Anti–TNF-α Therapy May Cause Neonatal Neutropenia

**abstract**

Although anti–tumor necrosis factor (anti-TNF) antibodies are associated with a clear risk of agranulocytosis in adults and are known to cross the placenta, monitoring of the absolute neutrophil count (ANC) in neonates born to mothers receiving these biological agents is not currently recommended. Here, we report on the first case series of 4 newborn patients with severe neutropenia born to mothers treated for ulcerative colitis with infliximab during pregnancy (including the third trimester). The newborns presented with severe neutropenia at birth, which was subsequently complicated by skin infections. The newborns’ ANCs returned to the normal range within 8 to 14 weeks, at which time infliximab could not be detected in the blood. Anti-TNF agents probably exert a direct, toxic effect on the bone marrow. Furthermore, the detection of a CD16 autoantibody in 1 mother–newborn pair suggests that infliximab can induce autoimmune neutropenia. Abnormally high levels of the CD16 autoantibody in newborn serum or immaturity of the fetal bone marrow might explain why neutropenia was observed in the child but not in the mother. We recommend the systematic measurement of ANC on cord blood at birth and (in the event of an infection) in the weeks thereafter.

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**KEY WORDS**
neonatal neutropenia, agranulocytosis, infliximab

**ABBREVIATIONS**
ANC—absolute neutrophil count
CBC—complete blood count
GA—gestational age
G-CSF—granulocyte colony-stimulating factor
HNA—human neutrophil antigen
TNF-α—tumor necrosis factor α

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Infliximab is a chimeric, monoclonal immunoglobulin G1 antibody directed against human tumor necrosis factor α (TNF-α). It is principally used to treat rheumatoid conditions and intestinal pathologies such as inflammatory bowel disease. Anti–TNF-α agents have proven efficacy and safety in the treatment of inflammatory diseases. However, neutropenia is a common adverse drug reaction and may occur in up to 16% of patients receiving anti-TNF therapies. This neutropenia can be severe (ie, an absolute neutrophil count [ANC] <0.5 × 10⁹/L) and can lead to life-threatening infections. Monitoring the ANC at baseline and after each infusion is recommended for patients receiving anti–TNF-α agents.

Inflammatory bowel disease particularly affects women of childbearing age. Indeed, women with potentially non-controlled bowel disease and who wish to conceive usually continue their treatment during pregnancy (with the exception of methotrexate, which is contraindicated). There is no consensus on anti–TNF-α therapy during pregnancy. As with other immunoglobulin Gs, infliximab can cross the placenta from the maternal circulation into the fetal circulation; indeed, fetal infliximab levels peak during the third trimester of pregnancy. Although infliximab’s effects on the fetus have not been characterized, registry studies in pregnant women receiving infliximab have not observed hematologic complications in the newborns.

To the best of our knowledge, there are no literature reports of neonatal neutropenia associated with the mother’s use of anti–TNF-α agents during pregnancy. Here, we report on 4 cases of severe agranulocytosis and infection in infants born to mothers treated with infliximab during pregnancy.

