

Inadvertent Use of Bevacizumab to Treat Choroidal Neovascularisation During Pregnancy: A Case Report

Ziqiang Wu,¹MD, Jingjing Huang,²MD, Srinivas Sadda,³MD

Abstract

Introduction: This study reports a case of bevacizumab administered to treat choroidal neovascularisation in a woman later discovered to be pregnant. **Clinical Picture:** A 25-year-old pregnant woman developed myopic choroidal neovascularisation in both eyes. **Treatment:** Both eyes were treated with a total of 3 intravitreal injections of bevacizumab sequentially. **Outcome:** Vision improved significantly in both eyes. There were no evident pregnancy-related complications at 1 year postpartum. **Conclusion:** Although anti-vascular endothelial growth factor (VEGF) therapy did not result in any detectable short-term adverse event in this mother and baby, the potential toxicity of these agents must be carefully considered in pregnant patients.

Ann Acad Med Singapore 2010;39:143-5

Key words: Anti-VEGF therapy, Pre-eclampsia, Vasculogenesis

Introduction

The recognition that vascular endothelial growth factor (VEGF) plays an important role in the pathogenesis of neovascular age-related macular degeneration (NVAMD) has led to the development of several intravitreal anti-angiogenic therapeutics. Ranibizumab (Lucentis, Genentech, San Francisco, USA) and pegaptanib (Macugen, OSI/Eyetech Pharmaceuticals, New York, USA) have been FDA-approved for the treatment of all forms of NVAMD in the United States, while bevacizumab (Avastin, Genentech) is gaining wide acceptance as an off-label therapy. All 3 may have efficacy against choroidal neovascularisation secondary to pathologic myopia.¹⁻³

Both bevacizumab and ranibizumab intravitreal injections may have effects outside of the intended treatment eye.⁴⁻⁶ While NVAMD is found in an older population, younger women of reproductive age develop choroidal neovascularisation from various aetiologies such as myopia (mCNV) or punctate inner choroidopathy.⁷ The use of VEGF-inhibitors is also on the rise in the treatment of ischaemic retinal diseases, including diabetic retinopathy and retinal vein occlusion, that are not infrequently diagnosed in younger patients. However, VEGF has important biological roles outside of the eye, including during various stages of pregnancy. We report a case of

inadvertent, off-label treatment of mCNV with bevacizumab and discuss the underlying basis for concern with a potential for medicolegal complications.

Case Report

A 25-year-old gravid 1, para 1 complained of metamorphopsia in the left eye for 2 to 3 days. At the time, her baby was 3 months old and was vaginally delivered without complications. She continued to breastfeed at the time of presentation but was gradually weaning off. The best corrected visual acuity (BCVA) was 20/60 right eye (OD) and 20/40 left eye (OS) with spherical equivalent of -18.5D in both eyes (OU). Ocular examination was unremarkable except for subtle subretinal haemorrhages in both maculae and tigroid fundi. Fluorescein angiography revealed areas of subfoveal choroidal neovascularisation in both maculae. After discussing the risk and benefits of treatment, including photodynamic therapy with verteporfin (Visudyne, Novartis) and the anti-VEGF intravitreal therapies, the patient elected an initial period of observation. A month later, BCVA had declined to 20/60 OU but she had not noticed any progression of symptoms. She was advised to wean off breastfeeding as quickly as possible and to avoid pregnancy. A week later, she reported decreased vision in both eyes, with BCVA of 20/200 OD and 20/60-2

¹ Center for Advanced Eye Care, Carson City, NV, USA

² The State Key Laboratory of Ophthalmology, Zhongshan Ophthalmic Center at Sun Yat-Sen University, Guangzhou, China

³ The Doheny Eye Institute, Department of Ophthalmology, Keck School of Medicine at University of Southern California, Los Angeles, CA, USA

Address for Correspondence: Dr Ziqiang Wu, Center for Advanced Eye Care, 1104 N. Division Street, Carson City, NV 89703, USA.

Email: ziqiangw@hotmail.com

OS. Fundus examination and optical coherence tomography (OCT) revealed mild macular oedema and persistence of subretinal haemorrhage OU. She had stopped breastfeeding and agreed not to resume. After repeat discussion of the risks, benefits and alternatives, she declined photodynamic therapy. In addition, due to limitations of insurance coverage, she declined ranibizumab and pegaptanib, but expressed an interest in the much less expensive bevacizumab therapy. She was carefully counselled that the treatment was not approved for intraocular use, and there were no randomised clinical trial data to support its safety and efficacy. Nonetheless, the patient wished to proceed with this treatment, and received bevacizumab 1.25 mg intravitreal injection in both eyes, performed 1 week apart. Six weeks later, BCVA had improved to 20/30 in both eyes, with resolution of subretinal haemorrhage and macular oedema OD and persistence of trace subretinal hemorrhage OS. She had not resumed breastfeeding, and stated that she was not pregnant. Intravitreal bevacizumab injection was repeated on the left eye. Three weeks later, the patient reported a positive pregnancy test, with the last menstrual period 5 weeks prior. Small subretinal scars were beginning to form in both maculae, and BCVA was 20/40 OU. Fortunately, without further treatment, her BCVA remained stable with no change in the minimal residual metamorphopsia. She also reported no pregnancy-related complications such as pre-eclampsia or preterm labour. The patient delivered a healthy 3.17-kg baby girl vaginally at 39 weeks gestation. Three weeks after delivery her BCVA remained 20/30 in both eyes, and the infant exhibited no developmental abnormalities. The mother and infant were followed for another 12 months and were not found to have any adverse effects.

