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LETTER

Safe use of tocilizumab in pregnant women with Takayasu arteritis: three case studies

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Takayasu arteritis (TAK) is an idiopathic large vessel vasculitis, which occurs most commonly in women of reproductive age. During pregnancy, TAK is associated with adverse pregnancy outcomes, including hypertensive disorders, preterm delivery and fetal growth restriction.[1] Hence, controlling the disease activity before conception and during pregnancy is highly important for women with TAK who wish to have children. Although prednisolone (PSL) is the first-line drug for TAK, remission is sustained in only 28% of patients with TAK for more than 6 months when PSL is reduced to 10 mg/day or less.[2]

Tocilizumab (TCZ) is a recombinant humanised anti-interleukin-6-receptor monoclonal IgG antibody with stable or improved activity against TAK. The steroid-sparing effects of TCZ were demonstrated in a randomised, placebo-controlled, double-blind study.[3] However, the safety and efficacy of TCZ in pregnancies complicated with TAK are unclear.

Herein, we describe the cases of three primiparous women with refractory TAK (table 1). TCZ treatment combined with PSL was required before pregnancy. The cardiovascular risks during pregnancy were very high in all cases: severe stenosis of the ostial right coronary artery in case 1, pulmonary hypertension resulting from bilateral pulmonary artery stenosis in case 2, and type V TAK of Numano scale and chronic hypertension in case 3. Therefore, TCZ treatment was maintained through pregnancy. All three women delivered vaginally at term without TAK relapse or adverse cardiovascular events. They also kept in good condition for the 1-year follow-up after delivery. Their neonates showed no signs of congenital anomalies or immunological disorders at birth and progressed with no physical or developmental problems for 1 year after birth.

Long-term use of high-dose glucocorticoids and the aggravation of maternal autoimmune disease itself may pose risks of adverse pregnancy outcomes. The American College of Rheumatology guideline strongly recommends a dose reduction of glucocorticoids to <20 mg/day of prednisone before trying to conceive. The three women in the report achieved well-controlled remission of TAK without adverse pregnancy outcome while using TCZ and 5–10 mg of PSL before and after conception.

Very few reports describe TCZ use during pregnancy, and the existing reports mainly include patients with rheumatoid arthritis. Nakajima *et al* reported the cases of 61 pregnant women exposed to TCZ, including two patients who continued TCZ throughout pregnancy.[4] They found no significant increases in miscarriage or congenital anomalies. Of the 36 live births, 5 (13.9%) neonates had birth weights <2500 g. However, in four of these five cases, TCZ was discontinued at the first trimester. Hoeltzenbein *et al* also reported no substantial increase in congenital anomalies (4.5% with co-medications included methotrexate in 21.1%), but increase in preterm birth (31.2%) in a study of 288 pregnant women exposed to TCZ.[5] In pregnancies complicated with rheumatoid arthritis, high disease activity increases the risk of preterm birth. The author speculated that TCZ treatment was discontinued in the majority of study patients after recognition of pregnancy, which might have led to increased disease activity and resulted in increased preterm birth, although the effects of TCZ exposure could not be excluded due to the lack of data. Moreover, a recent analysis of the

Table 1 Clinical backgrounds and pregnancy outcomes of three cases

	Case 1	Case 2	Case 3
Age at TAK diagnosis (years)	19	26	19
Angiographic classification of TAK (Numano scale) and involved vessels	Type IIa: ascending Ao aortic arch and its branches RCA	Type IIa+PA: ascending Ao aortic arch and its branches bilateral PA	Type V: ascending Ao aortic arch and its branches thoracic, descending Ao abdominal Ao coeliac artery superior mesenteric artery
Complications of TAK	Myocardial ischaemia due to severe stenosis of RCA	Pulmonary hypertension due to PA stenosis	Chronic hypertension
Age at TCZ administration (years)	24	26	20
Medications just before pregnancy	PSL 5 mg/day TCZ 162 mg/week Aspirin 100 mg/day	PSL 5 mg/day TCZ 162 mg/2 weeks Sildenafil 60 mg/day Warfarin	PSL 10 mg/day TCZ 162 mg/2 weeks Nifedipine 20 mg/day Aspirin 100 mg/day
Age at delivery (years)	26	30	34
Medications during pregnancy	PSL 5 mg/day TCZ 162 mg/week Aspirin 100 mg/day	PSL 5 mg/day in the first and second trimesters, 10 mg/day in the third trimester TCZ 162 mg/2 weeks Sildenafil 60 mg/day	PSL 10 mg/day TCZ 162 mg/2 weeks Nifedipine 20 mg/day Aspirin 100 mg/day
Gestational age at delivery (weeks+days)	37+4	39+4	38+1
Mode of delivery and anaesthesia	Forceps-assisted VD with epidural analgesia	Normal VD with epidural analgesia	Normal VD with epidural analgesia
Total blood loss (mL)	849	415	1073
Sex of the neonate	Female	Female	Male
Birth weight (g)	2521 (−0.4 SD)	2846 (−0.3 SD)	3041 (+0.7 SD)
Apgar score (1st min/5th min)	9/10	8/9	7/9
Congenital anomaly	No	No	No

Ao, aorta; PA, pulmonary artery; PSL, prednisolone; RCA, right coronary artery; TAK, Takayasu arteritis; TCZ, tocilizumab; VD, vaginal delivery.

WHO pharmacovigilance database reported no significant increase of fetal and neonatal adverse reactions to TCZ taken during pregnancy by women with autoimmune diseases.[6]

Based on the outcomes of these previous reports and our case series, the benefits of using TCZ during pregnancy in women with refractory TAK include preventing relapses and sparing PSL doses and may outweigh any possible harm, such as immunosuppression of neonates. Therefore, TCZ throughout pregnancy may lead to favourable clinical courses and pregnancy outcomes in patients with refractory TAK.

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REFERENCES

1 Partalidou S, Mamopoulos A, Dimopoulou D, *et al*. Pregnancy outcomes in takayasu arteritis patients: a systematic review and meta-analysis. *Sci Rep* 2023;13:546.
2 Maksimowicz-McKinnon K, Clark TM, Hoffman GS. Limitations of therapy and a guarded prognosis in an American cohort of Takayasu arteritis patients. *Arthritis Rheum* 2007;56:1000–9.
3 Nakaoka Y, Isobe M, Takei S, *et al*. Efficacy and safety of tocilizumab in patients with refractory Takayasu arteritis: results from a randomised, double-blind, placebo-controlled, phase 3 trial in Japan (the takt study). *Ann Rheum Dis* 2018;77:348–54.
4 Nakajima K, Watanabe O, Mochizuki M, *et al*. Pregnancy outcomes after exposure to tocilizumab: a retrospective analysis of 61 patients in Japan. *Mod Rheumatol* 2016;26:667–71.
5 Hoeltzenbein M, Beck E, Rajwanshi R, *et al*. Tocilizumab use in pregnancy: analysis of a global safety database including data from clinical trials and post-marketing data. *Semin Arthritis Rheum* 2016;46:238–45.
6 Dernoncourt A, Liabeuf S, Bennis Y, *et al*. Fetal and neonatal adverse drug reactions associated with biologics taken during pregnancy by women with autoimmune diseases: insights from an analysis of the world Health organization pharmacovigilance database (vigibase®). *BioDrugs* 2023;37:73–87.