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Long-term management of non-ischemic central retinal vein occlusion with fluocinolone acetonide intravitreal implant 190 μg (ILUVIEN®)

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Abstract

Introduction: Macular edema after central retinal vein occlusion is a common cause of vision loss. Upregulation of vascular endothelial growth factor and higher levels of inflammatory mediators have been involved in the pathogeny of the macular edema in central retinal vein occlusion.

Case report: The authors report a case with non-ischemic central retinal vein occlusion that was successfully treated with a single sustained-release fluocinolone acetonide intravitreal implant. After a course of repeated injections of shorter-acting corticosteroid, the affected eye presented a visual acuity of 20/200 and a central subfield foveal thickness of 587 μm. After fluocinolone acetonide in intravitreal implant and during a follow-up period of 12 months, a continuous and sustained increase in visual acuity until 20/25 with significant anatomical improvements and an acceptable safety profile was observed.

Conclusion: These results, demonstrate that fluocinolone acetonide intravitreal implant might be an effective treatment option in macular edema secondary to non-ischemic central retinal vein occlusion.

Keywords: central retinal vein occlusion, fluocinolone acetonide intravitreal implant, macular edema

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Introduction

Central retinal vein occlusion (CRVO) is a retinal vascular condition that can severely affect visual acuity, including sudden blindness.[1] Prevalence estimates indicate that CRVO affects ~2.5 million people >30 years of age in Europe.[2,3]

Visual loss after CRVO commonly occurs as a result of macular edema. The mechanism of macular edema in CRVO is not completely understood.[4,5] It has been described the main role of the elevated levels of vascular endothelial growth factor (VEGF) apart from the increased venous pressure. Upregulation of other inflammatory mediators and dysregulation of endothelial tight junctions have also been involved in the pathogeny.[5,6] Although laser photocoagulation has been considered for many decades the standard retinal vein occlusion (RVO) treatment,[7] inhibiting VEGF levels seemed to be a rational strategy for treating RVO. Multiple clinical trials have shown a significant reduction in plasma VEGF levels in CRVO patients after intravitreal (IV) injection of anti-VEGF agents.[8–11] The current approved treatment options include IV injections of ranibizumab (Lucentis®, Novartis Europharm Ltd, UK) and aflibercept (Eylea®, Bayer Pharma AG, Germany).[12,13] Moreover, IV corticosteroid agents such as triamcinolone and dexamethasone implant (Ozurdex®, Allergan Pharmaceuticals, Ireland) have also been studied and are currently considered valid therapeutic options in CRVO treatment due to their anti-inflammatory, antiangiogenic, and anti-edema properties.[2,14–16]

Vitrectomy with internal limiting membrane (ILM) peeling have also been suggested to be a

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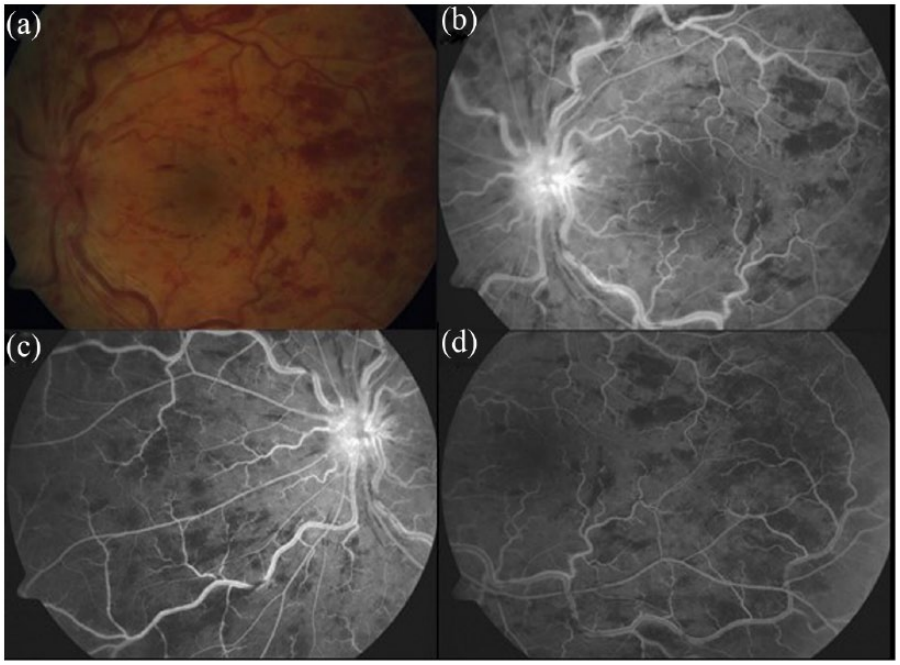

