Severe neutropenia in an infant after treatment with infliximab during pregnancy

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SUMMARY

We describe a 7-month-old girl with severe neutropenia born to a mother treated for ulcerative colitis with infliximab until the 24th week of pregnancy. Despite the recommendation of using Tumour Necrosis Factor inhibitors (TNFi) only in the first and second trimester of pregnancy, significant levels of TNFi in offspring are possible. Hence, drug-induced neutropenia should be considered in the differential diagnosis of infants with severe neutropenia if these were exposed to TNFi in utero. Moreover, additional information is given on the risk of infection and dysfunctional immune development in these new-borns.

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INTRODUCTION

Nowadays, inflammatory bowel disease (IBD), including ulcerative colitis (UC) and Crohn's disease (CD), are being treated with immunomodulating agents and biologicals.

Active disease and flare-ups of IBD during conception and pregnancy are associated with adverse pregnancy outcomes such as preterm delivery, low birth weight, intrauterine growth retardation, still birth, and spontaneous abortion.[1-6] Therefore, guidelines recommend conception during disease remission. In order to maintain quiescent disease during gestation, it may be necessary to continue treatment during pregnancy.[1] Biologicals, in particular Tumour Necrosis Factor inhibitors (TNFi), are currently the only systemic treatment option during pregnancy.[7] The most commonly used biologicals in IBD are infliximab (IFX) and adalimumab (ADA).[1]

Obviously, there are concerns about the administration of biologicals during pregnancy and its consequences on the foetus, such as risk of infection and dysfunctional immune development. In this case report, we describe severe neutropenia in an infant exposed to IFX in utero.

CASE REPORT

A 7-month-old girl was referred to the paediatric department of Ghent University Hospital by her paediatrician because of severe neutropenia (0.2-0.4x10^9/L) and recurrent infections. The pregnancy and delivery were uncomplicated and the infant was born at a gestational age of 40 weeks and four days. The mother was treated for UC with IFX till the 24th week of pregnancy and with mesalazine (3 grams a day) during the whole pregnancy.

The first months of life were uneventful, with the exception of one episode of oral candidiasis treated with miconazole orally. There was no omphalitis at neonatal age. She received routine vaccinations according to the recommended vaccination schedule in Belgium, except for the rotavirus vaccine which was contraindicated due the exposure to IFX in utero. Since the start of day-care at the age of 4,5 months, there were recurrent infections such as upper and lower respiratory tract infections with fever, and ultimately need for hospitalisation and intravenous antibiotics. During the first hospitalisation period, severe neutropenia (0.2x10^9/L) was detected for the first time. In the first weeks after discharge

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TABLE 1. Blood results.

	Results (at admission)	Results (Day after admission)	Reference value
Red blood cells (RBC)	4,23 x 10^6/µL	**3,44 x 10^6/µL**	3,7-5,3 x 10^6/µL
Haemoglobin	11,6 g/dL	**9,5 g/dL**	10,5-13,5 g/dL
Haematocrit	35,3 %	**28,5 %**	30-42 %
MCV	83,5 fL	82,8 fL	70-86 fL
MCH	27,4 pg/cell	27,6 pg/cell	23-31 pg/cell
MCHC	32,9 g/dL RBC	33,3 g/dL RBC	26-34 g/dL RBC
Blood platelets	**778 x 10^3/µL**	**497 x 10^3/µL**	150-450 x 10^3/µL
Mean platelet volume	9,9 fL	9,5 fL	9,3-12,7 fL
White blood cells (WBC)	10,99 x 10^3/µL	**6,51 x 10^3/µL**	7-15 x 10^3/µL
Normoblasts	<150/µL	<150/µL	<150/µL
Neutrophils	**0/µL (0,0%)**	**33/µL (0,5%)**	1500-7000/µL (38,9-74,9%)
Lymphocytes	8594/µL **(78,2%)**	4212/µL **(64,7%)**	3000-9000/µL (16,1-46,9%)
Reactive lymphocytes	**330/µL** (3,0%)	**488/µL (7,5%)**	0/µL (0-5%)
Monocytes	**1561/µL (14,2%)**	1165/µL **(17,9%)**	400-1200/µL (4,0-10,7%)
Eosinophils	**165/µL** (1,5%)	358/µL **(5,5%)**	200-600/µL (0,4-5,0%)
Basophils	**330/µL (3,0%)**	**260/µL (4,0%)**	10-100/µL (0,2-1,0%)
C-reactive protein (CRP)	**31,5 mg/L**	**43,5 mg/L**	<5,0 mg/L

