# CORRESPONDENCE

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## Vedolizumab Concentrations in the Breast Milk of Nursing Mothers With Inflammatory Bowel Disease

Dear Editors:

Vedolizumab, a monoclonal immunoglobulin (Ig)G1 antibody, has a favorable safety profile in nonpregnant and nonlactating patients.[1] The data on the safety of vedolizumab in reproduction is limited,[2,3] with currently none available in lactating mothers.

Before vedolizumab infusion, a breastmilk and a serum trough sample were collected from 5 mothers with inflammatory bowel disease (IBD) who were intentionally, fully breastfeeding their infants despite the lack of safety data. Thirty minutes after the infusion, another breastmilk and a serum sample were obtained for determination of vedolizumab concentration. Thereafter, breastmilk samples were collected twice daily for up to 14 days after the infusion of 300 mg vedolizumab. As a control, a healthy breastfeeding mother without IBD, supplied breastmilk samples once a day for 6 days.

Vedolizumab concentrations were determined in duplicate by enzyme-linked immunosorbent assay per the manufacturer's instructions (IDKmonitor, Bensheim, Germany). Written informed consent was obtained from all women. The Review Board in Denmark (1-16-02-645-16) and Germany (EA2/086/17) approved the study.

All women had received vedolizumab infusions before the infusion where breastmilk and serum samples were obtained (Figure 1, *top Table*). In all 5 cases where breastmilk samples were obtained right before the vedolizumab infusion a detectable concentration of 0.124 to 0.228 $\mu$g/mL was found. Vedolizumab was detectable in varying concentrations in all samples collected from 30 minutes to 14 days after the vedolizumab infusion (Figure 1, *bottom Graphic*). Vedolizumab concentration in the breastmilk peaked at 0.196 to 0.318 $\mu$g/mL on days 3 through 7. The peak vedolizumab breast milk concentration of 0.318 $\mu$g/mL was 1/179th of the corresponding concentration in serum equivalent to less than 1% (Figure 1, *top Table*). In all breastmilk samples from the unexposed control, vedolizumab was undetectable.

If the highest vedolizumab milk concentration measured in any of the samples (0.318 $\mu$g/mL) is multiplied by the amount of milk ingested by the infant, approximately 150 mL per kilogram of bodyweight per day,[4] the infant is estimated to receive 0.048 mg vedolizumab per kilogram bodyweight per day. Normal developmental milestones were recorded in all infants at the age of 3.5 to 10.0 months. All infants follow their national immunization program, and have received the inactive vaccines without complications.

This is the first study to report that vedolizumab, similarly to infliximab and adalimumab, is excreted into breastmilk at low concentrations.[5] Vedolizumab was detectable just before the infusion, indicating that the drug is detectable at any given time in between infusions. The peak vedolizumab milk concentration was less than 1% of the concentration in maternal serum. This is well under the recommended arbitrary cut off value of 10% for excretion of drugs into breast milk.[4]

IgG is primarily transferred to the offspring during pregnancy.[6] Preliminary results from the PIANO registry indicate detectable serum concentrations of vedolizumab in mothers and infants at the time of delivery.[7] This is in accordance with studies on maternal–fetal transport of other IgG antibodies, like infliximab and adalimumab.[8] Fully breastfed infants will primarily be consuming secretory IgA, but also a low content of IgG.[6] Uptake and transport of IgG from serum across the mammary epithelial barrier into the alveolar lumen is thought to occur primarily through an Fc receptor–mediated process.[6] Moreover, the Fc receptor has been identified on the mucosal surface of the human intestine, consistent with the hypothesis that the Fc receptor is involved in IgG recycling.[6] Furthermore, a distinct IgG Fc binding site has been identified within the intestinal mucus.[6] The IgG Fc binding protein is distinct from the Fc receptor. The Fc binding protein may block passage of IgG–antigen complexes to the enterocyte surface, thereby blocking their uptake and transport to the lamina propria, and perhaps allowing the complexes to be degraded in the intestinal lumen and excreted.[6] In theory, the presence of Fc receptors in the gastrointestinal tract could lead to absorption of vedolizumab and theoretically result in negative effects in the gut. In the present study, we demonstrate that a fully breastfed infant is estimated to receive a maximum dose of 0.048 mg vedolizumab per kilogram of bodyweight per day. This minute quantity is furthermore anticipated to undergo proteolysis in the stomach, and through the IgG Fc binding protein in the gastrointestinal tract, it may undergo degradation and finally excretion. Additional, larger studies including investigation of specimens collected from the exposed infants are warranted to investigate the impact of vedolizumab exposure through breastmilk on the infant's immune system, especially for coping with enteric and pulmonary infections.

