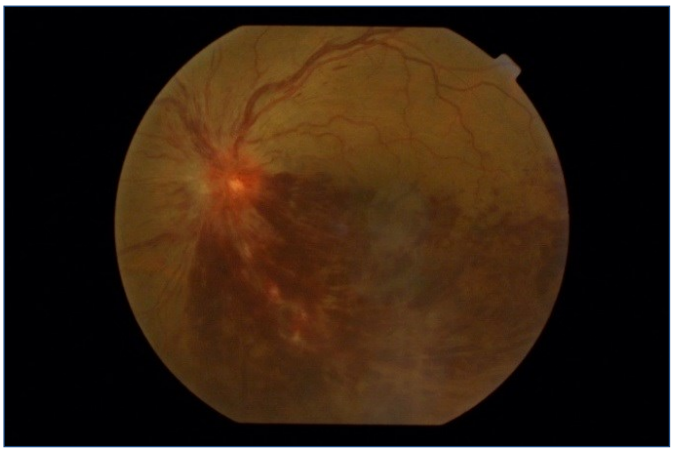

Fig. 4- Image of the left fundus 14 days after Ozurdex implantation

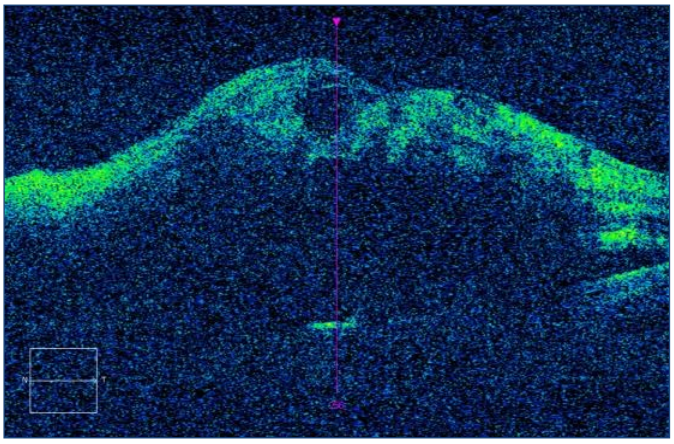

Fig. 5- OCT image of the left macula 14 days after implantation: CRT = 1061 µm

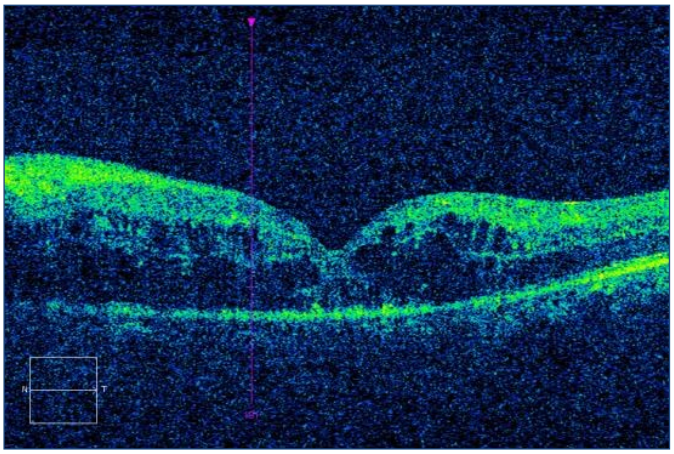

Fig. 6- OCT image of the left eye macula 114 days after implantation: CRT = 281 µm

Seven months after implantation, the patient noticed decreased visual acuity in the left eye: BCVA = 0.2. OCT showed a rebound increase in central retinal thickness: CRT = 749 µm [Fig-7]. Since there were no contraindications (LE IOP = 16 mmHg), it was decided to qualify the patient for reimplantation of Ozurdex. The procedure was performed in an operating theatre under aseptic conditions. After 30 days, examination of the left eye showed: BCVA = 0.5, LE IOP = 16 and LE NS = D–1.5; and OCT imaging of central retina [Fig-8] showed significant morphological improvement (CRT = 548 µm).