Figure 1. Left eye (a) fundus photography showing the presence of peripapillary hemorrhages and papillary edema with dispersed exudates and (b–d) fluorescein angiography showing presence of retinal hemorrhages, with perfusion over the peripheral retina and no visible neovascularization.

treatment for macular edema due to CRVO. Vitrectomy with posterior hyaloid removal and ILM peeling may contribute to a decrease macular edema due to the relief of any traction and by improving oxygenation of the vitreous cavity and retina after removal of inflammatory and permeability mediators present in the vitreous, including VEGF.[17,18]

Herein, we report the long-term results of a case of non-ischemic CRVO that was successfully treated with a single fluocinolone acetonide IV implant (ILUVIEN®, Alimera Sciences Limited, UK).

Case report

Three years ago, a 65-year-old male, with history of controlled arterial hypertension and without past ophthalmological history, was referred to our eye clinic due to vision loss in the left eye. He had been diagnosed with CRVO in the left eye a week before and promptly treated with deflazacort 30 mg and nepafenac (1 mg/ml). On our examination, the patient's best-corrected visual acuity (BCVA) was 20/100 in the left eye and 20/20 in the right eye, swinging-flashlight test was performed being normal with no relative afferent pupillary defect. The intraocular pressure (IOP) was 16 mmHg without therapy. At that time, dilated fundoscopy and optic coherence tomography (OCT – Cirrus HD-OCT, Carl Zeiss. Meditec Inc, Dublin, CA, USA) showed the presence of peripapillary hemorrhages and papillary edema with dispersed exudates (Figure 1(a)). Fluorescein angiography was then performed showing in the left eye a delay in arteriovenous transit time, retinal hemorrhages, vessel wall staining, with perfusion over the peripheral retina and no visible neovascularization (Figure 1(b)).

One day later, a dexamethasone IV implant (Ozurdex®, Allergan Pharmaceuticals, Ireland) was injected into the left eye (Figure 2(a)).

Visual acuity gradually improved in the following 2 months from 20/100 to 20/20 with a decrease on central subfield foveal thickness (CSFT) from 608 µm to 319 µm (Figure 2(a) and (b)). The IOP in the left eye increased from 16 mmHg to 30 mmHg in the second month after dexamethasone IV implant, without IOP change in the right eye. Bimatoprost + timolol (0.3 mg/ml + 5 mg/ml) eye drops were then initiated, at the second month after the first dexamethasone implant, and the IOP was successfully managed decreasing to

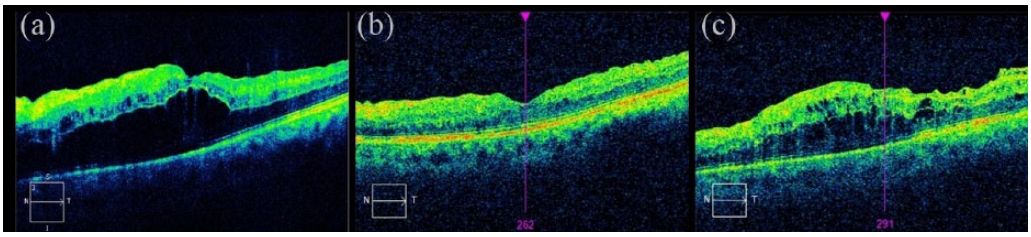

Figure 2. Left eye optic coherence tomography (a) before and (b) 2 months improvement after dexamethasone intravitreal implant injection and (c) recurrence of macular edema at 3 months post-dexamethasone intravitreal implant.

18 mmHg. Dilated fundoscopy revealed tortuous and dilated retinal veins with a significant reduction in macular edema on the left eye. Three months after, BCVA decreased again to 20/200 and the CSFT increased to 680 µm. One month later, the patient underwent vitrectomy with ILM peeling, presenting at the postoperative visit both improvements in macular anatomy and visual acuity (20/32), although macular edema could be encountered in the macular papillary beam. At the second month postoperative, the patient presented vision loss and OCT revealed macular edema worsening to 546 µm (Figure 2(c)). The IOP was stable at 18 mmHg with bimatoprost + timolol (0.3 mg/ml + 5 mg/ml). A second fluorescein angiography was performed during follow-up to rule out conversion into ischemia-typed RVO confirming the perfusion of peripheral retina and absence of neovascularization.

