Ranibizumab Treatment in a Type-1 Diabetic Patient for Macular Edema During Lactation

*Tip 1 Diyabetik Bir Olguda Gelişen Makula Ödeminin Laktasyon Sırasında Ranibizumab ile Tedavisi**

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ABSTRACT

It is known that pregnancy is an important risk factor for the development of diabetic retinopathy and diabetic macular edema. In this report the author describes a case of a female patient with diabetes mellitus (DM) type 1 who faced a progress of diabetic retinopathy (DR) during her pregnancy with a development of diabetic macular edema (DME) and a deterioration of visual acuity in the left eye. The patient had been under observation for DR, and she had panretinal argon laser treatment for severe non-proliferative form of DR for two years before pregnancy. During the third trimester of pregnancy, a significant reduction of visual acuity in the patients' left eye occurred as a result of a fast developing DME. The visual acuity of the right eye had already been detoriated before pregnancy because of submacular fibrosis. She received additional peripheral retinal laser photocoagulation. The delivery went without complications. A gradual improvement in VA was expected during the post-delivery period. Unfortunately there was no reduction of DME for postpartum three months. We discussed the option of intravitreal ranibizumab treatment and the patient had three monthly injections which were followed by seven days interruption of breastfeeding. No side effects were observed for the patient and the baby. The patient had an improvement in visual acuity and she is under observation for two years after three injections.

Key Words: Intravitreal anti-VEGF treatment, pregnancy, lactation.

ÖZ

Gebelik diyabetik retinopati ve diyabetik makülopati gelişimi için önemli bir risk faktörüdür. Bu yazıda Tip 1 diyabeti olan gebeliği sırasında diyabetik retinopatisi (DR) ilerleyen ve sol gözünde diyabetik makula ödemi (DMÖ) gelişerek görme keskinliği bozulan bir kadın olgu sunulmaktadır. Olgu DR nedeniyle kliniğimizde takip edilen, gebeliğinden iki yıl önce ileri nonproliferatif DR nedeniyle panretinal argon laser tedavisi tamamlanan bir olgudur. Gebeliğinin üçüncü trimestrinde hızlı gelişen bir DMÖ nedeniyle olgunun sol gözünde görme keskinliği belirgin olarak azalmıştır. Sağ gözde görme keskinliği subretinal fibrozis nedeniyle gebelik öncesinde de düşüktür. Olguya gebelik sırasında ilave periferal retinal laser uygulaması yapılmıştır. Doğum sorunsuz gerçekleşmiş ve gebeliğin sonlanmasından sonra görme keskinliğinde düzelme olması beklenmiştir. Ancak postpartum üçüncü ay kontrolünde DMÖ'de herhangi bir düzelme görülmemiştir. Olguyla intravitreal ranibizumab enjeksiyonu seçeneği görüşülmüş ve onay alınması üzerine üç ardışık aylık enjeksiyon uygulanmıştır. Enjeksiyonu takiben yedi gün süreyle emzirmeye ara verilmiştir. Olguda ve bebekte herhangi yan etkiye rastlanmamıştır. Görme keskinliğinde artış saptanan olgu, üç enjeksiyonu takiben iki yıldır takip edilmektedir.

Anahtar Kelimeler: İntravitreal anti-VEGF tedavisi, gebelik, laktasyon.

INTRODUCTION

It is known that pregnancy is a risk factor for the development of diabetic retinopathy (DR) and diabetic macular edema (DME) and can accelerate the course of DR. Nonproliferative and proliferative DR develop in 18-58% and 5-16% of type 1 diabetic women who become pregnant, respectively.[1] The increased cardiac output, increased plasma volume, increased retinal blood flow, and occasional onset of anemia concomitant with pregnancy can be associated with new onset DME which can resolve spontaneously after delivery. There can be spontaneous regression of changes in nonproliferative DR and even proliferative DR after delivery, but if high- risk proliferative retinopathy develops, panretinal laser photocoagulation is indicated.[2,3]

The use of intraocular anti-vascular endothelial growth factor (VEGF) drugs during pregnancy and lactation has been reported in a few cases but is fraught with concerns for adverse side effects for the fetus or the infant.

In this paper a case of a female patient with type-1 diabetes mellitus (DM) had progression of DR during pregnancy with a development of DME and a deterioration of visual acuity in the left eye is reported.

