INTRAVITREAL RANIBIZUMAB IN PREGNANT PATIENT WITH MYOPIC CHOROIDAL NEOVASCULAR MEMBRANE. A CASE REPORT

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SUMMARY

Aim: To present the case of a patient with myopic choroidal neovascular membrane (mCNV) in the 3rd trimester of pregnancy, who was treated with intravitreal ranibizumab.

Case Report: The 34-year-old patient was referred to the Department of Ophthalmology of the University Hospital Kralovske Vinohrady in January 2020 for mCNV on her right eye (RE). The patient was in the 34th week of pregnancy. Initial best corrected visual acuity (BCVA) was 68 ETDRS letters. Spherical equivalent of the RE was -11.5 dioptres, axial length of the RE was 27.7 mm. Pigmented CNV with small haemorrhage was present on the retina of the RE. Optical coherence tomography (OCT) of the RE showed a hyperreflective mass above the retinal pigment epithelium, central retinal thickness (CRT) was 310 µm. OCT angiography confirmed the presence of a classic CNV in the macula of the RE. Two weeks later, the hyperreflective lesion and oedema in the macula of the RE increased, the CRT was 329 µm, BCVA remained stable. After discussion with the patient and the treating gynaecologist, intravitreal ranibizumab was administered in the RE in the 36th week of pregnancy. On check-up 3 weeks later, we observed the decrease of macular oedema to 276 µm and the improvement of BCVA to 78 ETDRS letters. The patient delivered a healthy baby girl in the 39th week of pregnancy via caesarean section, postnatal adaptation of the newborn was normal. During further visits, the BCVA improved to 83 ETDRS letters and the macular oedema disappeared completely. 8 months after the first ranibizumab injection, the CNV reactivated, BCVA decreased to 72 ETDRS letters, oedema was present in the macula and the CRT was 309 µm. Another ranibizumab was administered into the RE. The patient then discovered that she was pregnant; according to calculations, she was in the 3rd week of pregnancy at the time of the second ranibizumab injection. After the second injection, BCVA improved to 79 ETDRS letters, macular oedema on the OCT disappeared and CRT decreased to 264 µm. The pregnancy was terminated per patient's request.

Conclusion: Intravitreal administration of ranibizumab in the 3rd trimester of pregnancy led to the improvement of BCVA and decrease of macular oedema in the patient with mCNV. The injection had no adverse effect on the pregnancy or the postnatal adaptation of the newborn. However, it is always necessary to consider the risk/benefit ratio when administering intravitreal antiVEGF drugs in pregnant patients. Thorough discussion with the patient is necessary.

Key words: myopic choroidal neovascular membrane, pregnancy, ranibizumab, antiVEGF

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INTRODUCTION

Intravitreal use of antiVEGF drugs showed very good efficacy in the treatment of diseases associated with the development of choroidal neovascular membrane (CNV) and macular oedema, such as the wet form of age-related macular degeneration (AMD) [1–4], CNV associated with pathological myopia [5–7], secondary CNV associated with other ocular diseases [8, 9], diabetic macular oedema or macular oedema after retinal vein occlusion [10–12]. Good results were also observed in the treatment of proliferative diabetic retinopathy [13]. At present, three antiVEGF drugs intended for intravitreal use are registered in the Czech Republic – ranibizumab (Lucentis, Novartis, Basel, Switzerland), brolucizumab (Beovu, Novartis, Basel, Switzerland) and aflibercept (Eylea, Bayer, Leverkusen, Germany). Bevacizumab (Avastin, Roche Pharma AG, Grenzach-Wyhlen, Germany) is sometimes utilised in off-label use, however it is not intended for intravitreal administration according to the Summary

of Product Characteristics (SmPC) [14]. Clinical studies showed a very good safety profile of these drugs [1, 5, 7, 8, 10, 11]. However, no study assessing the safety of intravitreal antiVEGF drugs in pregnant women has of yet been performed. Little information has been published about this topic. According to the SmPC, these drugs should only be used in pregnant women if the potential positive effect outweighs the possible risk to the foetus. Our aim is to present the case of a pregnant woman who received intravitreal ranibizumab for myopic CNV (mCNV).

