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Concentrations of subcutaneously administered belimumab in human breast milk of a woman with systemic lupus erythematosus: a case report

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Belimumab is a human immunoglobulin G1 (IgG1)-lambda monoclonal antibody that inhibits the B-cell survival factor BLyS. It is used as an add-on therapy in patients with active systemic lupus erythematosus (SLE), an autoimmune disease characterised by hyperactive B-cells. SLE affects mostly women in the fertile age and may flare up postpartum. Since convincing data on the safety of belimumab during breast feeding are lacking, women are advised against breast feeding when starting belimumab postpartum. These safety data are indispensable to adequately counsel patients.

We report on belimumab concentrations measured in breast milk of a woman with SLE, initiating treatment with subcutaneous belimumab because of a postpartum flare. Written informed consent was obtained.

The case concerns a 34-year-old woman with SLE, who delivered a healthy but dysmature son (p9) at term. Three months postpartum, she experienced a flare with pleuritis, cutaneous lupus, alopecia, lymphopenia and increased anti-double-stranded DNA antibody titres despite treatment with azathioprine, hydroxychloroquine and prednisone. After shared decision-making, belimumab was chosen as add-on therapy. She stopped breast feeding just before the first injection of subcutaneously administered belimumab at a dosage of 200 mg once a week. During the phasing out of breast feeding, she pumped breast milk to prevent engorgement. Milk samples were pumped in the evenings before the belimumab injections and collected 2 and 4 weeks after the initiation of belimumab. Samples were frozen at −20°C in the hospital. Belimumab concentrations were measured by using an in-house developed enzyme-linked immunoabsorbent assay (ELISA), which was validated using control samples.

Belimumab concentrations measured in the two samples were 0.264 µg/mL at day 14 and 0.885 µg/mL at day 28, respectively (see table 1). Next, the relative infant dose (RID) was used as a measure to estimate the exposure of the infant to belimumab used by the mother. An RID <10% is considered safe. The RID of belimumab was calculated from the concentration of belimumab in milk, the standard milk intake for infants (150 mL/kg/day), a maternal weight of 62 kg and the therapeutic dose of subcutaneous belimumab used in adults (fixed dose of 200 mg once weekly). The RID was 8.6% at day 14 (see table 1). Since our patient had only minimal production at day 28, no RID could be calculated at that time point.

In this case report, we show belimumab was transferred to human breast milk and belimumab concentrations increased over time during phasing out. The higher concentration of belimumab in breast milk found at day 28 compared with day 14 could be explained by the fact that serum belimumab concentrations will increase until steady-state level around 11 weeks after initiation of subcutaneous belimumab therapy.[1] However, the concentrations measured in breast milk were much lower than those measured in serum of adult patients 4 weeks after initiating subcutaneous belimumab therapy (around 70 µg/mL).[1] That serum concentration is 79 times higher than the concentration of belimumab in breast milk measured after 4 weeks of treatment with subcutaneous belimumab (0.885 µg/mL). Furthermore, the composition of breast milk changes over time and possibly also when phasing out. Our patient had only

Table 1 Belimumab concentrations measured in breast milk

Time	Day 1	Day 8	Day 14	Day 15	Day 22	Day 28
Subcutaneous administration of belimumab (dosage) (mg)	200	200		200	200	
Concentration of belimumab in breast milk (µg/mL)			0.264			0.885
Relative infant dose calculated* (%)			8.6			
Total IgG (µg/mL)			236			398

*We first calculated the estimated daily infant dose via breast milk (mg/kg/day) by multiplying the drug concentrations in breast milk (mg/mL) and the standard milk intake for infants (mL/kg/day). Next, we calculated the maternal daily dose using the fixed dose of 200 mg/week belimumab and the patient's weight of 62 kg. We calculated thereafter the relative infant dose (%) by using the formula: daily infant dose via breast milk (mg/kg/day)/maternal daily dose (mg/kg/day)×100%. For the exact calculations, see the online supplemental data.
IgG, immunoglobulin G.

minimal production of breast milk at day 28. Most likely, the concentration of belimumab increases due to the low volume and long stasis in the breast during phasing out. Fritzsche *et al* showed that levels of infliximab in breast milk increased when continuing infliximab use while phasing out breast feeding.[2] Safety data on other monoclonal antibodies in humans suggested low excretion of these drugs in breast milk.

Total IgG concentrations in the milk were in line with literature. If belimumab (an IgG1 monoclonal antibody) would be equally excreted in breast milk as total IgG, and concentrations of belimumab are extrapolated from this total IgG data, somewhat higher concentrations of belimumab in breast milk would be expected (see the online supplemental data). The actual serum level of belimumab in the infant is supposed to be low because of proteolysis in the infant's stomach and low intestinal absorption.

To our knowledge, two case reports were published on the use of intravenously administered belimumab during breast feeding,[3 4] of which only one of these cases reported on (low) levels of belimumab measured in breast milk.[4] Regarding the use of subcutaneously administered belimumab during breast feeding, unlike our study, only one other case report has been published.[5] This study reported lower concentrations in human breast milk (around 0.14 µg/mL at day 14 and around 0.10 at day 28), measured using dried filter paper samples. However, these results differ with regard to their use of dried filter paper samples compared with serum measurements and regular instead of phased-out breast feeding.

A limitation of our case report is a lack of information on the levels of belimumab in maternal and infant serum. The medical ethics committee only gave permission to investigate breast milk in order to minimise the burden for mother and infant. Since the RID does not take pharmacokinetics into account, the question remains whether excretion of belimumab in breast milk during phasing out is clinically relevant. Another limitation is that we could not measure the concentration of belimumab in breast milk when steady-state serum belimumab level was reached after 11 weeks of treatment, since our patient phased out breast feeding during 4 weeks.

In conclusion, this case report shows that subcutaneously administered belimumab was transferred to breast milk during phasing out. The concentrations measured in breast milk were much lower than those measured in serum of adult patients using subcutaneous belimumab. It is reassuring that the RID is below 10% at day 14. The actual serum level of belimumab in the infant is likely negligible because of proteolysis in the infant's stomach and low intestinal absorption. However, data on infant serum levels are currently not available and urgently needed in order to be able to weight the possible risk of transfer of belimumab to the infant against the positive effects of breast feeding for mother and infant.

We therefore propose to study concentrations of belimumab in serum and breast milk in women treated with belimumab during lactation and during phasing out. Ideally, also measurement of serum concentrations in their suckling infants should be performed.

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