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CASE SERIES

Rituximab and Canakinumab Use During Lactation: No Detectable Serum Levels in Breastfed Infants

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ABSTRACT

Introduction: In breastfeeding patients with chronic inflammatory rheumatic diseases, a postpartum flare may require the use of biologics. However, data on the safety of biologics during lactation are scarce, potentially impeding the decision-making process.
Case series: We report two cases of women in whom treatment with a monoclonal IgG antibody (rituximab or canakinumab) was indicated during the lactation period. In both cases, breastfeeding was continued, and drug levels in the mother's serum, in serial breast milk samples and in the infant's serum were measured. Both rituximab and canakinumab showed minimal drug concentrations in breast milk and no detectable levels in the infants' sera.
Conclusion: The lack of detectable levels of rituximab and canakinumab in the sera of breastfed infants reflects the poor oral bioavailability of these biologics and helps to promote their use in breastfeeding patients.

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Key Summary Points

In breastfeeding patients with chronic inflammatory rheumatic diseases, a postpartum flare may require the use of biologics.

In two cases of women, in whom treatment with rituximab or canakinumab was indicated during the lactation period, both biologics showed minimal drug concentrations in breast milk and no detectable levels in the infants' sera.

DIGITAL FEATURES

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INTRODUCTION

Women with chronic inflammatory rheumatic disases are at risk of disease flares during the postpartum period, often coinciding with lactation. Given the benefits of human milk for the infant [1], the World Health Organization recommends exclusive breastfeeding for the first 6 months of life. Most patients wish to continue breastfeeding, even if disease activity requires treatment adjustments. When discussing antirheumatic drugs with patients during lactation, the risk of active maternal disease needs to be balanced with the risk of the infant's exposure to the drug via breast milk. The number of biologic antirheumatic drugs that are considered to be compatible with breastfeeding are limited, mostly due to the lack of data on drug excretion into breast milk. This sparse body of data presents a challenge in the decision-making process with each individual patient. Here we report the cases of two women with rare chronic inflammatory rheumatic conditions, both with an indication for rituximab (RTX) or canakinumab treatment during lactation. Recommendations on the use of biologics during lactation, other than tumor necrosis factor (TNF) inhibitors, mainly focus on RTX and are based on the structural analogy of RTX to TNF inhibitor (for which more information is available) and a few case reports and a case series [2, 3]. Recommendations on the use of canakinumab during lactation are lacking. In general, large molecules like IgG are expected to pass poorly into mature human breast milk; however, it remains unclear whether clinically relevant quantities are uptaken by intestinal neonatal Fc receptors [4, 5]. The two cases reported here provide further data on the concentrations of RTX and canakinumab in breast milk and in the sera of the breastfed infants, and will aid in the decision-making process on the use of biologics in lactating women.

Both patients described in the two cases presented here provided informed consent for the measurement of drug levels in their blood, breast milk and their infant's blood. They also gave written consent for publication. The Ethics Committee of the University of Bern, Switzerland, waived the need for ethics approval in the present case series as it is not subject of the Federal Act on Research involving Human Beings (Human Research Act, HRA, 30 September 2011). The study was conducted in accordance with Helsinki Declaration of 1964 and its later amendments.

CASE 1

A 38-year-old woman, diagnosed with MPO-ANCA vasculitis in 2004, became pregnant with her second child in 2018. RTX treatment had been started after a flare in 2011 with initially two doses of 1000 mg. Since then, she remained in clinical remission receiving RTX 500 mg every 6 months. The last dose was given 6 weeks before conception. During pregnancy, remission was maintained with 5 mg prednisone per day. After an uneventful pregnancy, she delivered a healthy girl at term in October 2018 (41 weeks gestation, birth weight 3795 g, Apgar: 9/10/10), and the patient commenced breastfeeding.

At 4 months postpartum, the MPO-ANCA titre increased, yet no clinical signs of disease activity were present. Since previous MPO-ANCA rises were associated with a disease flare, treatment with RTX (500 mg) was restarted on 14 February 2019. The available sparse data on RTX use during lactation was discussed with the patient. She wanted to continue breastfeeding and gave written consent for the measurement of RTX concentrations in her breast milk, her serum and the serum of her breastfed infant. Breast milk was collected both prior to and for 4 consecutive days after RTX therapy.