| | Patient 1[b] | Patient 2 | Patient 3 | Patient 4 | Patient 5 |
|---|---|---|---|---|---|
| Diagnosis | Ulcerative colitis | Crohn's disease | Crohn's disease | Crohn's disease | Crohn's disease |
| Location and phenotype | Left-sided colitis | Small bowel disease, Inflammatory | Ileo-colonic, inflammatory | Ileo-colonic, inflammatory, perianal fistulae | Ileo-colonic, stenosing |
| Type of VDZ[a] treatment | Maintenance | Maintenance | Maintenance | Induction | Maintenance |
| Duration of VDZ[a] treatment (months) | 1a: 9<br>1b:11 | 28 | 14 | 0.5 | 31 |
| Total number of VDZ[a] infusions to date at the time of milk collection | 1a: 6<br>1b: 7 | 12 | 10 | 2 | 18 |
| Number of weeks since last infusion | 1a: 8<br>1b: 8 | 8 | 14[c] | 2 | 8 |
| Co-medication | None | None | None | Thiopurine | Thiopurine, Budesonide |
| Timing of VDZ[a] measurement in milk | 1a: 2 months &<br>1b: 4 months postpartum | 2 months postpartum | 2 months postpartum | 7months postpartum | 1 month postpartum |
| Disease state (physician global assessment) | Remission | Remission | Remission | Remission | Remission |
| Age (*y*) | 30 | 30 | 22 | 32 | 27 |
| Years since diagnosis | 5 | 10 | 5 | 8 | 19 |
| Body mass index (*kg/m2*) | 31 | 42 | 29 | 22 | 21 |
| Smoking status | Non-smoker | Non-smoker | Non-smoker | Non-smoker | Non-smoker |
| VDZ[a] serum trough concentration (*μg/mL*) | 1a: 7.3<br>1b: 10.0 | 6.9 | 0.5 | 42.1 | 26.8 |
| VDZ[a] serum maximum concentration 30 minutes after infusion (*μg/mL*) | 1a: -<br>1b: 210.0 | 128.1 | 210.0 | - | 116.0 |
| VDZ[a] serum concentration 7 days after the infusion (*μg/mL*) | -<br>- | 57.0 | - | - | - |
| Maximum VDZ[a] milk concentration (*μg/mL*) | 1a: 0.196 (day 5)<br>1b: 0.307 (day 5) | 0.318 (day 7) | - | 0.307 (day 3) | 0.244 (day 5) |
| Milk/serum ratio at day 7 post VDZ[a] infusion | -<br>- | 1/179 (0.56%) | - | - | - |

[a]VDZ, vedolizumab.
[b]Patient 1 provided samples twice, 1a symbolizes the first infusion and 1b the second infusion where milk and serum samples were obtained.
[c]scheduled to VDZ infusions every 8th week, however due to non-compliance to outpatient visits a duration of 14 weeks occurred.