Three more dexamethasone IV implants were injected in the course of a year with a mean interval between injections of approximately 3 months to control the frequent relapse in macular edema and associated visual acuity loss. During this period the vision ranged between 20/32 and 20/200, according to the presence of macular edema. This constant fluctuation on visual acuity was very limiting and uncomfortable for the patient being a frequent complaint. IOP tended to increase at the peak of effect of dexamethasone IV implant, maximum of 24 mmHg, but was well managed with the bimatoprost + timolol (0.3 mg/ml + 5 mg/ml) eye drops without additional topic medication or glaucoma surgery. The patient developed a corticonuclear cataract in the left eye with subsequent uneventfully cataract surgery, 1 year and 4 dexamethasone implants after the diagnosis of the CRVO. At the time of cataract surgery, topical glaucoma medication was switched from bimatoprost + timolol (0.3 mg/ml + 5 mg/ml) to brimonidine and timolol (2 mg/ml + 6.8 mg/ml). Constant recurrence of macular edema and visual impairment was observed despite repeated dexamethasone IV implants, in addition to compliance issues due to multiple IV injections. After 20 months and 6 dexamethasone implants since the diagnosis of the non-ischemic CRVO, a year ago the patient received a fluocinolone acetonide IV implant (ILUVIEN®, Alimera Sciences Limited, UK), although not licensed for this pathology. At the time of fluocinolone acetonide IV implant injection, the IOP was in 16 mmHg with brimonidine and timolol (2 mg/ml + 6.8 mg/ml). The benefit/risk ratio was evaluated and the patient gave and signed an informed consent. The patient presented in this report also has given informed consent for this publication.

After 12 months, visual acuity improved from 20/200 to 20/25 being stable since the first month after the injection of fluocinolone acetonide IV implant with a progressive decrease in CSFT from 578 µm to 392 µm, without significant changes since month 3 (Figure 3). The IOP remained controlled in the left eye during the fluocinolone acetonide IV implant follow-up, with brimonidine and timolol (2 mg/ml + 6.8 mg/ml) since the fluocinolone acetonide IV implant, increasing from 16 mmHg previous to fluocinolone acetonide IV implant to 18 mmHg at the last visit, without additional topic medication or glaucoma surgery. A maximum of 21 mmHg was noticed at the ninth month of follow-up, but after discussion with the patient additional therapy was not started and a better compliance was recommended. At the 10th month IOP was 16 mmHg with brimonidine and timolol (2 mg/ml + 6.8 mg/ml). In the right eye, IOP remained within normal parameters without therapy during all follow-up being 18 mmHg in the last visit. No additional IOP-lowering medication or procedure has been required during follow-up. No significant changes were noticed in the optic disc appearance and

