Case Report

Taiwan J Ophthalmol 2019;9:280-283

Access this article online

Quick Response Code:

Website:
www.e-tjo.org

DOI:
10.4103/tjo.tjo_87_17

Persistent vitreous hemorrhage after intravitreal injection of dexamethasone intravitreal implant in patients with diabetic macular edema

Meng-Syuan Li[1], Shwu-Jiuan Sheu[1,2]

Abstract:

We report three cases of persistent vitreous hemorrhage after injection of a biodegradable 0.7 mg dexamethasone intravitreal implant (Ozurdex, Allergan), (DEX) to treat and manage diabetic macular edema (DME); we also summarize available case reports and review the literature regarding persistent vitreous hemorrhage. All three patients underwent pars plana vitrectomy due to nonclearing vitreous hemorrhage after conservative treatment for 2–3 months. During operation, we noted the presence of neovascular membrane along the vascular arcade with taut posterior hyaloid; however, no posterior vitreous detachment (PVD) was found in any of three patients. The implants were carefully preserved, so were the effects in reducing macular edema. Persistent vitreous hemorrhage after DEX injection was rare but manageable without interrupting the effect on DME. Eyes with neovascular membrane but without PVD may be at risk of developing vitreous hemorrhage after DEX injection.

Keywords:

Diabetic macular edema, Ozurdex, vitrectomy, vitreous hemorrhage

Introduction

Diabetic macular edema (DME) is one of the major causes of visual impairment in people with diabetes.[1] It can occur in any stage of diabetic retinopathy including both non-proliferative and proliferative types. The pathogenesis of DME is complicated, and in addition to vascular endothelial growth factor (VEGF), it also involves inflammatory cytokines and even vitreoretinal interface abnormalities. Recently, pharmacotherapy, including anti-VEGF and steroids, has substantially advanced the management of macular edema. Of these, a biodegradable 0.7 mg dexamethasone intravitreal implant (Ozurdex, Allergan), (DEX) is the first intravitreally injectable biodegradable implant drug approved for the treatment of DME. Ozurdex has become popular due to its demonstrated efficacy in the treatment of DME and its favorable safety profile.[2] Aside from cataracts and ocular hypertension, vitreous hemorrhage has also been reported following treatment, but most cleared spontaneously in a short time and did not require surgical intervention.[2]

Here, we report the cases of three patients who developed persistent vitreous hemorrhage after intravitreal injection of DEX to treat DME; these case reports highlight the possibility of this complication in patients with neovascular membrane but no posterior vitreous detachment (PVD).

Case Reports

Case 1

A 63-year-old male patient with type 2 diabetes mellitus was referred to us under the impression of proliferative diabetic

[1]Department of Ophthalmology, Kaohsiung Veterans General Hospital, Kaohsiung, [2]School of Medicine, National Yang-Ming University, Taipei, Taiwan

Address for correspondence:
Prof. Shwu-Jiuan Sheu, Department of Ophthalmology, Kaohsiung Veterans General Hospital, No. 386, Dazhong 1st Road, Zuoying District, Kaohsiung 813, Taiwan.
E-mail: sjsheu@gmail.com

Submission: 17-09-2017
Accepted: 24-03-2018

How to cite this article: Li MS, Sheu SJ. Persistent vitreous hemorrhage after intravitreal injection of dexamethasone intravitreal implant in patients with diabetic macular edema. Taiwan J Ophthalmol 2019;9:280-3.

retinopathy (PDR) with DME following panretinal photocoagulation (PRP) and intravitreal injection of bevacizumab in both eyes. He then received an intravitreal injection of Ozurdex in the left eye due to persistent, recurrent macular edema (VA 2/60; central retinal thickness = 513 μm) after another eight intravitreal injections of ranibizumab (IVIR) (4 months after the last IVIR). Massive vitreous hemorrhage developed several days after the injection, and he received pars plana vitrectomy and PRP (The Alcon CONSTELLATION® Vision System) due to persistent vitreous hemorrhage 2 months later. During operation, the neovascular membrane along the vascular arcade with a taut posterior hyaloid and the absence of PVD was observed. The implant was preserved during vitrectomy. The first postvitrectomy optical coherence tomography (OCT) images showed a marked reduction of the central retinal thickness (259 μm 1 month after vitrectomy, 3 months after DEX). There was no recurrence of vitreous hemorrhage or macular edema through the end of the follow-up (9 months after DEX) [Figure 1]. No adjunctive DEX or anti-VEGF was used through the end of the follow-up.

