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Title: Exposure Concentrations of Infants Breastfed by Women Receiving Biologic Therapies for Inflammatory Bowel Diseases and Effects of Breastfeeding on Infections and Development

Short Title: Monoclonal antibody detection in breast milk

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Abbreviations

ADA – Adalimumab

ASQ – Ages and Stages Questionnaire

CD – Crohn's disease

CZP – Certolizumab pegol

CI – Confidence Interval

GOL - Golimumab

IBDU – Inflammatory Bowel Disease Unclassified

IFX – Infliximab

NAT – Natalizumab

OR – Odds Ratio

PIANO – Pregnancy in Inflammatory Bowel Disease and Neonatal Outcomes

TNF – Tumor Necrosis Factor

TNF-alpha -- TNF- α

UC – Ulcerative colitis

UST – Ustekinumab

VED - Vedolizumab

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Abstract

Background & Aims: Exposure to biologic and immunosuppressant agents during breastfeeding is controversial and there are limited data on safety. We investigated whether biologics are detectable in breast milk from women receiving treatment for inflammatory bowel diseases (IBD) and whether breastfeeding while on treatment is associated with infections or developmental delays.

Methods: We performed a multi-center prospective study of women with IBD and their infants, collecting breast milk samples (n=72) from patients receiving biologic therapy from October 2013 to November 2015. Drug concentrations were measured in all breast milk samples at several time points within 48 hrs of collection and within 168 hrs for some samples. Child development was assessed using the Ages and Stages Questionnaire 3 (ASQ3), completed by 824 women with IBD (treated or untreated) during pregnancy (620 breastfed and 204 did not). Data on childrens' health and development were obtained from mothers and pediatricians, along with information on mothers' medication exposure, IBD history, activity, and pregnancy, and post-partum complications. We used χ^2 or Fisher's exact test to determine associations between categorical values, and compared differences in continuous outcomes between groups using ANOVA models. The primary outcome was drug concentration of biologic agents in breast milk (from 72 women) at 1, 12, 24, and 48 hours after dosing, and also at 72, 96, 120, and 168 hrs from available samples. Secondary outcomes were a range of infant infections and ASQ3-defined developmental delays among all breast-fed infants.

Results: We detected infliximab in breast milk samples from 19 of 29 treated women (max 0.74 $\mu\text{g/mL}$), adalimumab in 2 of 21 treated women (max 0.71 $\mu\text{g/mL}$), certolizumab in 3 of 13 treated women (max 0.29 $\mu\text{g/mL}$), natalizumab in 1 of 2 treated women (max 0.46 $\mu\text{g/mL}$), and ustekinumab in 4 of 6 treated women (max 1.57 $\mu\text{g/mL}$); we did not detect golimumab in breast milk from the 1 woman receiving this drug. Rates of infection and developmental milestones at 12 months were similar in breastfed vs non-breastfed infants: any infection 39% vs 39% in controls ($P=1.000$) and milestone score 87 vs 86 in controls ($P=.9992$). Rates of infection and developmental milestones did not

differ among infants whose mothers received treatment with biologics, immunomodulators, or combination therapy, compared to unexposed infants (whose mothers received treatment with mesalamines or steroids or no medication).

Conclusions: In a study of women receiving treatment for IBD and their infants, we detected low concentrations of infliximab, adalimumab, certolizumab, natalizumab, and ustekinumab in breast milk samples. We found breastfed infants of mothers on biologics, immunomodulators, or combination therapies to have similar risks of infection and rate of milestone achievement compared to non-breastfed or infants unexposed to these drugs. Maternal use of biologic therapy appears compatible with breastfeeding.

