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Natalizumab during pregnancy and lactation

Undine Proschmann, Katja Thomas, Sandra Thiel, Kerstin Hellwig and Tjalf Ziemssen

Abstract

Background: Managing medication during pregnancy and lactation in multiple sclerosis (MS) patients needs to balance potential risks to the newborn with the substantial risks of ongoing disease activity.

Objective: To evaluate the potential transfer of natalizumab (NAT) into breast milk and into the serum of newborn babies in women who continued NAT treatment during pregnancy and lactation.

Methods: Serum samples of 11 mother–infant pairs and mother milk samples of a further 4 women were analyzed for free NAT using a HL60 cell-based fluorescence-activated cell sorting (FACS) assay. Two mother–baby pairs were analyzed for cell-bound NAT, very-late-antigen (VLA)-4 expression, and saturation with NAT on immune cells by FACS analysis.

Results: In the majority of the mother–infant serum pairs (6/11) and in all breast milk samples, free NAT was detectable. Cell-bound NAT was measurable in both mother–baby pairs with significant higher levels in babies. VLA-4 expression seems to be higher in newborns. Saturation with NAT was comparable between newborns and mothers.

Conclusion: NAT can pass placental barrier before delivery and into breast milk. Measurable NAT on neonatal lymphocytes may have functional impact. Further investigations are needed to clarify safety and risk of NAT exposure during pregnancy and lactation.

Keywords: Multiple sclerosis, relapsing remitting, natalizumab, pregnancy, breast milk, newborn

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Introduction

Multiple sclerosis (MS) is an autoimmune-mediated disease predominantly affecting women and with a median age of onset of approximately 30 years. Many of the affected patients are women in their childbearing years. Therefore, the safety of MS-directed disease-modifying therapies during pregnancy and lactation is a topic of increasing importance. The monoclonal antibody natalizumab (NAT) is approved for the treatment of highly active relapsing-remitting multiple sclerosis (RRMS). By blocking very-late-antigen (VLA)-4 on the surface of lymphocytes, it prevents transmigration of these cells via the blood–brain barrier (BBB) and reduces inflammation in the central nervous system.^{1,2} If a woman with highly active RRMS plans to become pregnant, risks of exposure with NAT during pregnancy have to be balanced with risks of returning disease activity after NAT cessation. NAT is classified as a pregnancy category C drug, which reflects the lack of adequate and well-controlled studies in humans. In animal studies on guinea pigs and cynomolgus monkeys, no fetotoxicity or teratogenic effects have been attributed to

NAT; however, varying results for increased abortion rates have been reported.^{3–5} Studies in guinea pigs and primates have shown that NAT can pass through the placental barrier in late-stage pregnancy and can cause hematological effects on fetal guinea pigs and primates.^{3,5} Other studies have not identified any impact on the fetus.⁴ Until now, human studies and case reports have documented mostly positive outcomes of pregnancy;^{6–10} however, results are limited by small sample sizes. Schneider et al.¹¹ reported a significant reduction in CXCL12-induced chemotaxis rate of T lymphocytes in two cases. In one case series, hematological alterations including thrombocytopenia, anemia, and leukocytosis were found in 12 women during 13 pregnancies and 10 newborns.¹² Currently, data available about NAT levels in breast milk, umbilical cord blood, and blood of the newborn are scarce. Haghikia et al.¹² detected NAT in serum of five mother–infant pairs, and Baker et al.¹³ reported one case with free NAT in breast milk. Here, we present NAT serum levels as well as cell-bound lymphocyte NAT saturation in 11 mother–infant pairs. Additionally, we have investigated the time course of

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Table 1. Clinical characteristics of the mothers.

Patient	Age (years)	Disease duration (years)	NAT infusion number	Relapses during pregnancy (<i>n</i>)	Relapse treatment	Prior treatment to NAT
M1	29	5	27	1	Steroids, 5g	Interferon beta-1b (Betaferon®), glatimeracetat
M2	39	5	37	0		Interferon beta-1a (Avonex®)
M3	31	9	n.a.	0		Glatimeracetat, interferon beta-1a (Rebif®)
M4	31	0.5	11	0		No prior treatment
M5	33	6	13	2	Steroids, 5g	Interferon beta-1a (Avonex, Rebif)
M6	32	10	64	0		Interferon beta-1a (Rebif)
M7	36	15	16	1	Steroids, 3g	Interferon beta-1a (Avonex), interferon beta-1b (Betaferon)
M8	32	7	64	0		Glatimeracetat, interferon beta-1a (Rebif)
M9	35	2	31	0		No prior treatment
M10	29	1	10	0		Interferon beta-1a (Rebif)
M11	29	0.5	10	0		No prior treatment

NAT: natalizumab; n.a.: not available.

