

## Clinical Communications

### Omalizumab concentrations in pregnancy and lactation: A case study

Jumpei Saito, PhD<sup>a</sup>, Naho Yakuwa, BPharm<sup>b</sup>,  
Noriko Sandaiji, BPharm<sup>a</sup>, Chiaki Uno, BPharm<sup>a,b</sup>,  
Sachiko Yagishita, BPharm<sup>b</sup>, Tomo Suzuki, MD<sup>c</sup>,  
Katsusuke Ozawa, MD<sup>c</sup>, Shunsuke Kamura, MD<sup>d</sup>,  
Akimasa Yamatani, PhD<sup>a</sup>, Seiji Wada, MD<sup>d</sup>,  
Haruhiko Sago, MD<sup>c,d</sup>, and Atsuko Murashima, MD<sup>b,e</sup>

#### Clinical Implications

- Omalizumab can cross the placenta to the fetus, and approximately 1/10,000 to 1/1000 of omalizumab in maternal serum is transferred into human breast milk.

Chronic urticaria is a pruritic skin disease characterized by the presence of wheals, angioedema, or both for more than 6 weeks. Omalizumab is a recombinant humanized IgG1 anti-IgE monoclonal antibody approved for the treatment of chronic urticaria.<sup>1</sup> International guidelines recommend nonsedating antihistamines once daily as first-line therapy for chronic spontaneous urticaria. If increasing doses of antihistamines or agents with other mechanisms are required, omalizumab is considered.<sup>2</sup> According to a registry-based prospective cohort study of pregnancy exposure, more than 99% of pregnancies led to live births in both the exposure ( $n = 250$ , 246 patients with first-trimester exposure) and control groups ( $n = 1153$ ), and the rate of major congenital anomalies in registry infants was similar to that in infants in the comparator cohort (approximately 8.0% in both groups).<sup>3</sup> Regarding omalizumab secretion into breast milk, because omalizumab is a large protein molecule, the amount in milk is likely to be very low. The manufacturer reported that 186 infants were breastfed during maternal omalizumab therapy and there was no increase in infectious complications, suggesting that omalizumab is acceptable for use during breastfeeding.<sup>4</sup> Considering these facts, omalizumab can likely be used with no harmful effects in pregnant and lactating women, fetuses, and breastfed infants, while maintaining a quality of life in pregnant women with chronic urticaria. Even though there are considerable epidemiological data about the safety of omalizumab in pregnant and lactating women, there is inadequate published information about the placental transfer of omalizumab and the exposure experienced by infants. In this report, we examined the safety of omalizumab in a fetus and breastfed infant with reference to the drug concentrations in maternal and infant blood and breast milk.

A 38-year-old woman developed rash and arthritis and was diagnosed with chronic urticaria. It was unknown if she had autoantibodies against the high-affinity IgE receptor. Before her fourth pregnancy, she received 2 cycles of monthly subcutaneous omalizumab at a dose of 150 mg. She was also treated with daily 10 mg ebastine (an antihistaminic agent) for her pruritus. She became pregnant (G4, P0) after *in vitro* fertilization using a frozen stored embryo. During pregnancy, she received 5 cycles of

monthly subcutaneous omalizumab at a dose of 150 mg with 10 mg of daily ebastine. Low-dose (81 mg) aspirin was also administered concurrently throughout gestation due to a history of habitual abortion. At 21 weeks of gestation, aneurysm of the fetal ascending aorta was identified during fetal echocardiography, and a connective tissue disorder was suspected. Omalizumab was discontinued at the fifth treatment (28 weeks of gestation) and ebastine was continued, but the patient's urticaria worsened. The patient delivered a male infant weighing 3498 g by vacuum extraction at 38 weeks and 4 days of gestation. The infant's Apgar scores at 1 minute and 5 minutes were 8 and 9, respectively. A skin defect in the upper portion of his umbilicus was found. Neonatal echocardiography detected no vascular abnormalities other than the aortic aneurysm, and no aortic or mitral regurgitation. In this case, it was inconclusive whether omalizumab use was associated with the patient's disease state or the adverse effects in her infant. After delivery, her symptoms of chronic urticaria were well controlled with ebastine monotherapy.