Clinicaltrials.gov no: NCT00904878

KEY WORDS: Crohn's disease, ulcerative colitis, breast milk, lactation

Introduction

Available data suggests that the use of biologic (monoclonal antibody) therapy during pregnancy does not lead to an increased rate of adverse pregnancy outcomes in women with inflammatory bowel disease (IBD) or their infants.¹⁻³ Given the harmful effect of active disease on pregnancy outcomes and the risk of flare with discontinuation of therapy, women are counseled to continue most IBD therapy throughout pregnancy.^{4,5} The biologic medications used to treat IBD currently include infliximab (IFX), adalimumab (ADA), certolizumab pegol (CZP), golimumab (GOL), vedolizumab (VED), natalizumab (NAT), and ustekinumab (UST). IFX, ADA, GOL, VED and UST are IgG1 monoclonal antibodies and can actively cross the placenta and be detectable in the infant at birth.⁶⁻¹⁰ CZP does not have a fragment crystallizable (Fc) portion; therefore, placental transfer is passive and minimal.⁹

The American Academy of Pediatrics recommends that women breastfeed for at least 6 months after birth.¹¹ However, existing data regarding the safety and transfer of biologic agents via breastmilk is limited to case reports and small case series.¹²⁻¹⁶ The aim of this study was to determine whether biologic agents are detectable in breast milk and to what degree, and to assess whether breastfeeding while on biologic agents impacts rate of infections and achievement of developmental milestones of children born to women with IBD.

Materials and Methods

This study is part of the Pregnancy in Inflammatory Bowel Disease and Neonatal Outcomes (PIANO) registry, started in 2007. The PIANO registry is a multicenter

national prospective study of pregnancy and neonatal outcomes in women with IBD and their infants among sites of the Crohn's Colitis Foundation Clinical Research Alliance. To date, over 1500 women have been enrolled from 30 sites in the United States. Collection and analysis of breastmilk was a predefined secondary endpoint.

Mothers who were enrolled in the PIANO registry completed standard comprehensive questionnaires at intake, during each trimester, at delivery, and at months 4, 9, and 12 from birth. Data included maternal demographics, age at IBD diagnosis, disease duration and location, disease activity, specific IBD medications used at conception and at each trimester, and complications during pregnancy and post-partum. History of breastfeeding was obtained when the child was 12 months of age, when mothers were asked whether they had breast fed, the duration of breastfeeding, reasons for never breastfeeding or for stopping, and additional details of IBD medications taken, stopped, or avoided during breastfeeding. The breastfeeding questionnaire was introduced to the cohort beginning in 2010.

For childhood illnesses, mothers and the child's pediatrician provided information about whether the infant was hospitalized, indication for hospitalization, and diagnosis of infection. Serious infections, defined as pneumonia, sepsis, abscess, bladder infection, cellulitis, meningitis and those requiring hospitalization, were separated from minor infections, including otitis media and upper respiratory tract infections. Outcomes of infants of mothers exposed to a biologic agent were compared to those of infants of mothers exposed to an immunomodulator (azathioprine/6 mercaptopurine), combination therapy (immunomodulator + biologic agent), and unexposed mothers (on mesalamine, steroids, or no medication). Mothers measured and reported infant developmental

milestones using the *Ages and Stages Questionnaire, Third Edition* (ASQ3) – a parent-completed developmental screening tool that assesses communication, gross motor, fine motor, problem-solving, and personal adaptive skills at specific ages from 2 to 60 months. Normative data have been collected from more than 2000 children from diverse ethnic and socioeconomic backgrounds. Suspected development delay is defined as an ASQ3 score 2+ standard deviations below national means.¹⁷

In order to characterize presence of monoclonal antibodies in breast milk, all actively breastfeeding women enrolled in the PIANO registry from October 2013 to November 2015 who were on a biologic medication were asked to provide breast milk samples (0.5-2 mL/sample). Samples were collected 1, 12, 24, and 48 hours after drug administration, at various time points after delivery. In December 2014, the protocol was amended to allow collection of additional samples at 72, 96, 120, and 168 hours after drug dosing.

The study was approved by the Institutional Review Boards at all participating sites, and all women provided written informed consent. All authors had access to the study data and reviewed and approved the final manuscript.

Outcome Measures

The primary outcome was the drug concentration/detection of the biologic agent in breast milk at 1, 12, 24, and 48 hours after dosing, and also at 72, 96, 120, and 168 hours when available. Secondary outcomes were a range of infant infections and ASQ3-defined developmental delays among all breast-fed infants.