RTX concentrations in serum and breast milk were measured using an enzyme-linked immunosorbent assay (ELISA; coating antibody: clone 137C6 [GenScript Biotech Corp., Piscataway, NJ, USA]; detection antibody: clone 194D7 [Genscript Biotech Corp]). As shown in Table 1, the serum concentration of RTX in the mother rose shortly after the infusion. Low RTX levels appeared in the breast milk 24 h after exposure and remained relatively stable at an average concentration of 0.0037 μg/ml. The relative infant dose (RID), which is an estimate

Table 1 Results on drug level measurement during lactation

Maternal condition, dose, application	Biologic	
	Rituximab, 500 mg, intravenous route	**Canakinumab, 150 mg, subcutaneous injection**
Maternal health condition	AAV	MWS
Maternal drug use		
During gestation	No	Gestation week 6 and 20
Postpartum	Postpartum week 19	Postpartum week 2, 16, 32
Drug level at birth		
Infant's serum level (umbilical cord blood), μg/ml	–	1.33
Maternal serum level, μg/ml	–	0.52
Drug level in BM		
Time postpartum/period of milk collection	Four months postpartum/ 4 days	Second and third week postpartum/13 days
C median (range), μg/ml	0.003 (0–0.004)	0.014 (0.004–0.023)
Cmax, μg/ml (time post-drug)	0.004 (day 2 post-RTX)	0.023 (day 8 post-canakinumab)
Infant dose from BM		
RID median (range), %	0.007 (0.006–0.007)	0.08 (0.03–0.16)
C in infant's serum after breastfeeding, μg/ml (time post-drug, time postpartum)	Not detectable (4 and 24 h post-RTX, 4 months postpartum)	Not detectable (10 weeks post-canakinumab, 26 weeks postpartum)
Maternal dose		
C prior to drug administration, μg/ml	Not detectable	0.52 (at birth), 0.94 (8 months pp)
C post-drug administration, μg/ml (time post-drug)	45.23 (4 h post-RTX)	1.5 (7 days post-canakinumab)

AAV ANCA-associated vasculitis,*BM* breast milk, *C* concentration, *Cmax* maximum serum concentration, *MWS* Muckle-Wells Syndrome, *RID* relative infant dose, *RTX* rituximab

of the theoretical infant dose received via breast milk (mg/kg/day) relative to the maternal dose (mg/kg/day), was below 0.01%. There were no detectable RTX levels in the infant's serum at neither 4 nor 24 h after the maternal infusion.

The patient continued breastfeeding for another 4 months. Her child developed normally during the following 2 years (weight and height percentile between 25 and 50 at 1 and 2 years of age, respectively), received all recommended vaccinations and did not experience any serious infections or allergies.

CASE 2

A 38-year-old woman, who had been diagnosed with Muckle-Wells syndrome (MWS) in 2000 and who was under canakinumab therapy 150 mg every 3–4 months, became pregnant in February 2018. To maintain remission,

treatment was continued during pregnancy and administered at gestational week 6 and 20. Thereafter, the canakinumab interval was extended until the postpartum period to minimize fetal drug exposure. In November 2018 a healthy girl was born at term (birth weight 2470 g, Apgar-Score 9/10/10). No abnormalities were noted. At the time of delivery, 17 weeks after the last canakinumab administration, the canakinumab concentration in the neonate's cord blood was 1331 ng/ml whereas the maternal serum level was 518.5 ng/ml (Table 1).

The patient started breastfeeding in combination with formula milk. A few days after delivery, the disease flared and resumption of treatment was indicated. The patient decided to continue breastfeeding and gave written consent for canakinumab measurements. She received her first dose at day 10 postpartum and the following doses at 16 and 32 weeks postpartum. Serial breast milk samples were collected on days 1–9 and day 13 after the first dose of canakinumab and analyzed for drug levels using an ELISA (coating: human IL-1 β, Genscript Biotech Corp.; detection antibody, no. 410902, BioLegend, San Diego, CA, USA). The canakinumab levels in the serial breast milk samples were minimal and ranged between 3.8 and 22.8 ng/ml (Table 1), resulting in a median RID of 0.1%. In comparison, the canakinumab level in the infant's serum at 6 months of age was undetectable (Table 1). The child developed normally in the following 2 years, with a normal height (93 cm) and weight (13 kg) at the age of 2 years. MWS in the child was ruled out by genetic testing. All vaccines were given as recommended by the Swiss Ministry of Health including the first live attenuated vaccine at 12 months of age.