**CASE 1**

A 24-year-old woman (M1) had been receiving infliximab (5 mg/kg every 7 weeks) for 2 years as a treatment of ulcerative colitis. The clinical response was good, and M1’s symptoms were under control. The woman expressed her wish to conceive and so the frequency of infliximab infusion was reduced to once every 8 weeks. The last injection was performed at 26 weeks and 5 days of gestation. Because a vaginal smear was positive for group B Streptococcus, M1 was treated with amoxicillin during labor. A male child (case 1) was born at a gestational age (GA) of 35 weeks and 3 days. The birth parameters were normal for this GA. The child was exclusively breastfed and was discharged to home on day 4. On day 15, the child’s parents discovered 2 inflammatory skin lesions with blisters (1 around the umbilicus and the second on the right flank). The child’s general condition was good, and there was no fever or other signs of infection. The child was hospitalized and treated with antibiotics (Supplemental Methods). A complete blood count (CBC; 8 × 10⁹ white blood cells/L) revealed neutropenia, with an absolute neutrophil count (ANC) of 0.05 × 10⁹/L, a lymphocyte count of 3.6 × 10⁹/L, and a monocyte count of 2.8 × 10⁹/L. The hemoglobin level was 11.2 g/dL, the platelet count was 373 × 10⁹/L, and the C-reactive protein level was within the normal range. Neutropenia was confirmed by an ANC of 0.09 × 10⁹/L 12 hours later. Bone marrow aspiration revealed arrest of maturation of late-stage granulocytic precursors, the almost complete absence of neutrophils, and no excess of blasts cells (Fig 1). Case 1 responded well to treatment with 5 µg/kg per day of granulocyte colony-stimulating factor (G-CSF) (Fig 2).

Maternal-fetal alloimmunization was ruled out by the absence of incompatibility between the human neutrophil antigen (HNA) genotypes and by negative cross-matching. Mother, father, and child had the same genotypes HNA 1a (−) 1b (++) 1c (−), HNA-3a (+) and both parents express HNA-2a. A neutrophil-specific CD16 autoantibody (anti–HNA-1b/NA2) was detected in the mother’s and child’s sera. The parents’ CBCs revealed the absence of neutropenia, even during M1’s pregnancy and concomitant infliximab treatment. At day 28 (13 weeks after the last infliximab injection), infliximab could not be detected in the mother’s blood but was still present in the child’s circulation (4.9 µg/mL). No neutralizing antibodies against infliximab were detected in the mother’s blood, and no infliximab was detected in the mother’s breast milk. Case 1 was discharged from the hospital after 2 weeks of treatment with intravenous cefazidime and ciprofloxacin (prescribed because Pseudomonas aeruginosa had been detected in pus from the lesions). The skin infection resolved completely. The interval between G-CSF injections was adjusted so that the ANC remained >1 × 10⁹/L. The infliximab blood assay was negative at 10 weeks of age and G-CSF treatment was withdrawn at 14 weeks of age, at which time the ANC was within the normal range. At 6 and 12 months of age, the ANC, immunoglobulin levels, and lymphocyte subtype counts were all within the corresponding normal ranges.

**CASES 2, 3, AND 4**

A 28-year-old woman (M2) was being treated for ulcerative colitis with infliximab during a triplet pregnancy. The woman had been taking clomiphene to induce ovulation. The last infliximab infusion was administered at 27 weeks and 1 day of gestation. The pregnancy was uneventful, and there was no gestational hypertension. Three girls (cases 2–4) were delivered via an elective cesarean procedure at a GA of 35 weeks. The birth parameters were normal for this GA, with birth weights of 1800 g (case 2), 2185 g (case 3), and 2185 g (case 4). In the first days of life, CBCs revealed severe neutropenia in
cases 2 and 3 (<0.5 \times 10^9 \text{ANC/L}) and moderate neutropenia in case 4 (1.1 \times 10^9 \text{ANC/L}). Cases 2 and 4 presented with Staphylococcus epidermidis skin infection and were therefore treated with intravenous antibiotics and G-CSF for 10 days. Case 3 presented with Enterobacter cloacae diarrhea and was treated with antibiotics and G-CSF for 8 days. As the 3 siblings recovered from their infections, the ANC increased steadily and were within the normal range at 6 weeks of age.

Maternal-fetal alloimmunization was ruled out by the absence of granulocyte antigen group incompatibility and by negative cross-matching. Both parents carried the same genotype HN1-1a(+), 1b(+), 1c (-), express HNA-2a, and there were no incompatibility in HNA-3, HNA-4 and HNA-5. Again, the parents’ CBCs revealed the absence of neutropenia, even during M2’s pregnancy and concomitant infliximab treatment. No anti-nuclear antibodies, anti–double-stranded DNA autoantibodies, or circulating CD16+ neutrophil-specific antibodies could be detected in M2’s blood. Urine samples for all 3 siblings were negative for cytomegalovirus by polymerase chain reaction analysis. At 1 year of age, the ANCs for the 3 siblings were all within the normal range.