CASE REPORT

Thirty one years old female type 1 diabetic patient had been under observation for DR for three years. She had received panretinal argon laser treatment for severe nonproliferative form of DR two years before pregnancy. Her Snellen visual acuity was 0.05 in the right eye and 0.8 in the left eye. Fundus examination showed submacular fibrosis and peripheral laser spots in the right eye and periperal laser spots with a normal macula in the left eye. During the third trimester of pregnancy, a significant reduction of visual acuity in the patients' left eye occurred as a result of a fast developing DME. Her visual acuities were 0.05 Snellen lines in both eyes. Fundus examination showed the same findings in the right eye and macular thickening and additional peripheral preretinal hemorrhages in the left eye. Santral macular thickness was 70 µm in the right eye and 567 µm in the left eye as measured using optical coherens tomography (OCT). She received additional peripheral retinal laser photocoagulation. The delivery went without complications; both the child and the mother were in a normal condition after the delivery. A gradual improvement in visual acuity was expected during the post-delivery period. Unfortunately there was no reduction of DME during the three months postpartum period. Fundus florescein anjiography showed diffuse macular edema and hyperfluorescense in the periphery due to neovascularization (Figure 1a and b). The patient received additional laser and she was informed about the option of intravitreal ranibizumab treatment. The next month she came with a decision and had three monthly injections which were followed by seven days interruption of breastfeeding. Informed consent was obtained before every procedure. No side effects were observed for the patient and the baby during the observation period. Her visual acuity improved to 0.7 Snellen lines and santral macular thickness of the left eye decreased to 194 µm (Figure 2 a-c). She is under observation for two years after three monthly injections.

DISCUSSION

Anti-VEGF drugs such as bevacizumab and ranibizumab are increasingly used in patients with choroidal neovascularization due to pathologies other than age-related macular degeneration, such as myopia and in patients with macular edema due to retinal vein occlusion or DM. These conditions often affect younger patients and include women of pregnancy potential.[4]

Bevacizumab can be detected in serum one day after intravitreal injection and remains stable for 7 days.[5] The aqueous half-life of a single 1.5 mg intravitreal injection of bevacizumab in a non-vitrectomized human eye is approximately 9.82 days.[6] In a rabbit model, unlike bevacizumab, ranibizumab was not detected in serum after 0.5 mg intravitreal injection.[7]

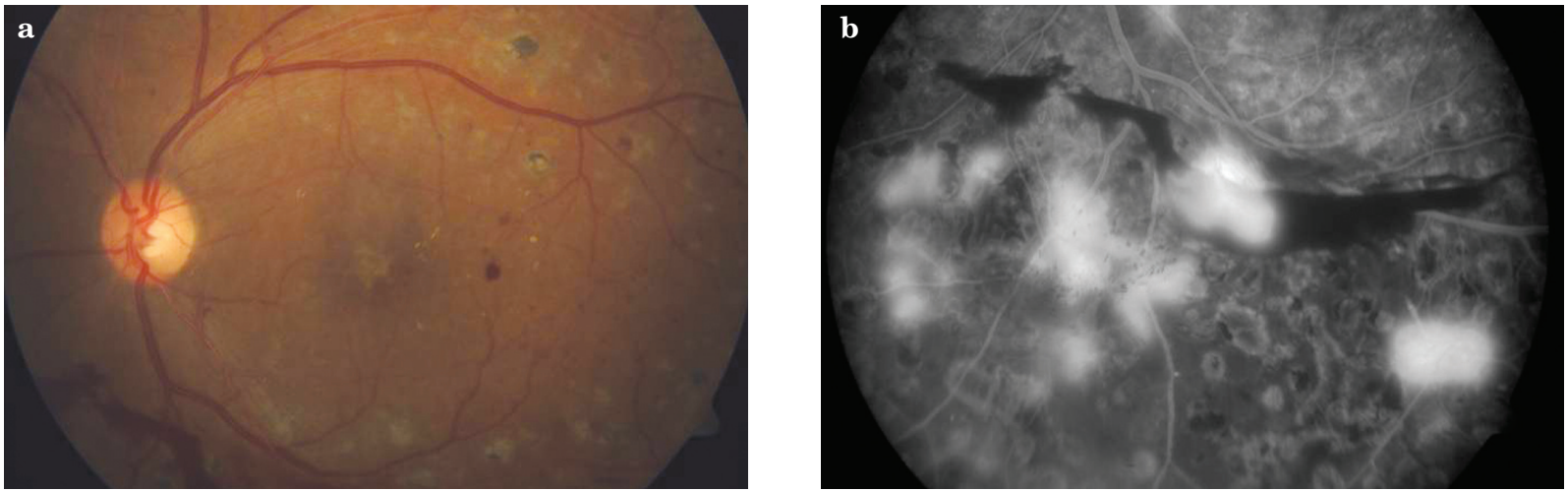

Figure 1a,b: *Color fundus (a) and fundus fluorescein anjiographic (b) photographs of the left eye. The fluorescein anjiography showed hyperfluorescense due to neovascularization in the periphery.*

We know that multiple injections are often necessary for the treatment of retinal diseases and inhibition of VEGF-A can potentially affect the developing embryo and the mother for a prolonged period of time. The amount of anti-VEGF antibodies needed to impact pregnancy is stil unknown.