Discussion

VEGF is a growth factor for angiogenesis and a regulator of vascular permeability.⁸⁻¹⁰ The VEGF gene family consists of VEGF-A, VEGF-B, VEGF-C, VEGF-D, and placental growth factor (PlGF). They have varying affinities for the 3 known VEGF receptor kinases — VEGFR1 (fms-like tyrosine kinase-1 or Flt-1), VEGFR2 (fetal liver kinase-1 and kinase domain region or Flk/KDR), and VEGFR3.^{11,12} VEGF-A is the target of the current anti-VEGF intravitreal therapies. It confers its biological activities by binding to VEGFR1 and VEGFR2 receptors, and has 9 known isoforms.

Recent studies suggest that hypertension is a disease of inadequate or abnormal response to angiogenic growth factors such as VEGF and PlGF.¹³ Two clinical models have demonstrated a link between inhibition of angiogenic growth factor activity and hypertension.¹³ A recent study suggests that both systolic and diastolic blood pressures may rise 3 weeks after a single 1.25 mg bevacizumab intravitreal

injection.¹⁴ This phenomenon occurs in as early as 1 week after injection and persists at 6 weeks in patients with pre-existing hypertension.¹⁴

Pre-eclampsia (hypertension and proteinuria during pregnancy, usually in the third trimester) is accompanied by high circulating levels of soluble VEGFR1, which forms inactive complexes with VEGF and PlGF.¹³ Therefore, pre-eclampsia may also be a manifestation of inadequate angiogenic growth factor activities. Pharmacological inhibition of VEGF decreases the levels of circulating angiogenic growth factors, thus potentially increasing the risk of pre-eclampsia. In fact, 2 common side-effects of intravenous bevacizumab are hypertension and proteinuria. Vasculogenesis, the formation of *de novo* blood vessels in the developing embryo, are also mediated by VEGF-A and PlGF.¹⁵ Therefore, anti-VEGF agents may influence both the mother and the fetus, and their effects may depend on the age of the fetus. Our patient, who received bevacizumab injections around the time of fetal conception, would not have been at risk for pre-eclampsia at that time. However, the vasculogenesis of the fetus, if anti-VEGF agents were used during critical phases of fetal development, could be adversely affected.

The critical roles of VEGF-A and PlGF in choroidal neovascularisation and in other ischaemic retinal diseases are well-known.¹⁶⁻¹⁸ Intravitreal injection of bevacizumab and ranibizumab, which are antibodies or antibody fragments against VEGF-A, appears to have effects in the contralateral eye.^{4,6} The underlying mechanism has not been precisely defined, but it is believed that bevacizumab may escape into the systemic circulation after intravitreal injection, possibly through an active transport mechanism.¹⁹ Bevacizumab can be detected in serum 1 day after intravitreal injection and remains stable for 7 days.¹⁹ The aqueous half-life of a single 1.5 mg intravitreal injection of bevacizumab in a non-vitreotomized human eye is approximately 9.82 days.²⁰ In a rabbit model, unlike bevacizumab, ranibizumab was not detected in serum after 0.5 mg intravitreal injection.²¹ However, the possible increased propensity for arterial thrombo-embolic events in patients receiving intravitreal ranibizumab injections suggests that it too may escape into systemic circulation.^{22,23} Because multiple injections are often necessary, inhibition of VEGF-A for the treatment of retinal diseases 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 and whether they are excreted in breast milk are unknown. Although the risk to fetuses or infants remains theoretical, it cannot be ignored because the consequences of abnormal fetal development are so devastating. Until more safety data in humans are available, pregnancy tests and counselling should be considered routinely for women of reproductive

age who may require intravitreal anti-VEGF therapy.

While ranibizumab and bevacizumab are currently the most common treatments for age-related choroidal neovascularisation in the United States, alternatives include photodynamic therapy with verteporfin and intravitreal pegaptanib injections. Verteporfin, similar to ranibizumab and bevacizumab, is designated Pregnancy Category C (Animal studies demonstrated teratogenicity in the fetus, but there are no adequate studies in humans. However, potential benefits may warrant use in pregnant women despite risks under some circumstances) (Source: verteporfin, ranibizumab, and bevacizumab product inserts). Photodynamic therapy as a class has been reported to cause DNA damage (Source: verteporfin product insert). Pegaptanib, an aptamer which selectively inhibits the VEGF-165 isoform involved in pathogenesis and is designated Pregnancy Category B (no teratogenicity in mice, but human studies are not yet available), may theoretically be a safer alternative in a young adult. This is because VEGF appears to have important roles in potentiating cellular adaptation to retinal ischaemia and in neuro-protection by reducing apoptosis.²⁴ Pan-VEGF inhibition with ranibizumab or bevacizumab, especially if repeated intravitreal injections are required, may have significant long-term consequences. For young female patients of reproductive age, the off-label use of anti-VEGF agents should be considered carefully. Educating the patient and documenting the discussion of such additional risks would appear critical in this clinical setting.

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