Determination of Drug Concentrations in Breast Milk: Drug concentrations in breast milk were measured by a previously described homogenous mobility shift assay for drug concentrations in serum.¹⁸ Briefly, eight standards were generated by a 1:2 linear dilution using normal human breast milk starting at 10ug/mL. Three positive controls were generated by spiking 2, 1, and 0.5 $\mu\text{g/mL}$ of drug into normal human breast milk. Twelve microliters of either standard, control, or patient sample were added to individual wells of a 96-well low protein binding round bottom plate. Normal human breast milk was added without labeled tumor necrosis factor TNF- α (TNF- α) as background subtraction or with labeled TNF- α as a negative control. Appropriate amounts of labeled TNF- α were added and final volume brought up to 300 μL s with 1x PBS/0.1XBBSA. The samples were then filtered using a 0.2 micron Millipore filter and 100 μL was injected onto the high performance liquid chromatography (HPLC). The TNF- α /drug complexes and the free TNF- α were then resolved on a Phenomenex Yarra size-exclusion column. A standard curve was generated by plotting the proportion-shifted area [bound TNF- α / (bound TNF- α + unbound TNF- α)] versus drug concentration. Patient samples and controls were then interpolated from this curve to determine the drug concentration. A similar process was used for non-TNF biologics. All samples were analyzed by Prometheus Labs, Inc. (San Diego, CA) at no cost.

Statistical Analysis

We examined univariate frequencies and distributional parameters of lab results, outcomes, and characteristics of the study population to identify outliers or implausible values, and to permit checking model assumptions. To estimate the associations between

maternal IBD drug exposures and developmental milestones and rates of infections, we calculated chi-square or Fisher's exact p-values for associations between categorical values, and estimated F-statistics using ANOVA models to determine differences in continuous outcomes between various exposure groups.

Results

Patient Characteristics

824 women completed the breastfeeding status questionnaire (Table 1). 620 (75%) women breastfed, and 204 (25%) did not. The average age of those who breastfed was 31.2 years, and the average duration of disease was 8.4 years. There was no difference in age ($p=0.8404$) or duration of disease ($p=0.3766$) between those who breastfed and those who did not. Of the women who breastfed, 58% had Crohn's disease (CD), 40% had ulcerative colitis (UC), and 2% had inflammatory bowel disease unclassified (IBDU). Of those who completed the breastfeeding survey, 72 women submitted breast milk samples. Women who provided breast milk samples were of similar age (31.8 years) and had similar disease duration (9.1 years) as women who did not. Women with lower gestational disease activity were more likely to provide breast milk samples, with women in the lowest quartile of disease activity more than 3 times as likely to provide a sample than those in highest quartile ($p=0.0361$). Of those women who submitted breast milk samples, 68% had CD, 28.6% had UC, and 3.6% had IBDU.

Among the 824 women with information on breastfeeding, there was no significant difference in breastfeeding status between those with CD, UC, and IBDU. The likelihood of breastfeeding decreased with increasing disease activity (Table 1). Among

women who breastfed, women with moderate (10.3%) or severe (0.2%) disease activity were less likely to breastfeed than women with no (72.3%) or mild (17.2%) disease activity ($p=0.0018$). Unexposed women (85%) were significantly more likely to breastfeed compared to women on immunomodulators (65%), biologics (75%) and combination therapy (67%) ($p<0.0001$) (Table 2). Compared to unexposed women, those on biologic monotherapy were half as likely to breast feed ($OR=0.53$ [CI 0.34-0.82]), while those on immunomodulators or combination therapy were even less likely (IM alone: $OR=0.32$ [0.20-0.51], combination therapy: $OR=0.35$ [0.20-0.61]). Women on biologic monotherapy were significantly more likely to breastfeed than women on combination therapy or immunomodulators ($OR=1.69$ [CI 1.12-2.55]).

Among women who did not breastfeed, the most common reasons were concerns about exposing their baby to IBD medications (40%, 48/121) and personal preference (24%, 19/121) (Figure 1). 10% of patients said their doctor recommended they not breastfeed. Sixteen of 26 patients who reported “other” for not breastfeeding provided specific reasons, which were primarily related to difficulty with milk production or latching and work schedules. Reasons for not breastfeeding were similar regardless of type of drug exposure. Few women (13%, 80/626) reported stopping an IBD medication during or after pregnancy in order to breastfeed. In addition, 12% (75/634) of women chose not to take an additional IBD medication in order to breastfeed. At one year, 28% (172/623) of women were still breastfeeding and 27% (171/623) had stopped due to personal preference or the baby’s age. Duration of breastfeeding did not differ among drug exposure groups, but women with higher disease activity breastfed for a shorter duration ($p=0.04$).