CASE REPORT

The 34-year-old patient was referred to the Department of Ophthalmology, University Hospital Kralovske Vinohrady in January 2020 for mCNV in her right eye (RE). She complained of decreased vision in her RE lasting for 3 months. The patient was in the 34th week of pregnancy at the time of the first visit; the course of pregnancy was physiological up to that point. It was the patient's second pregnancy; she already had 1 physiological delivery in the past. The patient took no medication, there was a high myopia of the RE in her ocular history. Initial best corrected visual acuity (BCVA) was 68 ETDRS letters in the RE and 85 ETDRS letters in the left eye (LE). There was a marked difference in both the refraction and axial length between the RE and the LE. Spherical equivalent in the RE was -11.5 dioptres, ocular axial length was 27.7 mm, spherical equivalent in the LE was -6.5 dioptres, ocular axial length was 25.8 mm. Examination of the anterior segment of both eyes was without any pathologies. On the retina of the RE, there was a pigmented CNV with a small haemorrhage (Fig. 1). In the periphery of the retina of the RE at 12 o'clock, there was a lattice degeneration with a small atrophic retinal hole. Posterior segment examination of the LE was without any pathologies. Optical coherence tomography (OCT) of the RE showed a hyperreflective lesion above the retinal pigment epithelium, central retinal thickness (CRT) was 310 µm (Fig. 2A). OCT angiography showed a classic CNV in the macula of the RE. We concluded the findings as a CNV in pathological myopia. Because of the pregnancy of the patient and the relatively discreet finding, we decided to observe the patient. We performed barrage laser around the atrophic hole in the RE and we scheduled a check-up in 14 days.

On the check-up in February 2020, the BCVA was stable. However, there was a slight increase in the oedema and the hyperreflective lesion in the macula, CRT was 329 µm (Fig. 2B). After discussion with the patient and her treating gynaecologist, injection of intravitreal ranibizumab in the RE was indicated. It was also recommended that delivery be performed via caesarean section (CS), due to the risk of bleeding from the active mCNV during vaginal delivery. The patient was informed in detail about all possible risks connected with the ranibizumab injection for her and the foetus, before the injection. The patient accepted the risks and signed the informed consent for intravitreal injection of ranibizumab. Injection was performed in the 36th week of pregnancy in the standard regimen used in our Clinic, with no complications.

On the visit 3 weeks after the injection and 1 week before the planned CS, the BCVA improved to 78 ETDRS letters, CRT decreased to 276 µm and the haemorrhage in the macula was absorbed (Fig. 2C). Another ranibizumab injection was not indicated, and the next visit was scheduled in 6 weeks. In the meantime, the patient delivered a healthy baby girl in the 39+0 weeks via CS. Postnatal adaptation of the newborn was normal, Apgar score was 10-10-10. On the check-up 9 weeks after the ranibizumab injection, BCVA improved again to 83 ETDRS letters, CRT was 277 µm. We continued to follow the patient regularly. In October 2020, 8 months after the first ranibizumab injection, the mCNV in the macula of the RE reactivated and BCVA decreased to 72 ETDRS letters. Oedema appeared again on the OCT; CRT was 309 µm (Fig. 2D). Another ranibizumab injection was administered into the RE. After the injection, pregnancy was confirmed in the patient. According to the calculations, the patient was in the 3rd week of pregnancy at the time of the second ranibizumab injection. After the second injection, BCVA improved again to 79 ETDRS letters, oedema disappeared, and CRT decreased to 264 µm (Fig. 2E). The pregnancy was terminated per patient's request. We continue to follow the patient in our Clinic.

DISCUSSION

Around 5–10 % of patients with pathologic myopia develop mCNV. It is generally small, type 2 – classic – CNV. It often develops close to the fovea and is associated with rapid BCVA decline and metamorphopsia.