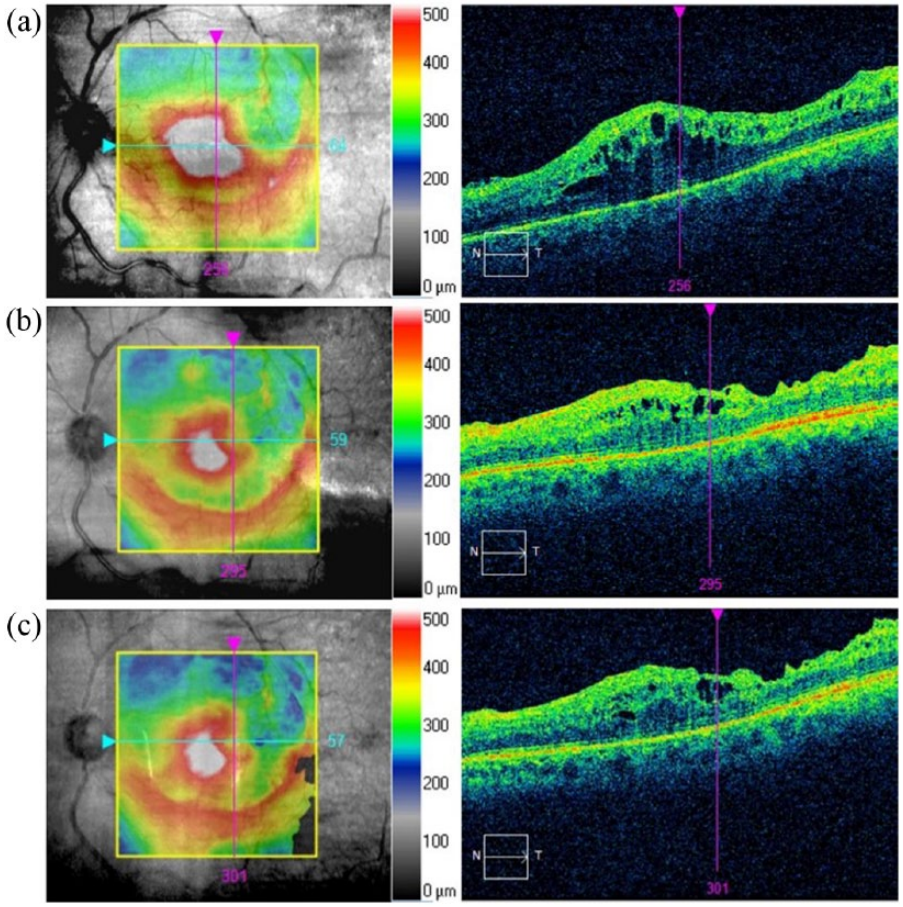

Figure 3. Left eye optic coherence tomography (a) before, (b) 3 months, and (c) 12 months after injection of fluocinolone acetonide intravitreal implant. (a) BCVA: 20/200; CSFT: 578 µm; IOP: 16 mmHg; (b) BCVA: 20/32; CSFT: 397 µm; IOP: 18 mmHg; (c) BCVA: 20/25; CSFT: 392 µm; IOP: 18 mmHg.

morphology during follow-up, the mean Retinal Nerve Fibre Layer (RNFL) at the Cirrus HD-OCT was 92 µm at the time of the injection of fluocinolone acetonide IV implant and remained stable through the follow-up, being 91 µm at the 12th month.

Despite the good functional and anatomical results observed at the 12th month without additional therapies, it is still possible to observe residual macular edema on the OCT (Figure 3(c)). However, the patient is pleased with his current visual acuity, being stable and independent of IV injections for long time with a significant improvement in his quality of life, not being interested and rejecting any additional treatment.

Discussion

In this case report, the treatment with a single fluocinolone acetonide IV implant was effective in one eye with chronic macular edema secondary to non-ischemic CRVO with an acceptable safety profile. Visual and anatomical improvements were continuous and sustained more than 12 months. Visual acuity improved from 20/200 to 20/25 and CSFT reduced from 578 µm to 392 µm.

It is well known that IV steroid administration has an anti-inflammatory role reducing vascular permeability, inhibiting leucocyte movement, suppressing homing and migration of inflammatory cells, stabilizing tight junctions, and inhibiting prostaglandins and other cytokines.[10,12] In this particular case steroids, namely, dexamethasone IV implant (Ozurdex®), were used as first-line therapy instead of anti-VEGF due to the presence of non-ischemic characteristics and after confirmation of perfusion over the peripheral retina on the fluorescein angiograph. Also, the authors have long experience and good results with steroids in

the management of non-ischemic CRVO and the patient was not pleased or motivated with the expectation of monthly injections of anti-VEGF.

Macular edema in RVO is a condition that persists for a considerable time, and its treatment is also prolonged.[19] Close monitoring for a long time is required in these patients, and as needed in regimens enable tailoring of treatment to individual patients.[19] The efficacy and safety of dexamethasone IV implant in patients with either CRVO or branch retinal vein occlusion (BRVO) has been well defined in prospective multicenter studies.[19–21] However, today, studies and experience from clinical practice have shown that dexamethasone IV implant requires long-term repeated treatments to control the macular edema, prevent vision loss, and increase the chance of visual improvement.[20–22]

To our knowledge, there are no published cases of IV treatment of macular edema secondary to CRVO with fluocinolone acetonide IV implant. Fluocinolone acetonide IV implant is a slow-release implant approved for the treatment of vision impairment associated with chronic diabetic macular edema (DME), considered insufficiently responsive to available therapies.[23] Prospective studies in DME with fluocinolone acetonide IV implant have shown a pharmacokinetic profile that enables a sustained and continuous release of a low dose corticosteroid (0.2 µg/day) over 3 years with a single injection.[23–25] Therefore, long-term therapy with fluocinolone acetonide IV implant would reduce significantly the burden of frequent treatments for the patient. Indeed, Sivaprasad and colleagues,[26] assessed the impact of injection therapy on patients with DME or RVO and concluded that patients' quality of life was heavily affected and reducing the appointment burden to achieve the same visual outcomes and the provision of additional support for patients to attend appointments would greatly benefit those receiving IV injection therapies for DME and RVO.

To the best of our knowledge, this is the first case publish of the use of fluocinolone acetonide IV implant to treat macular edema secondary to non-ischemic CRVO. Still, larger cohort, prospective phase III studies should be performed to confirm the pharmacokinetics and long-term benefits of fluocinolone acetonide IV implant 190 µg in both CRVO and BRVO.

Conclusion

Fluocinolone acetonide IV implant (ILUVIEN®) was found to be effective and safe at 12-month follow-up in a patient with chronic macular edema secondary to non-ischemic CRVO. Fluocinolone acetonide IV implant might be an effective treatment option in macular edema secondary to non-ischemic CRVO. Longer follow-up is required to assess the duration of action of the implant.

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Conflict of interest statement

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