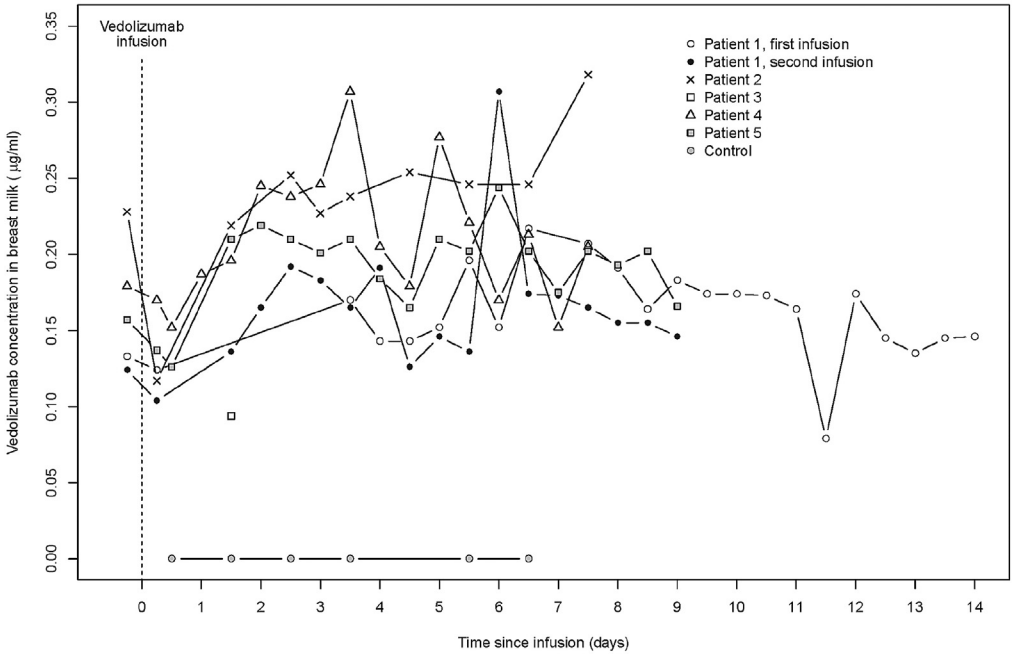


**Figure 1.** (*Top*) Characteristics of 5 vedolizumab treated lactating women with inflammatory bowel disease. (*Bottom*) Vedolizumab concentrations in breastmilk from lactating women before and after vedolizumab infusion.

## Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at https://doi.org/10.1053/j.gastro.2017.08.067.

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**Conflicts of interest**
The authors have made the following disclosures: MJ, JK, and DCB have received speaker's fees from and/or served as scientific advisers to Takeda, the manufacturer of vedolizumab. The remaining authors disclose no conflicts. Takeda had no role in the design, collection of data, or interpretation of the results of this study.

**Most current article**

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# Hepatitis B Virus Infection and Hepatitis C Virus Treatment in a Large Cohort of Hepatitis C–Infected Patients in the United States

Dear Editors:

The rare emergence of hepatitis B virus (HBV) reactivation among hepatitis C virus (HCV)-infected patients receiving direct-acting antiviral (DAA) therapy raises questions about how many HCV-infected patients have active, past, or latent/occult HBV co-infection, and their DAA treatment experience[1–3] We sought to characterize these factors, including possible post-DAA reactivation, among HCV patients in the Chronic Hepatitis Cohort Study (CHeCS), a "dynamic" observational study conducted at 4 large integrated U.S. health care systems. Study methods have been described elsewhere.[4]

Among 14,099 HCV-diagnosed patients still alive and infected in 2014, we analyzed DAA treatment and HBV serologic and DNA assays performed as part of routine clinical care at any time in the patient's history through the end of 2016. (Ongoing DAA treatment ascertainment for 2016 was still pending and unavailable for 1143 cohort patients [8.1%].) We reviewed all alanine aminotransferase (ALT) values during the 12 months after the initiation of therapy for elevation.