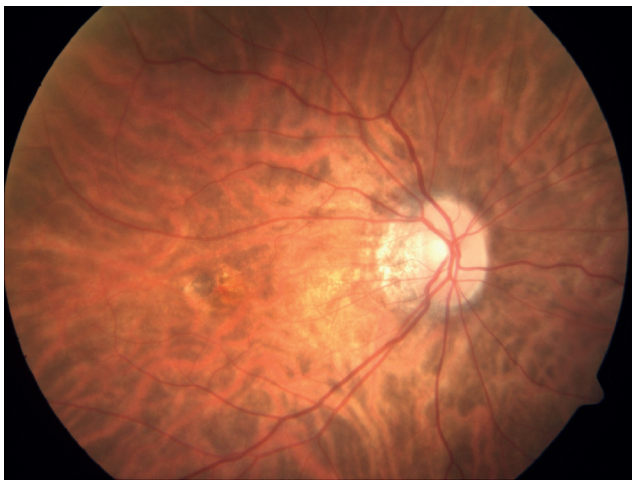

Figure 1. Fundus photograph of the right eye. Pigmented myopic choroidal neovascular membrane and small haemorrhage are visible

OCT, fluorescein angiography and OCT angiography are used in the diagnostics of mCNV [15, 16]. At present, antiVEGF drugs are used for treatment of mCNV with very good results [5–7].

Several case reports were published on the use of ranibizumab in pregnant patients [17–20]. In one of these patients, abortion occurred after the intravitreal administration of ranibizumab. Injection was performed in the 5th week of pregnancy [17]. Several cases of abortion were described after intravitreal bevacizumab [21–23]. In all these cases, the patients were in the first trimester of pregnancy. However, the risk of spontaneous abortion is highest in this period, even in healthy patients [24]. Because of this, it is difficult to determine the effect of intravitreal antiVEGF drugs on the risk of spontaneous abortion. In one patient treated with intravitreal bevacizumab, preeclampsia developed and it was necessary to perform CS for foetal distress. However, this patient had several risk factors for preeclampsia. Also, the period between the bevacizumab administration and the occurrence of preeclampsia in this patient was 26 weeks [25].

Vascular endothelial growth factor (VEGF) plays an important role in the growth of the placenta and early embryogenesis and in the later foetal development [26, 27]. It also plays a role in the implantation of the embryo, and the lower VEGF expression may affect the incidence of spontaneous abortions in the early stages of pregnancy [28]. In the animal studies, intravitreal administration of ranibizumab had no influence on the incidence of developmental toxicity nor teratogenicity, and had no influence on the foetal weight nor the structure of the placenta [29]. Intravitreal administration of bevacizumab led to lower foetal and placental weight in rats, when administered in the early or middle stages of pregnancy [30]. Intravenous administration of bevacizumab in rabbits was associated with embryotoxicity and teratogenicity and led to the reduction of both foetal and maternal weight [14]. In aflibercept, embryotoxicity was proven in both the intravenous and subcutaneous administration, however, achieved systemic exposure was substantially higher than the maximum exposure observed after intravitreal administration in humans [31]. No animal reproduction studies have been conducted with brolucizumab [32].