Omalizumab concentrations were measured in the maternal blood in the third trimester of pregnancy and in the cord blood immediately after delivery (Figure 1). Because the calibration range for omalizumab quantification was 0.5 to 200.0 ng/mL, samples were diluted 1 to 10,000 times and fell within the range of the standard curve. The concentrations in the maternal blood on 2 different days approximately 12 weeks after her last omalizumab injection were 4378.8 ng/mL (2 days before delivery) and 3239.9 ng/mL (1 hour after delivery). The concentration in the cord blood was 9967.1 ng/mL on the day of delivery (approximately 12 weeks after her last omalizumab injection). The omalizumab concentration in the infant's serum on the day of delivery was 11,288.7 ng/mL, and it decreased to 9950.5 ng/mL after 2 days. The infant was exclusively breastfed, at a frequency of 6-12 times per day until at least 4 months after birth. Because omalizumab concentrations in breast milk were low compared with those in maternal serum (Figure 1), omalizumab exposure due to breastfeeding is likely also low.

Previous studies described that maternal antibodies in pregnant women are transported across the chorionic villi by the neonatal Fc receptor to provide immunity to the newborn. Immunoglobulin concentrations in fetal blood increase steadily from early in the second trimester until delivery, with most antibodies being transferred during the third trimester. By the end of gestation, the levels of immunoglobulins such as infliximab and adalimumab in umbilical cord blood and neonatal serum often exceed maternal levels.<sup>5</sup> In our case, omalizumab was discontinued at 28 weeks of gestation, and the omalizumab concentrations in maternal serum and her umbilical cord blood at delivery were 3239.9 and 9967.1 ng/mL, respectively. The median ratio, expressed as a percentage of cord to maternal drug level, was 308%. This is comparable to the placental transfer of other biologic agents.<sup>6</sup>

According to the reports of pharmacokinetic analysis, omalizumab reached the steady-state concentrations by 12 weeks after repeated monthly subcutaneous dosing of 150 mg omalizumab and cleared slowly from circulation with a terminal elimination half-life of 17 to 23 days.<sup>4,7</sup> Although the actual

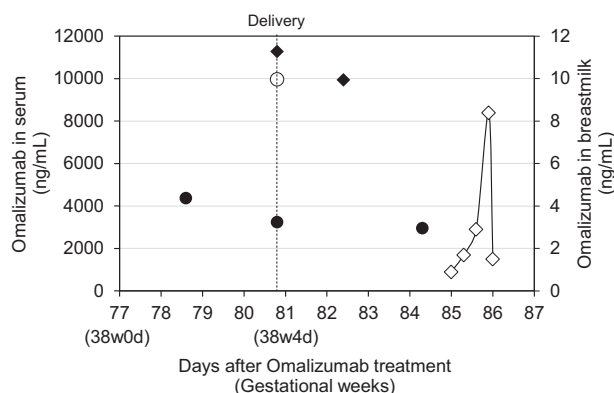


**FIGURE 1.** Omalizumab concentrations in serum and breast milk. X-axis, days after omalizumab treatment and gestational weeks; left-axis, omalizumab concentration in serum; right-axis, omalizumab concentration in breast milk. Closed circles, maternal serum; closed squares, infant serum; open circle, umbilical cord blood; open squares, breast milk.

maternal serum concentration at 28 weeks of gestation was unknown, omalizumab might have reached the steady-state trough level (approximately 15,000 ng/mL)<sup>7</sup> and gradually decreased over 10 weeks. Considering these facts, the observed maternal serum concentration at her delivery (3239.9 ng/mL) was an acceptable value. Furthermore, the observed omalizumab concentrations in this infant's serum were lower than levels seen in pediatric patients treated with 75 to 375 mg of omalizumab every 2 or 4 weeks, a dosing regimen that has been proven to be well tolerated.<sup>8</sup> In fact, there was no typical adverse effect such as anaphylaxis, nasopharyngitis, and infections after birth in our case.<sup>4,8,9</sup> Further study is encouraged to clarify the mother-to-child transmission of omalizumab and the safety profile of the drug.

## Acknowledgments

The authors would like to thank Mariko Takagai for her administrative assistance. They are also grateful to the lactating mother for donating her precious breast milk.

J. Saito, N. Yakuwa, N. F. Sandaiji, C. Uno, and S. Yagishita analyzed the data. J. Saito, N. Yakuwa, T. Suzuki, H. Sago, A. Yamatani, and A. Murashima designed the research study. All of the authors wrote and revised the manuscript.