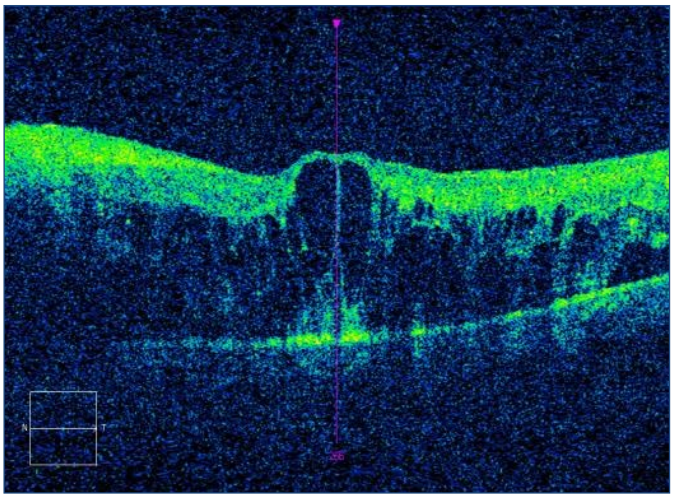

Fig. 7- OCT image of the left eye macula 7 months after implantation: CRT = 749 µm

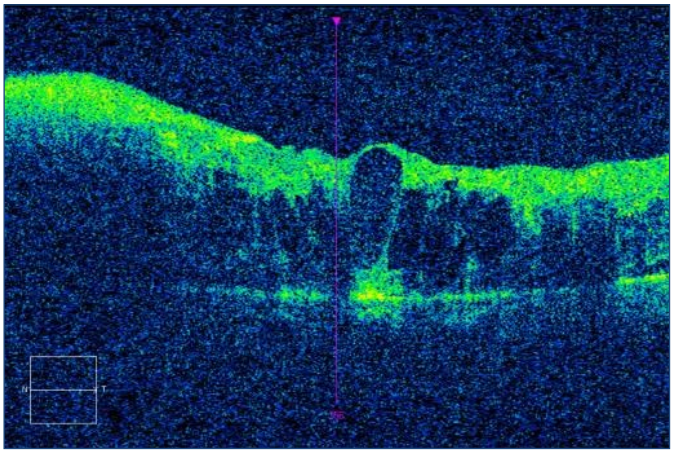

Fig. 8- OCT image of the left eye macula 30 days after reimplantation: CRT = 548 µm

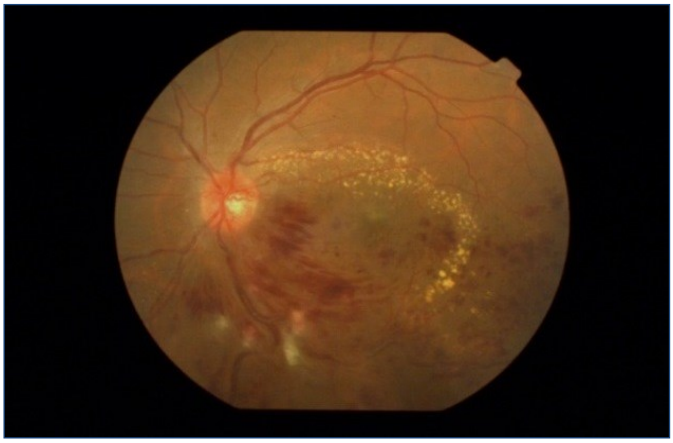

Fig. 9- Image of the left eye ocular fundus 30 days after reimplantation of Ozurdex

After another 45 days, the patient reported further improvement in visual acuity: BCVA = 0.7, LE IOP = 16 mmHg and LE NS = D–0.75; examination of the ocular fundus [Fig-9] showed reduced extravasation and reduced retinal oedema: CRT = 310 µm [Fig-10].

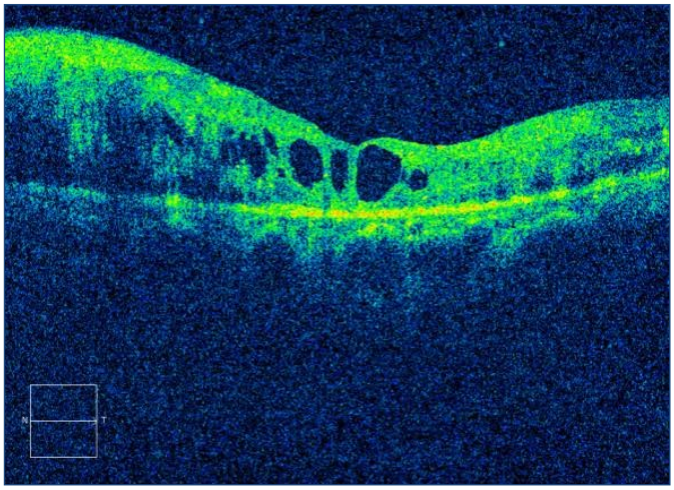

Fig. 10- OCT image of the left eye retina 75 days after reimplantation: CRT = 310 µm