Breast Milk Concentrations

Seventy-two women submitted breast milk samples: 29 IFX, 21 ADA, 13 CZP, 1 GOL, 6 UST, and 2 NAT (Table 3). Only 10% (7/72) of women were taking concomitant immunomodulators. Date of the last dose of drug prior to delivery was available for 19 women, with a mean of 41.7 (range 7-98) days.

Infliximab

Among the 29 women on IFX, only one woman was on a concomitant immunomodulator. Nineteen of 29 (66%) women had at least one sample with a detectable breast milk infliximab concentration. Maximum breast milk concentration was detected between 24 and 48 hours after infusion (range 0.15 – 0.74 µg/mL). Seventeen (59%) women who submitted samples had drug detected at 48 hours (mean concentration 0.2 µg/mL). Eight women submitted samples 168 hours after infusion, of whom 5 had detectable concentrations. All those with detectable concentrations at 72 hours or later also had detectable concentrations between 1 and 48 hours after infusion (mean concentration 0.1 µg/mL).

Adalimumab

Twenty-one women on ADA submitted breast milk samples, and 4 of those were on an immunomodulator. ADA was detected in breast milk in only 2 patients (9.5%), one on an immunomodulator, with the maximum concentration seen between 12 and 24 hours after injection (range 0.45 – 0.71 µg/mL). Seven women provided breast milk samples out to 7 days, and ADA was undetectable at all time points in those women.

Certolizumab pegol

Thirteen women on CZP submitted breast milk samples and 2 of them were also on an immunomodulator. Drug was detected in 3 women (23%) on CZP alone, with peak concentrations seen between 12 and 48 hours (range 0.27 – 0.29 µg/mL). Two women with undetectable concentrations in the first 48 hours after injection submitted breast milk samples out to 7 days, and CZP was undetectable at all time points.

Golimumab

One woman on GOL submitted breast milk samples up to 7 days after her injection. Drug was not detected in any of the samples.

Ustekinumab

Six women on UST provided samples. None were on a concomitant immunomodulator. UST was detected in 4 of 6 (67%) samples, with peak concentrations seen between 12 and 72 hours after injection (range 0.72-1.57 µg/mL). All of the mothers with detectable concentrations submitted samples out to seven days and 3 of those had concentrations detected beyond 48 hours.

Natalizumab

Two women on NAT submitted breast milk samples out to 48 hours. Drug was detected in breast milk in one woman at 12 hours and 24 hours (0.26 and 0.46 µg/mL).

Infection, growth, and development

Among the 824 women with breastfeeding data, per the ASQ3, there was no increased risk of developmental delay or lack of milestone achievement at 12 months in infants who were breastfed compared to non-breastfed (Table 4), and ASQ3 scores of breastfed infants did not differ by maternal medical therapy (Table 5). There was no

difference in rates of infection among infants who were breastfed and those who were not (Table 4). Breastfed infants exposed to immunomodulators, biologics, or combination therapy had similar milestone achievement and were also not more likely to have an infection in the first 12 months of life compared to unexposed infants or infants who were not breastfed (Table 5). This was true for all infections and also when excluding otitis media, the most common infection. Of note, breastfed infants were numerically more likely (39% vs. 36%) to attend daycare and/or have a sibling in daycare (62% vs. 48%).

Discussion

This is the largest prospective observational study evaluating biologic breast milk transfer from women with IBD to their infants and includes data for nearly all of the biologic medications currently used to treat IBD. In this study, IFX, ADA, CZP, UST, and NAT were all detected in breast milk samples, but at very low concentrations. Concomitant immunomodulator use did not affect drug detection in breast milk. Among the cohort of 824 infants, breastfeeding while on biologic therapy did not adversely impact the rate of infection or achievement of developmental milestones compared to not breastfeeding.

Recommendations have historically been for women on anti-TNF α or biologic therapy to avoid breastfeeding. However, breastfeeding should be low risk, as IgA is the predominant immunoglobulin found in breast milk and the biologic agents evaluated here are all in the IgG subclass.^{19,20} Therefore, secretion and transfer in breast milk should be minimal.