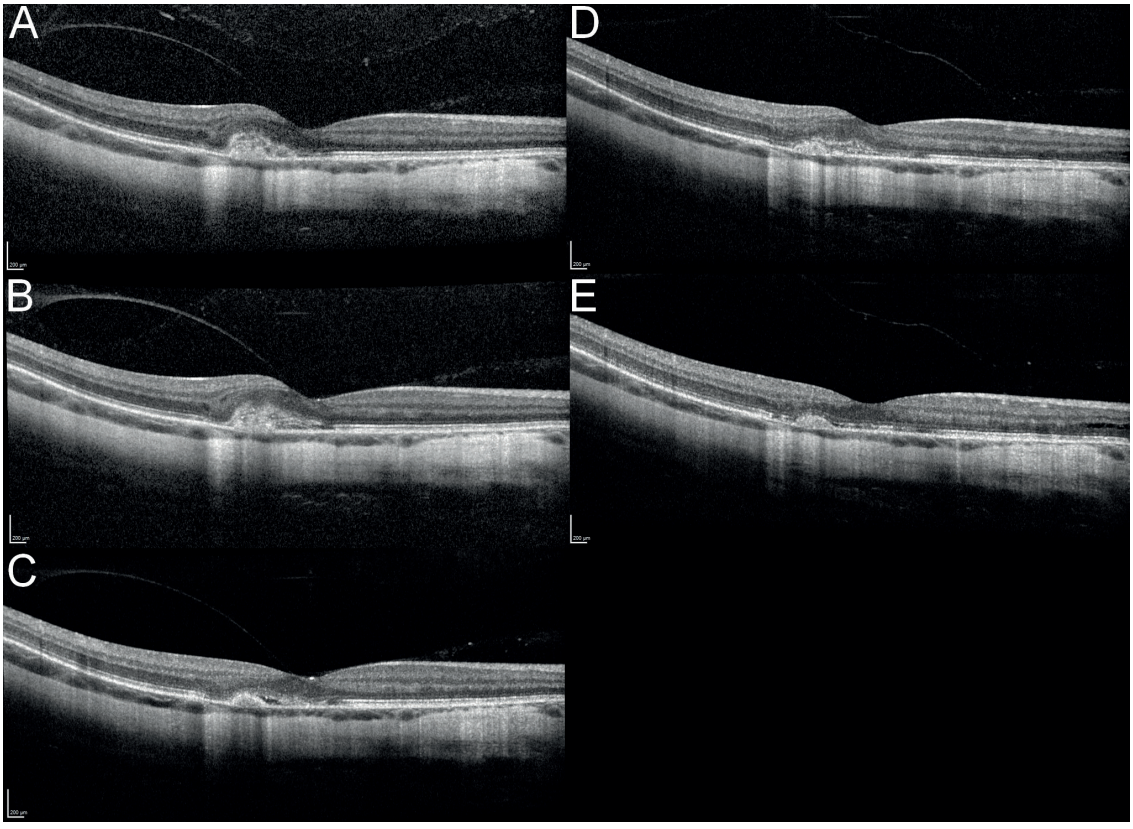

Figure 2. Optical Coherence Tomography of the macula of the right eye
A) Initial finding, hyperreflective lesion in the macula above the retinal pigment epithelium is present, best-corrected visual acuity (BCVA) 68 ETDRS letters, central retinal thickness (CRT) 310 µm.
B) Finding 14 days after the initial visit, increase in the lesion size and macular oedema are visible, BCVA 68 ETDRS letters, CRT 329 µm.
C) Finding 3 weeks after the ranibizumab injection, BCVA 78 ETDRS letters, CRT 276 µm.
D) Reactivation of the myopic neovascular membrane, BCVA 72 ETDRS letters, CRT 309 µm.
E) Finding after the second ranibizumab injection, BCVA 79 ETDRS letters, CRT 264 µm.

In our patient, we recommended delivery via CS for the presence of active CNV with haemorrhage in the macula of the RE. Delivery via CS is usually recommended in patients with high myopia as a prevention of retinal breaks and retinal detachment. However, it was never proven that vaginal delivery increases the risk of retinal detachment [33, 34]. Nevertheless, cases of retinal haemorrhage after the Valsalva manoeuvre in women during labour were described [35]. We have not found any case in the literature of retinal haemorrhage caused by vaginal delivery in a patient with active CNV.

CONCLUSION

Intravitreal administration of ranibizumab in the 3rd trimester of pregnancy led to the improvement of BCVA and a decrease of macular oedema in the patient with mCNV. The injection had no adverse effect on the pregnancy or the postnatal adaptation of the newborn. Nevertheless, it is always necessary to consider the risk/benefit ratio when administering intravitreal antiVEGF drugs in pregnant patients. Thorough discussion with the patient is necessary.

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