DISCUSSION

We report here two cases of breastfeeding patients who required the use of biologics due to signs of worsening disease postpartum. The transfer of the IgG1 monoclonal antibodies, RTX and canakinumab, into breast milk was expected to be low due to the low content of IgG in human breast milk [6]. The predominant immunoglobulin in breast milk is IgA, ranging from about 900 μg/ml in colostrum to about 400 μg/ml in mature milk [6, 7]. By contrast, the content of IgG in mature breast milk is approximately 1/20 of the IgA levels [6]. Among the IgG subclasses, IgG1 represents the lowest proportion in mature milk, with levels of about 5 μg/ml [6]. The concentrations of RTX and canakinumab in breast milk were clearly < 1 μg/ml, as confirmed previously in other studies on RTX [8, 9]. These data confirm the low transfer of IgG1 monoclonal antibodies into breast milk. Similarly, low concentrations of various other biologics (e.g. infliximab, certolizumab, adalimumab, golimumab, ustekinumab, natalizumab) have been found in the breast milk of women receiving treatment, independent of application mode, half-life or time to maximum serum concentration, emphasizing that IgG-based molecules all pass poorly into breast milk [10, 11].

What matters to our breastfeeding patients is the question of whether this minimal transfer of canakinumab or RTX into breast milk is clinically relevant to their infant. An estimate widely used to express the drug exposure of the breastfed infant is the RID. The low concentrations of canakinumab and RTX in the breast milk of our patients and the weight-adjusted maternal doses translated into a reassuring median RID of $< 0.1\%$. In partially breastfed infants, as in case 2, the RID ratio is overestimated. Generally, drugs with a RID of $< 10\%$ are regarded as safe when breastfeeding [4]. However, the RID is a theoretical estimate, not a real-time measurement of drug transfer into the infant's bloodstream. The uncertainty revolves around the question of whether these low quantities of monoclonal antibodies swallowed by the suckling infant can be absorbed by the gastrointestinal tract and detected in the infant's bloodstream. Binding sites of IgG molecules, such as the neonatal Fc receptor (FcRn), are indeed expressed across different species and on different tissues, such as the placenta and intestinal epithelial cells [5], the latter providing the prerequisite for intestinal absorption. In rodents, passive immunity of the neonate via protective IgG is delivered via the placenta as well as through breast milk.

However, the situation in humans is clearly in favour of the transplacental pathway [7, 12], as shown by therapeutic serum levels of IgG monoclonal antibodies such as canakinumab, infliximab or adalimumab in neonates after in-utero exposure during late gestation [13–15]. Fetal exposure can be reduced by avoiding the biologic drug during the third trimester, or even beyond gestational week 20, as in our patient with MWS. The transplacentally acquired canakinumb level in the infant's cord blood was clearly below therapeutic levels [16] and continued to decrease, becoming undetectable despite repeated maternal doses during the observed lactation period. This underlines the poor intestinal absorption of monoclonal IgG antibodies. Similar pharmacokinetics have been described in one breastfed infant exposed to infliximab during pregnancy and lactation [14]. By contrast, a subtherapeutic serum level of infliximab was found in one breastfed infant 5 days after the maternal infusion; however, no detectable drug levels were seen in the sera of two other breastfed infants after maternal treatment with adalimumab or infliximab [13]. In our patients, there were no detectable levels of canakinumab or RTX in the sera of the breastfed infants. Gastrointestinal proteolysis is likely to be the predominant mechanism destroying the integrity of luminal monoclonal IgG antibodies, thereby explaining the poor oral bioavailability of these biologics as a whole.

In conclusion, increasing data on the pharmacokinetics of biologics in lactating patients aids the shared decision-making process. Our cases reveal minimal transfer of canakinumab and RTX into breast milk, and no detectable levels of these biologics in the bloodstream of the breastfed infants. Thus, we conclude that canakinumab and RTX can be used to maintain disease control in breastfeeding patients. However, more pharmacokinetic data are needed in this field. Notably, it remains to be determined whether the transfer of monoclonal antibodies into breast milk can be altered in different clinical scenarios, such as in prematurely born infants or in the case of mastitis, with a possible increase in paraepithelial transfer of larger molecules.