Current data evaluating the concentrations of the anti-TNF α drugs IFX, ADA, and CZP in breast milk are limited to case reports.^{8,9,12-16} These have demonstrated trivial transfer of IFX,¹³⁻¹⁶ ADA,^{12,14} CZP,²¹ and UST²² similar to our study.

Monoclonal antibody therapy may be absorbed to some small degree from the gut. An infant who had no intrauterine infliximab exposure and was only exposed to the drug through breast milk after the mother initiated IFX in the post-partum period had a serum concentration of 1.7 $\mu\text{g/mL}$ five days after the mother's second IFX infusion.¹⁴ The mechanism of absorption is not clear, but it has been postulated to involve the FcRn, which is expressed in a variety of neonatal tissues, and the intestinal cells of adults and fetuses.^{23,24}

We considered whether it would be helpful to understand the serum pharmacokinetics of these biologic medications in order to predict degree and timing of detectable breast milk concentrations by looking at the drug half-life and C_{max} (time to maximum serum concentration). T_{1/2} and C_{max} for each agent are listed in Table 6.^{22,25-29}

For IFX, eight women submitted samples to 168 hours of whom five had detectable concentrations beyond 48 hours as well as between 1 and 48 hours after infusion. Therefore, it is unlikely that we missed any samples with detectable IFX concentrations beyond 48 hours among the women who did not have detectable concentrations between 1 and 48 hours and extended data. For ADA, it is possible that drug would be detected with sampling out to 7 days when peak serum concentration occurs. However, in our small sample, peak breast milk concentration was seen 12-24 hours after dosing and no drug was detected in seven women who provided samples out to 168 hours. Similarly, two women on CZP who provided samples to 168 hours did not

have detectable breast milk concentrations at any time point. In our small sample size for UST, peak breast milk concentrations were seen 12-72 hours after injection and drug was detected beyond 48 hours in 75%. Finally, for NAT, neither of the two women in our study submitted samples beyond 48 hours. However, as was the case in a prior case report, drug could be detected with extended sampling.³⁰

Finally, the overall rate of breastfeeding in the PIANO registry was 75%, which is slightly lower than the average rate of 81.1% of infants that start to breastfeed in the United States.³¹ Our study shows that significantly fewer women taking immunomodulators and biologics breastfeed compared to women not on these medications. The most common reasons for not breastfeeding were concern for drug transfer to the infant and personal preference. Physician recommendation was also influential. Better data and provider and patient education should help increase rates of breastfeeding in this population.

This study has several strengths and limitations. It is the largest long term, prospective observational study of nursing mothers and their infants. Breast milk concentrations were measured at multiple time points and infants were followed to at least one year. In addition, breast milk concentrations were analyzed using assays that calibrated the standard curve with breast milk. All drug concentrations were analyzed with this assay methodology. One limitation is that the sample sizes were small for GOL, NAT and UST. Next, lack of extended breast milk samples collected may be important. Only 22/72 (14%) women submitted breast milk samples between 48 hours and 168 hours after drug dosing. Whereas infusion-based medications have a C_{max} immediately after infusion, injection-based drugs have a longer time to C_{max}. Though this was not

seen in our small sample of injection-based drugs, it is possible that the drugs could be detected with extended sampling. Next, breastfeeding in general has been associated with lower rates of infection, including otitis media.^{32,33} We looked at all infections, including otitis media, as well as infections excluding otitis media in order to be able to capture more serious infections. We also queried mothers regarding daycare exposure. Though our sample size with breastmilk samples is small, the overall cohort of 824 women with breastfeeding data is well characterized and supports the low risk associated with breastfeeding on biologic therapy.

Finally, infant cord drug concentrations at birth and serum concentrations after birth as a result of placental transfer may have a greater impact on infection and development outcomes than breast milk transfer, and time of breast milk sample after delivery may also be important. In this study, breast milk samples were mostly obtained within 3 months of delivery, when some concentration of placental transfer would be present. We did not have serum samples from all infants who also had breast milk concentrations, so we were unable to perform this analysis. However, among 14 infants who did have serum concentrations at birth, there was no correlation between infant serum concentration, age at breast milk sample, or days between blood and breast milk sample. There was also no correlation between age at breast milk sample and detection in breast milk. Further, prior studies have shown no difference in infection outcomes in infants exposed in utero to biologic monotherapy based on concentration of the drug in infants at birth.^{34,35} Therefore, while lack of placental transfer data is a limitation of our study, it is not likely to have an impact on infection outcomes.