Case 2

A 29-year-old female with type 2 diabetes mellitus presented with severe non-PDR in the right eye and PDR in the left eye, as well as severe DME in both eyes. Because of recurrent DME after IVIR (three instances), she received an intravitreal injection of Ozurdex in the left eye then in the right eye. The interval between DEX and the last treatment with ranibizumab was 2 months. Both eyes responded well, and the central retinal thickness of the left eye decreased from 1014 to 291 μm; however, vitreous hemorrhage developed in the left eye 1.5 months after DEX [Figure 2]. Pars plana vitrectomy (The Alcon CONSTELLATION® Vision System), PVD creating, internal limiting and neovascular membrane peeling, and PRP were performed 2 months later due to increased vitreous hemorrhage in the left eye. A neovascular membrane along the vascular arcade with taut posterior hyaloids and the absence of PVD were noted intraoperatively. The implant was preserved. The postoperative OCT showed no recurrence of macular edema through 3 months after operation, which was 6 months after DEX injection.

Case 3

A 30-year-old male patient had poorly controlled hypertension and type 2 diabetes mellitus for 1 year. He came to our outpatient clinic for the treatment of blurred vision in the right eye, and PDR with DME, as well as hypertensive retinopathy in both eyes, were noted. He was first referred to an internist to achieve systemic control of his diabetes mellitus. Limited PRP was administered in the left eye owing to vitreous hemorrhage, and an intravitreal injection of Ozurdex was administered in the right eye due to the progression of DME (VA 6/20; 717 μm). Vitreous hemorrhage occurred 1 week later, as well as secondary glaucoma (21–23 mmHg), which was controlled with brimonidine tartrate ophthalmic solution (Alphagan *P*, Allergan). OCT showed a reduction in macular edema (198 μm). Limited PRP was performed in the right eye 2 weeks after vitreous hemorrhage. Pars plana vitrectomy ([The Alcon CONSTELLATION® Vision System]) and fluid-gas exchange with 20% octafluoropropane (C_3F_8) was performed due to persistent vitreous hemorrhage for 2 months. A neovascular membrane along the vascular arcade with taut posterior hyaloids and the absence of PVD was noted intraoperatively. The implant was preserved. Recurrent macular edema was noted 10 months after first DEX. There was no vitreous hemorrhage noted after repeated injection of DEX in the same eye [Figure 3].

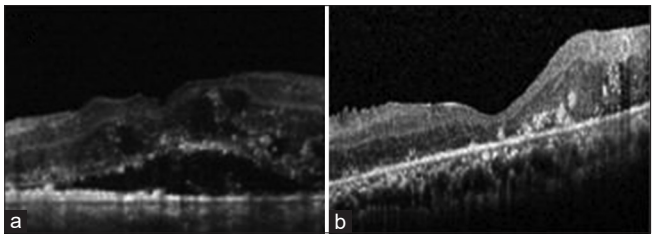

Figure 1: Optical coherence tomography and color fundus photography of case 1. (a) Optical coherence tomography before Ozurdex® injection. (b) Optical coherence tomography three months after Ozurdex® injection

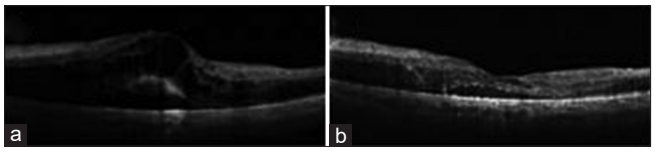

Figure 2: Optical coherence tomography and color fundus photography of case 2. (a) Optical coherence tomography before Ozurdex® injection. (b) Optical coherence tomography one month after Ozurdex® injection