Discussion

Of among abnormalities within the retinal vascular network, branch retinal vein occlusion is considered the second most common cause of visual acuity loss after diabetic retinopathy [1]. Central retinal vein occlusion (CRVO) and branch retinal vein occlusion (BRVO) are usually associated with advanced atherosclerosis, hyperlipidaemia, diabetes mellitus or other systemic diseases.

Cystoid macular oedema may be the most severe complication of venous occlusion, leading to reduced visual acuity and pathological neovascularisation. CMO is caused by many factors, the following being considered most important: interruption of the blood-retina barrier, hydrostatic effect resulting from increased venous blood pressure, presence of numerous pro-inflammatory cytokines and over-production of vascular endothelial growth factor (VEGF) induced by hypoxia [3].

Cystoid macular oedema secondary to retinal vein occlusion develops because of local inflammation spreading through pro-inflammatory cytokines and disruption of the blood-retina barrier. Of the cytokines responsible for CMO, the most significant effects are described as related to IL-1(interleukin 1), IL-6 (interleukin-6) and TNF-alpha (tumor necrosis factor-alpha) which, take part in inducing and maintaining inflammatory reactions [10]. These mediators are responsible for loosening of junctions between endothelial and retinal pigment epithelial cells. TNF-alpha also initiates neovascularisation and vasomotor reactions. In the therapeutical approach of the mechanism towards the oedema, corticosteroids play a key role based on their anti-inflammatory properties and inhibition of angiogenesis [8,10]. According to the literature, periocular injections of triamcinolone are highly effective in the treatment of CMO secondary to retinal vein thrombosis [4]. The limitation of this method is need to frequently repeat the injections, which increases the risk of local complications. The use of a biodegradable implant containing sustained-release dexamethasone allows to achieve the target concentration at the pathologically changed site with one implantation only. In a phase II study with an intravitreal implant containing dexamethasone 350 µg and 700 µg used in patients with CMO, after 6 months the improvement in BCVA by at least 2 lines was achieved in 27% of patients in the first group and 36% of patients in the second group. What is also emphasised is an increased intraocular pressure (IOP), which can be effectively treated with only one hypotensive agent, though [11,12].

Conclusions

In the presented patient with CMO secondary to BRVO, the use of an intravitreal biodegradable implant containing dexamethasone (Ozurdex) resulted in improved visual acuity and reduced retinal oedema. The first implantation of a biodegradable implant containing dexamethasone resulted in partial improvement of functional and morphological state of central retina. A six-month follow-up after reimplantation of Ozurdex showed functional and morphological stabilisation of central retina. What is worth emphasizing is the fact that the improvement in visual acuity and morphological state of retina were significantly better after the second implantation compared with the improvement in visual acuity after the first implantation.

List of Abbreviations

CRVO: Central Retinal Vein Occlusion

BRVO: Branch Retinal Vein Occlusion

CMO: Cystoid Macular Oedema

VEGF: Vascular Endothelial Growth Factor

BCVA: Best Corected Visual Acuity

RE NS: Right Eye Near Sight

RE IOP: Right Eye Intraocular Preasure

LE NS: Left Eye Near Sight

LE IOP: Left Eye Intraocular Preasure

CRT: Central Retinal Tickness

IL-6: Interleukin -6

IL-1: Interleukin -1

TNF-alpha: Tumor Necrosis Factor - alpha

Consent: Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Authors Contributions: AK, have made substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data. KMM, DŚ, AG, DR & MN, have been involved in drafting the manuscript and revising it critically for important intellectual content. All authors read and approved the final manuscript.

Acknowledgment: We would like to give special thanks to Wanda Romaniuk, professor in Medical University of Silesia, Head of the Chair and Clinic of Ophthalmology for her guidance and help.

Competing Interests: The authors declare that they have no competing interests.

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