NAT levels in breast milk of four mothers up to 5.5 months after delivery.

Methods

Patients

Pregnancy cohort. Serum from a total of 11 mother–infant pairs was analyzed for free NAT. Serum samples were collected directly after delivery. The majority of blood samples from the newborn were taken from the umbilical cord. Two of the 11 patients were treated with standard dose of NAT (300 mg monthly) during whole pregnancy, and one patient had received NAT during first trimester and then decided to discontinue treatment, restarting the drug at a later date during the pregnancy due to relapse. In the other eight patients, NAT therapy was withdrawn between 6 and 2 months before delivery. Measurement of cell-bound NAT, VLA-4 expression, and saturation with NAT was performed for 2 of the 11 pairs (Table 1). Three women presented with MS relapses during pregnancy; one woman had two relapses. In two of these three women, NAT treatment was withdrawn 3 and 6 months before the relapse and one woman was retreated with NAT during pregnancy. The patient with two relapses had received NAT treatment during whole pregnancy. All of three patients received intravenous corticosteroids for relapse treatment. Additionally, blood samples were collected from 9 newborns of the 11 mother–infant pairs for evaluation of hematological alterations.

Breastfeeding cohort. For the analysis of free NAT in the breast milk, breast milk samples from four mothers were collected prospectively (Table 2). None of these women suffered from a relapse during pregnancy or postpartum period. All patients from cohort 2 received monthly NAT infusions with the standard dose of 300 mg during pregnancy and breastfeeding period.

The study was performed according the Declaration of Helsinki, and the study protocol was approved by the Ethics Committee, Faculty of Medicine, Dresden University of Technology and Department of Neurology, St. Josef-Hospital, Ruhr University Bochum. All patients provided written informed consent.

Analyses

For the analysis of free NAT concentration, serum samples (undiluted and diluted 1:10 to 1:750) were added to HL60 cells in order to perform a HL60-based fluorescence-activated cell sorting (FACS) assay as previously described.¹⁴ To measure cell-bound NAT, VLA-4 expression, and NAT saturation, peripheral blood mononuclear cells were isolated from heparinized blood samples using Biocoll separating solution (Biochrom Ag) and Ficoll Paque (Amersham Biosciences) in LeucoSep tubes (Greiner Bio One). Cells were then stained with fluorescence-labeled anti-CD3 (BD Biosciences), anti-CD19 (BD Biosciences), anti-immunoglobulin (Ig)-G4 (Southern Biotech), and anti-CD49d (BD Biosciences).

Table 2. Patient characteristics of the breastfeeding mothers.

Patient	Age (years)	Disease duration since RRMS diagnosis (years)	Total number of NAT infusion (<i>n</i>)	Relapses during pregnancy (<i>n</i>)	Prior treatment to NAT	EDSS before delivery	NAT treatment during pregnancy
M12	29	5	36	0	Interferon beta 1-a	1.5	Yes
M13	25	1	9	0	Interferon beta 1-a	2.0	Yes
M14	34	4	55	0	No prior treatment	1.5	Yes
M15	36	3	45	0	Fingolimod	2.5	Yes

RRMS: relapsing-remitting multiple sclerosis; NAT: natalizumab; EDSS: Expanded Disability Status Scale.

Table 3. Hematological characteristics of the newborn.

Newborn	Anemia	Thrombocytopenia
N1	no	no
N2	n.a.	n.a.
N3	no	yes
N4	yes	yes
N5	yes	yes
N6	yes	no
N7	no	no
N8	n.a.	n.a.
N9	yes	no
N10	yes	no
N11	no	no

n. a.: not available.

antibodies. Isotype and negative cells were used as controls. Laboratory findings reported in Table 3 were obtained using routine blood analyses in certified diagnostic laboratories.

Maternal breast milk samples were collected up to 145 days after delivery and frozen at -20°C directly after collection. For analysis of free NAT, samples were first thawed and then centrifuged for separation of lipids. Afterwards, $10\text{ }\mu\text{g}$ of undiluted and diluted (1:10 and 1:100) breast milk samples were added to HL60 cells, and the same HL60-based FACS assay described above was applied.