There are only very limited data about the use of anti-VEGF agents in pregnant or nursing women. Ranibizumab and bevacizumab, according to FDA categories of drug safety during pregnancy, are in category C. This means that animal studies showed teratogenicity in the fetus, but there are no adequate studies in humans. However, when there are potential benefits, they can be used in pregnant women despite the risks under some circumstances.[8]

To the best of our knowledge there is only one report including the anti-VEGF treatment in pregnancy. In this report by Wu et al.,[8] bevacizumab was administered to treat myopic choroidal neovascularisation in a 25-year-old woman later discovered to be pregnant. Both eyes of the patient were treated with a total of three intravitreal injections of bevacizumab sequentially which were followed by vision improvement in both eyes.

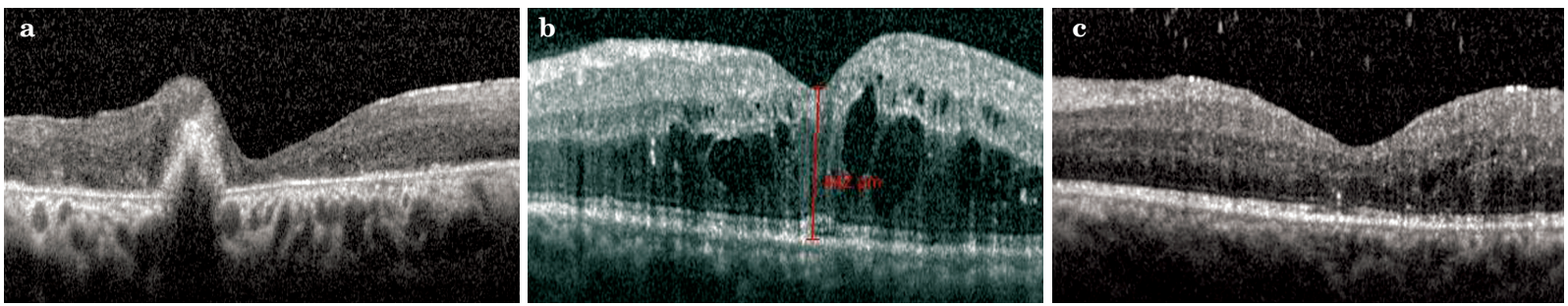

Figure 2a-c: *OCT scans of right eye (a), left eye before treatment (b), left eye after 3 monthly injections (c). Central macular thickness was measured as 567 µm before treatment and decreased to 194 µm after intravitreal injections in the left eye. Central macular thickness of the right eye was 70 µm.*

They found no evident pregnancy-related complications at one year postpartum period. They also reported that although the risk to fetuses or infants remains theoretical, it cannot be ignored until more safety data in humans are available. They recommended to consider pregnancy tests and counselling routinely for women of reproductive age who may require intravitreal anti-VEGF therapy.

When we search the literature we found only one case report about the intravitreal anti- VEGF treatment during lactation. In this case report, a 32-year-old woman, who was breastfeeding her 12-week-old son, with a diagnosis of scar-associated choroidal neovascularization in her left eye received one intravitreal injection of bevacizumab and three monthly injections of ranibizumab and the VEGFA levels of serum and breast milk samples were analyzed after the injections.[9] They reported that after bevacizumab injection, the serum VEGFA level decreased rapidly within one week to an undetectable level. The VEGFA level in breast milk slowly decreased, from 13.3 ng/mL to 8.6 ng/mL after 2 weeks, marking a decrease of 35%. In the following weeks, the VEGFA level recovered slowly. During this time, bevacizumab was detected in the serum with a peak concentration after one week besides no free bevacizumab was detected in breast milk at any time. When they evaluate the results of ranibizumab four days after injection, the serum VEGFA level decreased only by 10% and began to increase again after only three more days. The level of VEGFA in breast milk remained stable without significant alterations. They reported that there was a significant effect of treatment with intravitreal bevacizumab, but not ranibizumab, on VEGFA levels in serum and breast milk. This distinction was explained by a difference in the molecular structure of the proteins.

In this reported case, we observed no side effects of intravitreal ranibizumab injections for the patient and the baby during the follow-up period of two years. Previous studies reported that there was no ranibizumab in serum after intravitreal injection and systemic exposure to ranibizumab estimated to be very very low due to elimination on reaching systemic circulation from the vitreous.[7]

Although ranibizumab seems to be safe for breastfeeding woman in theory we prefered to interrupt lactation for 7 days.

It is known that, VEGF is present in high concentrations in breast milk and binds to specific receptors on cells derived from intestinal epithelium.[10] Pan-VEGF inhibition with ranibizumab or bevacizumab, especially if repeated intravitreal injections are required, may have significant long-term consequences and potential risks to fetuses or infants. If anti-VEGF treatment is required in nursing women, ranibizumab should be preferred to bevacizumab because of a lower effect on VEGFA levels in the serum and breast milk. Besides educating the patient and documenting the discussion of such additional risks would appear critical in this clinical situation.

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