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Authors' contributions. Nicole Bosshard performed the analysis and interpretation of the results, and drafted and revised the manuscript. Astrid Zbinden collected the samples, analysed the data and drafted the manuscript. Klara Kristin Eriksson performed the drug level measurements, analysed the findings and drafted the manuscript. Frauke Förger was responsible for the clinical management of the patients, for data analysis and interpretation as well as for manuscript revisions. All authors read and approved the final version of the manuscript.

Disclosure of interest. Nicole Bosshard, Astrid Zbinden, Klara Kristin Eriksson and Frauke Förger have nothing to disclose.

Compliance with Ethics Guidelines. Both patients described in the cases above gave consent for the measurement of drug levels in their blood, breast milk and in their infant's blood. They also gave written consent for publication. The Ethics Committee of the University of Bern, Switzerland, waived the need for ethics approval in the present case series as it is not subject of the Federal Act on Research involving Human Beings (Human Research Act, HRA, 30 September 2011). The study was conducted in accordance with Helsinki Declaration of 1964 and its later amendments.

REFERENCES

1. Victora CG, Bahl R, Barros AJ, et al. Breastfeeding in the 21st century: epidemiology, mechanisms, and lifelong effect. Lancet. 2016;387(10017):475–90.

2. Gotestam Skorpen C, Hoeltzenbein M, Tincani A, et al. The EULAR points to consider for use of antirheumatic drugs before pregnancy, and during pregnancy and lactation. Ann Rheum Dis. 2016;75(5):795–810.

3. Sammaritano LR, Bermas BL, Chakravarty EE, et al. American College of Rheumatology guideline for the management of reproductive health in rheumatic and musculoskeletal diseases. Arthritis Care Res. 2020;72(4):461–88.

4. Datta P, Baker T, Hale TW. Balancing the use of medications while maintaining breastfeeding. Clin Perinatol. 2019;46(2):367–82.

5. Israel EJ, Taylor S, Wu Z, et al. Expression of the neonatal Fc receptor, FcRn, on human intestinal epithelial cells. Immunology. 1997;92(1):69–74.

6. Rodriguez-Camejo C, Puyol A, Fazio L, et al.. Antibody profile of colostrum and the effect of processing in human milk banks: implications in immunoregulatory properties. J Hum Lactation. 2018;34(1):137–47.

7. Hurley WL, Theil PK. Perspectives on immunoglobulins in colostrum and milk. Nutrients. 2011;3(4):442–74.

8. Bragnes Y, Boshuizen R, de Vries A, Lexberg A, Ostensen M. Low level of rituximab in human breast milk in a patient treated during lactation. Rheumatology. 2017;56(6):1047–8.

9. Krysko KM, LaHue SC, Anderson A, et al. Minimal breast milk transfer of rituximab, a monoclonal antibody used in neurological conditions. Neurol Neuroimmunol Neuroinflamm. 2020;7(1):1.

10. Matro R, Martin CF, Wolf D, Shah SA, Mahadevan U. Exposure concentrations of infants breastfed by women receiving biologic therapies for inflammatory bowel diseases and effects of breastfeeding on infections and development. Gastroenterology. 2018;155(3):696–704.

11. Clowse ME, Forger F, Hwang C, et al. Minimal to no transfer of certolizumab pegol into breast milk: results from CRADLE, a prospective, postmarketing, multicentre, pharmacokinetic study. Ann Rheum Dis. 2017;76(11):1890–6.

12. Zheng W, Zhao W, Wu M, et al. Microbiota-targeted maternal antibodies protect neonates from enteric infection. Nature. 2020;577(7791):543–8.

13. Fritzsche J, Pilch A, Mury D, Schaefer C, Weber-Schoendorfer C. Infliximab and adalimumab use during breastfeeding. J Clin Gastroenterol. 2012;46(8):718–9.

14. Vasiliauskas EA, Church JA, Silverman N, Barry M, Targan SR, Dubinsky MC. Case report: evidence for transplacental transfer of maternally administered infliximab to the newborn. Clin Gastroenterol Hepatol. 2006;4(10):1255–8.

15. Egawa M, Imai K, Mori M, Miyasaka N, Kubota T. Placental transfer of canakinumab in a patient with Muckle-Wells Syndrome. J Clin Immunol. 2017;37(4):339–41.

16. Zhuang L, Chen J, Yu J, et al. Dosage considerations for canakinumab in children with periodic fever syndromes. Clin Pharmacol Ther. 2019;106(3):557–67.