Statistical analysis

Data are expressed as mean values with standard deviation. The unpaired *t*-test was used for group comparisons. $p < 0.05$ was considered statistically significant. All statistical analyses were performed using Graph Pad Prism 5.

Figure 1. Free NAT concentration in blood. Free natalizumab (NAT) serum concentration levels (●) in mothers and their newborns were determined using a HL60 cell-based assay. In the majority of mother–infant pairs (6/11), free NAT was detectable in a range from 69 to 19,700 ng/mL.

Results

Free NAT is present in serum of treated mothers and their newborn

Free NAT was detectable in the majority of the mother–infant serum pairs (6/11) (Figure 1). NAT was only detectable when the last infusion was given less than 75 days before delivery. In general, the mother–infant serum pairs with the most recent exposure to NAT infusion had the highest NAT levels. Levels of free NAT concentration ranged between 69 and 19,700 ng/mL in newborns, and between 122 and 19,200 µg/mL in mothers, indicating a great inter-individual variability. In four of the mother–infant pairs with detectable NAT, the concentration was higher in the mothers than in the newborns, whereas in two other mother–infant pairs, NAT levels were higher in the infants than in the mothers (Figure 1).

Figure 2. Cell-bound NAT, VLA-4 expression, and NAT saturation in blood. Mean fluorescence intensity (MFI) values for (a) cell-bound NAT, (b) very-late-antigen (VLA)-4 expression, and (c) saturation with NAT on CD3+ T-cells and CD19+ B-cells were observed in the two newborns (●) and their mothers (■). Negative controls (▲) were included. * $p < 0.05$; ** $p < 0.01$.

Cell-bound NAT, VLA-4 expression, and saturation with NAT on T- and B-cells

Cell-bound NAT, VLA-4 expression, and saturation with NAT were measured on CD3+ T-cells and CD19+ B-cells of four mother–baby pairs. A mean fluorescence intensity (MFI) of NAT on the cell surface of 1634 ± 116.1 was observed on CD3+ T-cells of the newborns compared to a significant lower MFI of 925.3 ± 63.25 in the respective mothers ($p = 0.012$) (Figure 2(a)). On CD 19+ B-cells, MFI was 1366 ± 70.37 in the newborns and 910.8 ± 100.7 in the mothers (difference statistically significant $p = 0.015$)

(Figure 2(a)). There was no significant correlation between free and cell-bound NAT. For VLA-4 expression on CD 3+ T-cells, an MFI of 2014 ± 423.1 was measured in the newborns and 1106 ± 188.1 was recorded in the respective mothers (Figure 2(b)). On CD 19+ B-cells, MFI was 1378 ± 118.2 in the babies and 1066 ± 128.0 in the mothers. VLA-4 expression was lower in the mothers compared to the newborns, but did not reach statistical significance (Figure 2(b)). There was no significant difference in NAT saturation on CD3+ T-cells and CD19+ B-cells between mothers and their newborns (Figure 2(c)).

Hematological abnormalities in the newborn

Hematological abnormalities were found in six newborns including anemia ($n=5$) and thrombocytopenia ($n=3$). In two newborns, both anemia and thrombocytopenia were detected (Table 3). The mothers of the newborns with hematological abnormalities received their last NAT infusion between 3 and 1 month before delivery. Occurrence of hematological alterations seems to be associated to NAT treatment during the third trimester. We could not observe a clear association between the amount of free NAT in the newborn and detectable hematological alterations.

NAT is detectable in breast milk of NAT-treated breastfeeding mothers

NAT was detectable in the majority of the breast milk samples of all four mothers with a concentration range between 2 and 412 ng/mL, presenting again with a large inter-individual variability (Figure 3). The concentration level of free NAT in breast milk was significantly correlated ($r=0.2271$) to the time period since the last NAT infusion (Figure 4).