**DISCUSSION**

Persistent neutropenia in a newborn is uncommon and requires prompt investigation. In the cases reported here, sepsis was not severe enough to account for persistent, severe neutropenia. ANCs returned to normal values within 8 to 14 weeks of treatment. No neutropenia was observed during the subsequent 18-month follow-up period, confirming that the condition was acquired and not inherited. Although maternal-fetal alloimmunization was our initial hypothesis, HNA genotyping and cross-matching between maternal serum and freshly isolated paternal granulocytes were negative in both families. Given that none of the cases had been exposed to other marrow-suppressing agents, we attribute the observed, severe neutropenia to the anti–TNF-\alpha agent taken by the mothers during their respective pregnancies.

The mechanism underlying neutropenia related to anti–TNF-\alpha antibodies has not been characterized. It has variously been suggested that (1) T-cell lymphocytes act against neutrophil precursors and (2) anti–TNF-\alpha therapy changes the cytokine environment and thus inhibits granulocyte differentiation in the bone marrow. Infliximab may also impair the production of granulocytes by inducing...
antineutrophil autoantibodies and thus autoimmune agranulocytosis.7,17 Indeed, we detected a CD16 autoantibody in M1 and case 1. Before each ant–TNF-α infusion, M1’s ANCs were within the normal range. Furthermore, no CD16 autoantibodies were detected before the first infliximab infusion. Abnormally high levels of the CD16 autoantibody or immaturity of the fetal bone marrow might explain why neutropenia was observed in the newborn but not in the mother.

In the vast majority of cases, the benefits of anti–TNF-α agents outweigh the risks during pregnancy. Indeed, active inflammatory bowel disease in the mother can lead to adverse pregnancy outcomes, such as spontaneous abortion or preterm delivery.12,18,19 In line with the literature, we observed high neonatal infliximab concentrations several months after birth. It has been suggested that a newborn’s reticuloendothelial system is too immature to clear the antibody quickly.11,20,21 Breastfeeding is not contraindicated in mothers treated with anti–TNF-α agents.9 In the present cases and in 2 literature reports10,22 (but not a third publication23), infliximab was absent from breast milk. Reports on >300 pregnancy outcomes in women receiving infliximab suggest that the use of anti–TNF-α agents in pregnancy is associated with a low fetal and neonatal risk.12,18,24 Nevertheless, the potential side effects of infliximab on the fetus and the newborn have been poorly evaluated to date. Few authors have reported on cases of mothers treated with infliximab up until delivery.12 Although no infections in the newborns were reported, the white blood cell count was not monitored in most cases and the frequency of neutropenia in this setting may be underestimated. Last, the European Crohn and Colitis Organisation Consensus on the management of Crohn disease has recommended avoiding the use of infliximab during the last trimester of pregnancy because the effects of exposure on the newborn are not known6; hence, this restriction may explain the rarity of neonatal neutropenia in this setting.

The cases presented here emphasize the risk of severe infection associated with drug-related neutropenia in neonates and infants. Furthermore, physicians must also be aware of the risk associated with some immunizations of infants exposed to infliximab in utero. Indeed, a case of fatal disseminated bacille Calmette-Guerin infection has been reported in an infant whose mother was treated with infliximab throughout her pregnancy (for Crohn disease).25 We suggest that more attention should be paid to the ANC in both mothers treated with infliximab (especially during the third trimester) and in their children (at birth and during the first 6 months). We recommend the systematic performance of a CBC on cord blood at birth and (in the event of an infection) in the weeks thereafter. Additional studies are needed to estimate the true frequency of this type of neutropenia and to better understand associated factors and the underlying pathology.

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