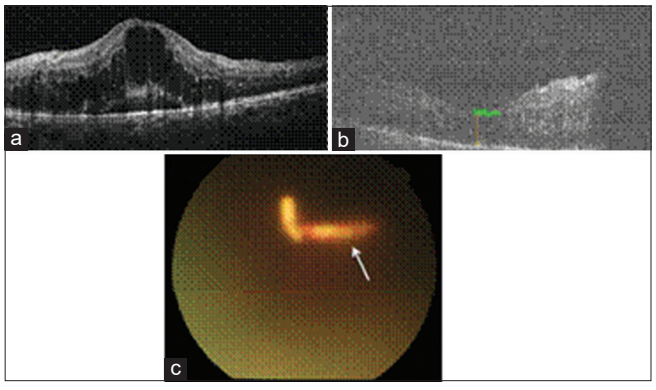

Figure 3: Optical coherence tomography and color fundus photography of case 3. (a) Optical coherence tomography before Ozurdex® injection. (b) Optical coherence tomography two months after Ozurdex® injection. (c) VH after Ozurdex® injection. The white arrow pointed out the implant

Discussion

Ozurdex injection is thought to be a safe and effective procedure to treat noninfectious uveitis, macular edema induced by retinal-vein occlusion and DME. Vitreous hemorrhage has been reported following DEX injection, but most instances cleared spontaneously in a short period of time and did not require surgical intervention. In the MEAD (Macular Edema Assessment of implantable DEX in Diabetes) study, vitreous hemorrhage related to treatment was reported in 3.5% of patients treated with DEX 0.7 mg, in 4.1% of patients treated with DEX 0.35 mg, and 0.0% of patients who received placebo.[2] The BEVORDEX (bevacizumab versus intravitreal dexamethasone for DME) study reported that two patients in a group of 46 patients developed vitreous hemorrhage after receiving Ozurdex injection to treat DME.[3] In the present report, only three patients developed vitreous hemorrhage among our past 190 patients who received DEX injections, and none occurred in non-DME patients. The common intraoperative findings in our cases were the presence of neovascular membrane along the vascular arcade with taut posterior hyaloids and the absence of PVD. Fortunately, the DEX implant was preserved after vitrectomy and maintained the effect of DEX, as expected.

The causes of spontaneous vitreous hemorrhage involve disruption of normal retinal vessels and bleeding from these diseased retinal vessels or from abnormal new vessels. PDR, retinal tear, proliferative retinopathy after retinal vein occlusion, and PVD without retinal tear are the most common causes of spontaneous vitreous hemorrhage.[4] Intravitreal injection of Ozurdex may induce faint vitreous hemorrhaging due to the disruption of normal vessels at the injection site, which clears spontaneously. In a case report, vitreous and retinal hemorrhage occurred immediately following Ozurdex injection in a vitrectomized eye and was caused by the implant hitting the retina.[5] Further, DEX injection or any type of intravitreal injection may cause a shock wave in the vitreous and hence abnormal vitreomacular traction.[6] Clemens *et al*. observed the formation of a macular hole 12 days after an uneventful Ozurdex injection.[7] These reports indicate that the injection may cause a drag force on the vitreous gel, inducing vitreoretinal traction at the posterior pole. Eyes with an abnormal vitreomacular interface are expected to have a higher risk of induced retinal tears or disruption of vessels. Abnormalities of the vitreomacular interface have been well documented in many diseases including diabetic retinopathy and retinal occlusion.

In this report, all three cases presented with a neovascular membrane but without PVD. The combination of abnormal vitreoretinal interface and neovascularization in our diabetic patients posed a greater risk of developing massive vitreous hemorrhage after DEX injection. Others have also reported that steroids can downregulate the effect of VEGF and upregulate fibrosis formation.[8,9] These actions may aggravate the formation of tractional membranes and the development of vitreous hemorrhage. Our experiences support the speculation that intravitreal injection of DEX might increase fibrosis and further promote traction and the disruption of fragile neovascular membranes. Although vitrectomy is supposed to decrease the level of inflammatory cytokines in the eye, a certain amount of recurrent or persistent DME persisted after vitrectomy. Its continued effectiveness in reducing macular edema among our patients supports the effectiveness of DEX in vitrectomized eyes.[10] Further management depends on the patient's status and the severity of retinal change.

Conclusion

Persistent vitreous hemorrhage after Ozurdex injection was rare but manageable and did not interrupt the effect on DME. Eyes with neovascular membrane but no PVD may be at risk of developing vitreous hemorrhage after Ozurdex injection.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Financial support and sponsorship

Nil.

Conflicts of interest

The authors declare that there are no conflicts of interests of this paper.

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