In conclusion, lactation is compatible with the use of maternal biologic therapy based on minimal transfer rates in breast milk and no association with infant infections and achievement of developmental milestones. Continued long term prospective data collection is necessary, and more data is needed to characterize the pharmacokinetics of the newer biologic agents GOL, UST, and VED.

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Figure 1. Decision NOT to Breastfeed by Drug Exposure

Legend: Reasons patients did not breastfeed based on drug exposure. Group A: thiopurine exposure only, Group B: biologic exposure only, Group AB: combination therapy exposure

Table 1. Maternal Characteristics

	Overall PIANO N = 824	Breastfed: Yes N=620	Breastfed: No N=204	Breastmilk Sample: Yes N=72
Age, Mean (SD)	31.2 (4.6)	31.2 (4.5)	31.3 (4.9)	31.8 (3.2)
Duration of disease (yrs) Mean (SD)	8.5 (6.2)	8.4 (6.3)	8.8 (6.0)	9.1 (7.1)
Disease Type, N (%)				
UC	316 (38.3)	250 (40.3)	66 (32.4)	8 (28.6)
CD	487 (59.1)	357 (57.6)	130 (63.7)	19 (67.9)
IBDU	21 (2.5)	13 (2.1)	8 (3.9)	1 (3.6)
Medication, N (%)				
Control	244 (29.6)	208 (33.5)	36 (17.6)	0 (0)
Group A	158 (19.2)	102 (16.5)	56 (27.5)	0 (0)
Group B	322 (39.1)	243 (39.2)	79 (38.7)	65 (91.3)
Group AB	100 (12.1)	67 (10.8)	33 (16.2)	7 (9.7)
Biologic, N (%)				
Infliximab	228 (28)	168 (27)	60 (29)	29 (40.3)
Adalimumab	136 (17)	99 (16)	37 (18)	21 (29.2)
Certolizumab	72 (9)	54 (9)	18 (9)	13 (18.6)
Golimumab	1 (0)	1 (0)	0 (0)	1 (1.4)
Natalizumab	12 (1)	8 (1)	4 (2)	2 (2.8)
Ustekinumab	1 (0)	1 (0)	0	6 (8.3)
Disease Activity, N (%)				
None	562 (69.5)	441 (72.3)	121 (60.8)	55 (77.5)
Mild	152 (18.8)	105 (17.2)	47 (23.6)	13 (18.3)
Moderate	89 (11.0)	63 (10.3)	26 (13.1)	2 (2.8)
Severe	6 (0.7)	1 (0.2)	5 (2.5)	1 (1.4)

UC = ulcerative colitis, CD = Crohn's disease, IBDU = Inflammatory Bowel Disease
Unclassified

Table 2. Breastfeeding and drug exposure

Group	Breastfed		Total
	No	Yes	
Unexposed, N (%)	36 (15)	208 (85)	244
Group A: Thiopurine exposure, N (%)	56 (35)	102 (65)	158
Group B: Biologic exposure, N (%)	79 (25)	243 (75)	322
Group AB: Combination therapy exposure, N (%)	33 (33)	67 (67)	100
Total, N (%)	204 (25)	620 (75)	824

Table 3. Breastmilk Drug Levels/Data

Drug	Total Patients, N	Total patients with a detectable level, N (%)	Peak [Range], ug/mL	Peak time [range], hrs
Infliximab	29	19 (66%)	0.74 [0.15-0.74]	24-48
Adalimumab	21	2 (9.5%)	0.71 [0.45-0.71]	12-24
Certolizumab	13	3 (23%)	0.29 [0.27-0.29]	24-48
Golimumab	1	0 (0%)	N/A	N/A
Ustekinumab	6	4 (66.7%)	1.57 [0.72-1.57]	12-24
Natalizumab	2	1 (50%)	0.46	24

Table 4. Effect of breastfeeding on growth, developmental milestones and infection

