Tocilizumab throughout pregnancy in two patients with severe Takayasu's arteritis

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Takayasu's Arteritis (TAK) is a very rare and potentially life-threatening large-vessel vasculitis that affects predominantly women of childbearing age[1]. Pregnant women with TAK are at a higher risk for adverse pregnancy outcomes such as pre-eclampsia and intrauterine growth restriction[1]. However, the optimal management of this condition during pregnancy remains an unmet need. We report two cases of patients with severe TAK who were successfully treated with tocilizumab (IgG1-type monoclonal antibody against interleukin-6 receptor) throughout pregnancy, with no abnormalities recorded in their offspring.

The first case refers to a 21-year-old woman with a 3-year diagnosis of multisegmental TAK involving the thoracic aorta and supra-aortic vessels, with bilateral retinal vasculitis and moderate aortic regurgitation. At disease presentation her C-reactive protein (CRP) was 3.32mg/dl and her erythrocyte sedimentation rate (ESR) was 70mm/h. She was initially treated with prednisolone (20mg/day) and methotrexate (25mg/weekly), but due to persistent disease activity and poor treatment compliance, monthly intravenous tocilizumab (8mg/kg) was added with subsequent decrease of her inflammatory markers (CRP 0.03 mg/dl and ESR 10 mm/h). Four months later, due to severe stenosis of both primitive carotids, she underwent an arterial bypass from the ascending aorta to the distal right primitive carotid and suffered an intraoperative ischemic stroke resulting in permanent left hemiparesis. Three months after surgery, having suspended methotrexate by her own decision and against medical advice, she became pregnant. Attending to the patient's severe disease phenotype, we decided to maintain tocilizumab in association with prednisolone 10mg/day, and her disease remained under control. Forty-nine days after the last tocilizumab infusion, at 37 weeks' gestation (WG), an elective caesarean section (CS) was performed resulting in a healthy newborn weighting 2720g (Apgar score of 9/9/10). No congenital defects or serious infections during the first 6 months of life were recorded. Moreover, there was no increase in her inflammatory markers during and after pregnancy.

The second patient was a 24-year-old woman with a 6-year history of TAK involving the thoracic aorta, with an ascending aortic aneurism and severe aortic valve regurgitation. At disease presentation she had a CRP of 16mg/dl and an ESR of 120mm/h. She conceived while in disease remission (i.e. asymptomatic and with CRP 0.11 mg/dl and ESR 2 mm/h) and under treatment with subcutaneous tocilizumab (162mg/ /weekly) and prednisolone (10mg/day). However, from the 24 WG onwards, she began complaining of progressive fatigue, palpitations and orthostatic lypotimia. Doppler ultrasound of head and neck vessels and magnetic resonance of thoracic vessels showed no signs of active disease. Serial echocardiograms however, displayed gradual worsening of the aortic aneurysm dimensions – from 47 mm diameter before conception to 56 mm at 32 WG. Given the high risk for aortic rupture[2], an elective CS was performed at 32 WG and 6 days, 5 days after last tocilizumab infusion, and a newborn weighting 1900g was born (Apgar score of 9/10/10). An isolated patent *foramen ovale* related to prematurity was diagnosed. After the CS, the patient underwent an uneventful Bentall procedure (replacement of the aortic valve and ascending aorta). As in the first case, there was no increase in inflammatory markers documented during and after pregnancy.

There is currently very scarce evidence on the use of tocilizumab during pregnancy[3–6]. Due to the limited

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TABLE I. SUMMARY OF THE PUBLISHED CASE REPORTS ON TOCILIZUMAB USE THROUGHOUT PREGNANCY

Reference	Disease	TCZ route/dose and interval	Concomitant medication	Last TCZ infusion (days before delivery)	Gestational age at delivery	Apgar score at 1/5 minutes	Birth weight (in grams)	Congenital defects	[TCZ] in maternal blood* (in ng/ml)	[TCZ] in umbilical cord blood* (in ng/ml)
Saito et al, 2019[8]	AOSD	iv/400mg every 4 weeks	PDN and tacrolimus	27 days	40 weeks+ 5 days	10/10	2792	None	4893.2	682.9
Tada et al, 2019[9]	RA	iv/8mg/kg every 4 weeks	PDN	24 days	38 weeks	Not specified	3276	None	6170 (1 day before delivery)	5490
Morijama et al, 2019[10]	TAK	sc/162mg every 2 weeks	PDN	Not specified	39 weeks + 4 days	8/9	3188	None	13304	1009

AOSD: adult-onset Still's disease; iv: intravenous; PDN: prednisolone; RA: rheumatoid arthritis; sc: subcutaneous; TAK: Takayasu's arteritis; TCZ: tocilizumab; [TCZ]: tocilizumab levels.* unless otherwise specified, tocilizumab levels were measured at delivery.

data on its safety[7], effective contraception is strongly recommended, and tocilizumab is frequently withdrawn before conception or during the first trimester. Three case reports have fully disclosed tocilizumab use throughout pregnancy[8–10] but only one in a patient with TAK (Table I). As in both our cases, no abnormalities were reported in the newborns. In addition, tocilizumab levels were measured in the umbilical cord blood at the time of delivery and were lower than expected (<100% of those in the mother's blood), as opposed to what has been described for natural IgG antibodies (145-152%[9,10]). Nevertheless, considering that tocilizumab still reaches the fetal blood, our cases are important examples of its apparent safety over the offspring. Moreover, they support the use of tocilizumab during pregnancy in an extremely rare condition such as TAK, in which treatment management during gestation still remains unclear.

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