The prevalence of hepatitis B surface antigen (HBsAg)/HBV DNA and total hepatitis B core antibody (anti-HBc) positivity varied by demographics including gender, race, and age (Table 1). Among 14,695 HCV patients, 10,551 (74.8%) had been tested for HBsAg and/or HBV DNA and of these 115 (1.1%) had $\geq$1 positive test (Table 1). In these patients with a positive test for HBsAg and/or HBV DNA, 26 (22.6%) had only 1 positive test (thus, chronic vs acute infection status could not be confirmed) and 42 (36.5%) had become HBsAg/HBV DNA negative by 2016; the remaining 47 (40.9%) had confirmed chronic HBV infection with positive tests for HBsAg and/or HBV DNA $\geq$6 months apart. Among 13,984 patients without a positive test for HBsAg or HBV DNA, 5298 (37.9%) were tested for anti-HBc and of these 2136 (40.3%) were positive, indicating possible prior infection (Table 1). Among all total anti-HBc positive persons, 788 (14.9% of those tested) were "isolated" anti-HBc positive, with negative HBsAg and negative anti-HBs, indicating either possible resolved infection with waning antibody levels, occult infection, or a false-positive test. In the 11,848 HCV patients (84.0%) without prior/current HBV infection (no positive tests for HBsAg/HBV DNA or anti-HBc), 5999 (50.6%) were tested for hepatitis B surface antibody (anti-HBs), and of these 1923 (32%) were positive indicating immunity (Table 1). Among patients negative or not tested for markers of HBV infection or immunity the majority (7745, or 54.9% of the cohort) did not have record of any HBV vaccination in electronic health record data.

Across the entire cohort, 3836 (27.2%) had received DAA therapy (Table 1). The proportions achieving a sustained virologic response (SVR; about 90%) and with post-DAA ALT elevations were similar across groups. Among the 115 patients ever HBsAg or HBV DNA positive, 25 (21.7%) were treated and of these 1 (4.0%) was identified as having a single ALT level above the upper limit of normal during the 4–52 weeks after therapy initiation. Among these DAA-treated patients, pretreatment HBV disease activity was infrequently measured, but when data were available the HBV DNA level was low (Table 1, footnote). Only 7 ever-HBsAg/DNA positive patients (28.0%) who received DAA therapy had HBV DNA testing after therapy initiation. Of these, 5 (62.5%) were DNA negative or below the test lower limit of detection both before and after therapy and 2 (28.6%) had low levels of HBV DNA (Table 1, footnote).

## Supplementary Materials and Methods

Five mothers with IBD who were fully breastfeeding their infants while being treated with vedolizumab were asked to participate in this documentation study. From medical records we retrieved information on patient characteristics and medical treatment.

Prior to vedolizumab infusion, a breast milk and a serum trough sample were collected. Thirty minutes after the infusion, another breast milk and a serum sample were obtained for determination of vedolizumab concentration. On the day of vedolizumab infusion, two additional milk samples were collected. Thereafter, breast milk samples were collected twice daily for up to 13 days after the infusion of 300 mg vedolizumab. All IBD patients filled-in a formula recording date and time of day for collection of the milk sample. One of the IBD patients supplied milk and serum samples in relation to two different infusions. Another IBD patients supplied an extra serum sample at day 7 after the vedolizumab infusion. A control, a healthy breast-feeding mother without IBD, who did not receive any kind of medical treatment supplied breast milk samples once a day for six days.

Clotted blood samples were spun within an hour. Serum were frozen in aliquots at minus 80 degrees Celsius. Milk samples were initially kept at minus 20 degrees Celsius in the patients' home until the day after the final milk sample had been obtained. The milk samples were collected and transported on dry ice to the laboratory. Milk samples were stored at minus 80 degrees Celsius together with serum samples until analysis. Serum and milk vedolizumab concentrations were measured by enzyme-linked immunosorbent assay (ELISA) (IDKmonitor, Bensheim, Germany) according to the manufacturer's instructions. Samples were tested in duplicate and the average expressed as $\mu$g/ml serum. The coefficient of variation between assay wells was less than 10%. In case of very low or very high concentrations, the sample was re-tested in a different dilution. In case of a variation greater than 10% between the two results, a new analysis in duplicate was performed. The lower limit of detection was 0.01 $\mu$g/ml for vedolizumab. In control experiments, false-positive results for blank sera and milk were not seen. The presence of antibodies to vedolizumab was not assessed.

Written informed consent was obtained from all participating women. The study was approved by the Danish Data Protection Agency (reference 1-10-72-269-16), by the Regional Ethical Review Board in Denmark (reference 1-16-02-669-16), and by Charité's institutional review board in Germany (EA2/086/17).