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Research Letter

The Concentration of Etanercept in Human Milk and Infant Outcomes

To the Editor:

According to the National Institutes of Health, up to 23.5 million Americans (> 7% of the population) suffer from an autoimmune disease, and women are 2 times more likely to be diagnosed with an autoimmune disease than men.[1,2] Medications such as etanercept (ETN) may be required for treatment of maternal disease during lactation. This can be problematic for lactating individuals due to the paucity of data on the safety of those medications for the nursing infant. Given that human milk is the recommended primary source of nutrition for infants until 6 months of age and a complementary source of nutrition until at least 12 months of age, it is critical to study medications that are used to treat autoimmune diseases during lactation.[3]

ETN is a tumor necrosis factor inhibitor prescribed for rheumatoid arthritis (RA), psoriatic arthritis, ankylosing spondylitis (AS), plaque psoriasis, and polyarticular juvenile idiopathic arthritis.[4] To date, published case reports have described ETN levels in 16 human milk samples collected from 4 women.[5-8] The concentrations ranged from 2 ng/mL to 75 ng/mL, with the majority of samples between 2 ng/mL and 7.5 ng/mL. In addition, 7 infant serum levels were measured; levels were undetectable in 4 of the samples.[5-8] The objective of this study was to add to the existing but limited literature on levels of ETN in human milk and to describe infant adverse events, growth, and neurodevelopmental screening outcomes.

Between 2014 and 2018, 6 lactating persons residing in the United States who reported current use of ETN consented to participation in the Human Milk Biorepository at the University of California San Diego (UCSD). Participant characteristics are shown in the Table. All 6 had been treated with ETN for either RA or AS during pregnancy and postpartum up to the time of enrollment. Each participant provided written consent, completed a maternal interview to collect demographics, maternal and child health history (including growth measures and infant adverse events [AEs]), and details regarding medication and other exposures for the 14 days prior to milk sample collection. Human milk samples were collected using a standardized protocol that has been described previously.[9] The study was approved by the UCSD Institutional Review Board (IRB protocol #130658).

Screening for neurocognitive abilities of the breastfed children was performed by maternal report using the Ages and Stages Questionnaire 2 at ≥ 1 timepoints when the child was between the ages of 4 and 30 months.[10] A child was considered typically developing if all the domain scores were above the cut-off scores established for the instrument, and a child was considered at risk if ≥ 1 of the domain scores was below the cut-off score for that domain. ETN levels were measured using a validated, commercially available monoclonal antibody-based enzyme immunoassay (Eagle Bioscience, IG-AA102).

Table. Selected characteristics of maternal and infant participants enrolled in the Human Milk Biorepository with exposure to ETN between 2014-2018, n = 6.

	N= 6, n (%)
Maternal age, yrs, median (range)	36.3 (30.7-41.8)
Maternal ethnicity	
Non-Hispanic	6 (100)
Maternal race	
White	6 (100)
Maternal education, yrs	
College graduate	4 (66.7)
Postgraduate	2 (33.3)
Household income	
$10,000-$49,999	1 (16.7)
> $60,000	5 (83.3)
Maternal BMI[a]	
Normal weight (18.5-24.99)	6 (100)
Parity	
1	1 (16.7)
> 1	5 (83.3)
ETN dose	
25 mg 2× per week	1 (16.7)
50 mg 1× per week	5 (83.3)
Indication for ETN	
Ankylosing spondylitis	2 (33.3)
Rheumatoid arthritis	4 (66.7)
Infant age, months, median (range)	10.3 (2.5-24.4)
Infant sex	
Female	4 (66.7)
Male	2 (33.3)
Term birth	
Term	6 (100)
Breastfeeding status	
Exclusive breast milk	2 (20)
Breast milk with solid foods	4 (80)
Supplemental formula	0 (0)
Hours since last feeding/expression	5.14 (1.50-10.50)

Values are expressed as n (%) unless otherwise indicated. [a] BMI = bodyweight in kilograms divided by height in meters squared. ETN: etanercept.

Concentrations of ETN were log-transformed and linear regression models were used to estimate log concentrations and their 95% CIs in relation to time since last ETN injection, dose of ETN, maternal age, BMI, parity, infant age, infant sex, and time since last feed or milk expression. All statistical analyses were performed using R version 3.4.1 (R Foundation for Statistical Computing).

ETN was detectable in all 6 samples (100%). The median (IQR) concentration was 12.9 ng/mL (6.0-46.9 ng/mL). The estimated relative infant dose (RID) with a 150-mL/kg/day milk intake was 1.9% (range 0.9-7.0). Both infant age (months) and maternal age (years) were positively associated with the log concentration of ETN, whereas hours since last feeding was not

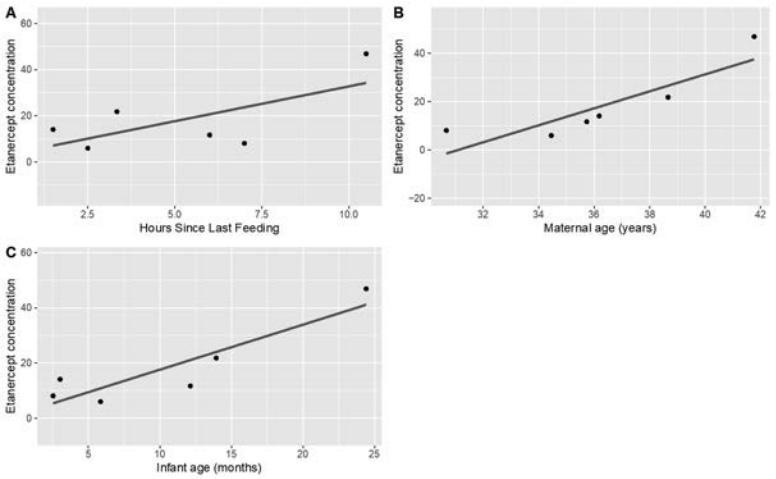

Figure. Plots of log-transformed etanercept concentrations vs (A) hours since last feeding, (B) maternal age, and (C) infant age.

(log concentrations 1.63, 95% CI 0.53-2.73, $P = 0.02$; 3.51, 95% CI 0.79-6.23, $P = 0.02$; 3.02, 95% CI -1.64 to 7.67, $P = 0.15$, respectively; Figure). No other covariate was significantly associated with log concentrations of ETN (data not shown). There were no serious AEs reported for any infant. One mother reported a nonserious rash and high-pitched crying in her infant, both of which resolved without intervention. All infants had growth measures within normal range at their 6-month well-child visit. Five participants completed at least 1 infant developmental screening questionnaire. Of these, 3 were typically developing in all domains between 12 and 24 months of age, one was at risk in 1 domain at 12 months of age and later scored in the typically developing range at 30 months of age, and one was at risk in 1 domain at 12 months of age with no further follow-up.

These data are reassuring regarding the safety of ETN in lactating individuals and their children. ETN concentrations in human milk from lactating individuals diagnosed with RA or AS were associated with an estimated RID of 1.9% with an upper 95% CI limit of 7.0%. These values were below the acceptability level of 10% for presumed safety in infants.[11-13] These data are consistent with the previous literature, which also found low levels of ETN in human milk.[5-8] These preliminary data suggest that systemic infant exposure to ETN through human milk ingestion would be minimal.

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