<sup>a</sup>Department of Pharmacy, National Center for Child Health and Development, Tokyo, Japan

<sup>b</sup>Japan Drug Information Institute in Pregnancy, National Center for Child Health and Development, Tokyo, Japan

<sup>c</sup>Division of Obstetrics, Center for Maternal-Fetal, Neonatal and Reproductive Medicine, National Center for Child Health and Development, Tokyo, Japan

<sup>d</sup>Division of Fetal Medicine, Center for Maternal-Fetal, Neonatal and Reproductive Medicine, National Center for Child Health and Development, Tokyo, Japan

<sup>e</sup>Division of Maternal Medicine, Center of Maternal-Fetal, Neonatal and Reproductive Medicine, National Center for Child Health and Development, Tokyo, Japan

This work was supported by the Research Program from the Japanese Agency for Medical Research and Development (JP19mk0101086h0003) awarded to A. Murashima and by a domestic research and development grant from National Center for Child Health and Development (2019C-6) awarded to J. Saito.

This study was approved by the ethics committee of the National Center for Child Health and Development, and the participant provided written informed consent.

Conflicts of interest: A. Murashima has received research grants from Astellas Pharma and Chugai Pharmaceutical, and has received lecture fees from Astellas Pharma Inc., Chugai Pharmaceutical Co. Ltd., and Bristol-Myers K.K. The rest of the authors declare that they have no conflicts of interest.

Received for publication March 12, 2020; revised May 22, 2020; accepted for publication May 26, 2020.

Available online ■ ■

Corresponding author: Jumpei Saito, PhD, Department of Pharmacy, National Center for Child Health and Development, Okura 2-10-1, Setagaya-ku, Tokyo 157-8535, Japan. E-mail: [saito-jn@ncchd.go.jp](mailto:saito-jn@ncchd.go.jp).

2213-2198

© 2020 American Academy of Allergy, Asthma & Immunology

<https://doi.org/10.1016/j.jaip.2020.05.054>

## REFERENCES

1. Tonacci A, Billeci L, Pioggia G, Navarra M, Gangemi S. Omalizumab for the treatment of chronic idiopathic urticaria: systematic review of the literature. *Pharmacotherapy* 2017;37:464-80.
2. Moolani Y, Lynde C, Sussman G. Advances in understanding and managing chronic urticaria. *F1000Res* 2016;5:F1000. Faculty Rev-177.
3. Namazy JA, Blais L, Andrews EB, Scheuerle AE, Cabana MD, Thorp JM, et al. Pregnancy outcomes in the omalizumab pregnancy registry and a disease-matched comparator cohort. *J Allergy Clin Immunol* 2020;145:528-536.e1.
4. XOLAIR® (omalizumab) for injection, for subcutaneous use, full prescribing information. South San Francisco, CA: Genentech USA Inc.; 2014. Available from: [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2015/103976s5224lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/103976s5224lbl.pdf). Accessed April 24, 2020.
5. Wilcox CR, Holder B, Jones CE. Factors affecting the FcRn-mediated trans-placental transfer of antibodies and implications for vaccination in pregnancy. *Front Immunol* 2017;8:1294.
6. Mahadevan U, Wolf DC, Dubinsky M, Cortot A, Lee SD, Siegel CA, et al. Placental transfer of anti-tumor necrosis factor agents in pregnant patients with inflammatory bowel disease. *Clin Gastroenterol Hepatol* 2013;11:286-92.
7. Zielen S, Lieb A, De La Motte S, Wagner F, de Monchy J, Fuhr R, et al. Omalizumab protects against allergen-induced bronchoconstriction in allergic (immunoglobulin E-mediated) asthma. *Int Arch Allergy Immunol* 2013;160:102-10.
8. Odajima H, Ebisawa M, Nagakura T, Fujisawa T, Akasawa A, Ito K, et al. Long-term safety, efficacy, pharmacokinetics and pharmacodynamics of omalizumab in children with severe uncontrolled asthma. *Allergol Int* 2017;66:106-15.
9. Chipps BE, Lanier B, Milgrom H, Deschildre A, Hedlin G, Szefer SJ, et al. Omalizumab in children with uncontrolled allergic asthma: review of clinical trial and real-world experience. *J Allergy Clin Immunol* 2017;139:1431-44.