Discussion

Here, we present a systematic evaluation of peripheral blood samples and breast milk of NAT-treated mothers and their newborns. Transport of maternal antibodies via placental barrier starts in the second trimester with rates increasing as the pregnancy progresses.¹⁵ Unsurprisingly, monoclonal antibodies are also transported via placental barrier, and this has been reported for the therapeutics adalimumab and infliximab.¹⁶ The placental transport of the monoclonal antibody NAT was first described by Haghikia *et al.*¹² In our study, we could also detect free NAT in serum of newborns in all mother–infant pairs, providing the last NAT infusion was not longer than 2.5 months ago, which is in line with our previous pharmacokinetic data.¹⁴ NAT levels demonstrate a great deal of inter-individual variability. Here, we could demonstrate for the first time that the cell-bound NAT concentration is higher on infant CD3+ T-cells and CD19+ B-cells compared to the cells of the mother. Additionally, we observed that the exposure to NAT during the third trimester of pregnancy is associated with hematological abnormalities including anemia and thrombocytopenia in the newborns. Despite the small sample size of our analysis, these data indicate that NAT is present in newborns and might have the potential to act as a functional blocker of VLA-4. In order to evaluate the functional impact of placental NAT transport, further investigations of cell-bound NAT, VLA-4 expression, NAT saturation,

and the change in these parameters over time are needed. We also demonstrate that NAT is detectable in the breast milk including a significant association with the time since the last NAT infusion. According to the conventional model of drug passage into breast milk, large molecules such as maternal immunoglobulins can pass into colostrum because of the wide spaces between mammary epithelial cells. The pores begin to close at onset of lactogenesis and are fully closed by days 10–14 postpartum, which prohibits the direct passage of molecules with a molecular weight higher than 800 Da. According to this model, biosynthetic monoclonal antibodies should not pass into breast milk due to their molecular weight of about 140,000 Da. Nevertheless, for some monoclonal antibodies, such as etanercept, infliximab, and ipilimumab, passage into breast milk has already been demonstrated.^{17–19} In accordance with Baker *et al.*,¹³ we were also able to show that NAT is transferred into breast milk, and that levels of free NAT appear to increase over time. So far, a steady state for the breast milk is not determined. The intestinal transfer of maternal IgG from colostrum to the neonate is sparse in humans.²⁰ Gut closure occurs before birth and only a little amount of immunoglobulins is absorbed via intestine after birth.^{21,22} Post-closure uptake of IgG can occur via the neonatal Fc receptor (FcRn). FcRn, also known as Brambell receptor, is a major histocompatibility complex (MHC) class I-like molecule. Lu *et al.*²³ mentioned that the FcRn protects immunoglobulin G (IgG) from catabolism, and that FcRn is also responsible for IgG absorption in the small intestine of neonatal rats. By immunohistochemical analyses, Israel *et al.*²⁴ demonstrated that FcRn is also expressed in human epithelial cells. Shah *et al.*²⁵ observed that the FcRn is expressed in the stomach, small intestine, and colon of human fetal. Additionally, Israel *et al.*²⁶ demonstrated that human fetal FcRn could bind IgG with similar characteristics to that seen in neonatal rats. Therefore, it might be possible that small amounts of monoclonal antibodies are transported from the gut to the plasma of the newborns. In order to recommend women on monoclonal antibodies concerning drug safety during lactation, more data are needed regarding NAT levels in breast milk, and ideally in infant plasma as well.

Due to the fact that potential hematology complications like thrombocytopenia and anemia can occur, we recommend in accordance with Haghikia *et al.*¹² that patients receiving NAT for the whole duration of pregnancy should give birth in a hospital with significant pediatric experience, and that the newborns should be screened for hematological adverse events such as those listed above.

Figure 3. Free NAT in breast milk. Free NAT concentration in breast milk (■) was analyzed in four mothers (a–d) using a HL60 cell-based assay. Timepoints of NAT infusion (↓) and delivery (↑) are shown. In the majority of breast milk samples, free NAT was detectable with a range of 2–412 ng/mL.

Although our observation is limited by the small sample size and by the different breast milk sample collection procedures, our data clearly show that NAT can pass the placental barrier, is detectable in newborns after delivery, and is transferred into breast milk. Our data emphasize the need to carefully

outweigh risks and benefits in the clinical decision to continue NAT treatment during pregnancy and lactation. If therapy is continued, babies should be carefully screened for hematological abnormalities. Further investigations, using standardized sample collection protocols, are needed to fully understand the

Figure 4. Correlation between free NAT in breast milk to time since last NAT infusion. Free NAT concentration in breast milk is correlated to time since last NAT infusion with Spearman's rank correlation coefficient of 0.2271.

mode and impact of NAT-transfer from mother to newborn via breast milk.

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Declaration of Conflicting Interests

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