Outcome [Infant Age]	Overall PIANO N=824	Breastfed: Yes N=620	Breastfed: No N=204	P Value
NICU stay, [0-12M] N (%)				
No	728 (88)	552 (89)	176 (86)	0.3141
Yes	96 (12)	68 (11)	28 (14)	
Milestone scores [12 M] Mean (SD)	87 (10)	87 (9.7)	86 (11)	0.9992
Infection, any [4 M] N (%)				
No	705 (86)	533 (86)	172 (84)	0.4869
Yes	116 (14)	84 (14)	32 (16)	
Infection, any [9 M] N (%)				
No	512 (68)	384 (68)	128 (69)	0.8555
Yes	236 (32)	179 (32)	57 (31)	
Infection, any [12 M] N (%)				
No	500 (61)	376 (61)	124 (61)	1.0000
Yes	324 (39)	244 (39)	80 (39)	
Infection, no OM, [4 M] N (%)				
No	755 (92)	569 (92)	186 (91)	0.6564
Yes	66 (8)	48 (8)	18 (9)	
Infection, no OM, [9 M] N (%)				
No	643 (86)	487 (87)	156 (84)	0.4654
Yes	105 (14)	76 (13)	29 (16)	
Infection, no OM, [12 M] N (%)				
No	659 (80)	495 (80)	164 (80)	0.9198
Yes	165 (20)	125 (20)	40 (20)	

NICU = Neonatal intensive care unit, M = Months, OM = Otitis media

Table 5. Effect of drug exposure on infant growth, development and infection among breastfed infants

	Overall N=620	Unexposed N=208	Group A N=102	Group B N=243	Group AB N=67	P Value
Duration breastfed M (SD)	7.4 (4.2)	7.2 (4.2)	7.3 (4.1)	7.4 (4.2)	7.2 (4.4)	0.9788
Milestone scores [12M] mean, (SD)	87 (10)	87 (11)	87 (9)	88 (9)	88 (9)	0.5491
NICU stay, [12M] N (%)						
No	552 (89)	191 (92)	93 (91)	212 (8)	56 (84)	0.3141
Yes	68 (11)	17 (8)	9 (9)	31 (13)	11 (16)	
Infection, any [4M] N (%)						
No	533 (86)	182 (88)	93 (92)	201 (83)	57 (87)	0.4869
Yes	84 (14)	26 (13)	8 (8)	41 (17)	9 (14)	
Infection, any [9M] N (%)						
No	384 (68)	126 (68)	64 (70)	153 (67)	41 (68)	0.8555
Yes	179 (32)	58 (32)	28 (30)	74 (33)	19 (32)	
Infection, any [12M] N (%)						
No	376 (61)	114 (55)	68 (67)	153 (63)	41 (61)	1.0000
Yes	244 (39)	94 (45)	34 (33)	90 (37)	26 (39)	
Infection, no OM [4M] N (%)						
No	569 (92)	193 (93)	98 (97)	215 (89)	63 (95)	0.6564
Yes	48 (8)	15 (7)	3 (3)	27 (11)	3 (5)	
Infection, no OM [9M] N (%)						
No	487 (87)	163 (89)	84 (91)	188 (83)	52 (87)	0.4654
Yes	76 (13)	21 (11)	8 (9)	39 (17)	8 (13)	
Infection, no OM [12M] N (%)						
No	495 (80)	160 (77)	86 (84)	197 (81)	52 (78)	0.9198
Yes	125 (20)	48 (23)	16 (16)	46 (19)	15 (22)	

Group A = thiopurine exposure alone, Group B = Biologic exposure alone, Group AB = combination therapy exposure, M = months, NICU = Neonatal intensive care unit, OM = Otitis media

Table 6. Biologic Pharmacokinetics and peak breast milk level

Drug	Half Life	Cmax	Time of peak BM level in study
Infliximab ²⁵	8-9.5 days 192-228 hours	Immediately after infusion	24-48 hours
Adalimumab ²⁶	14 days	5-131 hours	12-24 hours
Certolizumab ²⁷	14 days	56-171 hours	12-48 hours
Golimumab ²⁸	14 days	48-144 hours	NA
Ustekinumab ²²	15-45 days	168 -312 hours (7-13 days)	12-72 hours
Natalizumab ²⁹	11 days	Immediately after infusion	24 hours

BM = breast milk