from hospital she developed a unilateral acute otitis media with fever and subsequently a tonsillitis/pharyngitis, which were treated with oral antibiotics for ten days.

Afterwards, she suffered from diaper dermatitis which was cured with Daktozin ointment. After a new blood check confirming severe neutropenia (0.4x10^9/L), she was referred to the paediatric haemato-oncology department of Ghent University Hospital. Severe neutropenia in the peripheral blood was confirmed (*Table 1*), and further investigations such as bone marrow aspiration and determination of anti-granulocyte antibodies were requested. A bone marrow aspiration (*Table 2*) showed toxic granulation and a left shift with relative maturation arrest at the level of band cells, but without any other abnormalities (normal erythropoiesis and megakaryopoiesis, no blast excess).

The patient was treated with granulocyte-colony stimulating factor (G-CSF) at an initial dose of 5 µg/kg/day subcutaneously, which rapidly resulted in increasing neutrophil counts. G-CSF dose was titrated to 2.5 µg/kg/day 3x/week to obtain neutrophil levels in the normal range and successfully tapered and stopped at the age of eleven months.

Repeated measurement of anti-granulocyte antibodies demon-

TABLE 2. Bone marrow microscopic results.

	Results	Reference value
Blast	0,5%	
Myeloblast	0,5%	0,2-5,0%
Promyelocyte	**12,0%**	0,5-10%
Neutrophil myelocyte	**26,5%**	5,0-15%
Eosinophil myelocyte	1,0%	1,0-7,5%
Neutrophil metamyelocyte	7,5%	5,0-15,0%
Eosinophil metamyelocyte	1,5%	1,0-7,5%
Neutrophil band cell	13%	5,0-15,0%
Neutrophil	1,0%	1,0-15,0%
Eosinophil	2,5%	1,0-7,5%
Lymphocyte	**14,5%**	15,0-50,0%
Plasmocyt	0,5%	0-2,0%
Pronormoblast	5,5%	
Basophil normoblast	1,0%	0,5-5,0%
Polychromatophil normoblast	11,0%	5,0-20,0%
Acidophil normoblast	**1,5%**	5,0-12,5%
Myelocyt/erytrocyt ratio	3,4%	2,5-10%

strated positive titres. To exclude severe congenital neutropenia (SCN), genetic testing (ELANE gene, HAX1 gene, G6PC3 gene, JAGN1 gene) was conducted and was found negative.

DISCUSSION

IFX, as used by the mother in this case report, is a chimeric monoclonal IgG1 antibody against TNF-α.[1,7-11] It binds both the soluble and transmembrane form present on activated T-cells and macrophages. In this way, it induces complement-dependent and antibody-dependent cell-mediated cytotoxicity, resulting in inhibition of the pro-inflammatory properties of this cytokine.[7,11]

TNFi are classified by the Food and Drug Administration (FDA) in category B, which means that animal studies have failed to demonstrate a foetal risk and that there are no adequate and well-controlled studies in pregnant women.[1,4,10,12] Most of these studies cannot find a statistical significant increased risk for adverse pregnancy outcomes, congenital abnormalities, harm to the foetus, etc., compared with unexposed IBD pregnancies.[1,5,6,12,13]

IgG antibodies (both maternal and therapeutic) are actively

transported across the placenta during the third trimester of pregnancy by the Fc receptor neonatal molecule.[1,2,5,7,10,11] The transport during the first trimester, when the organogenesis takes place, is very minimal so no teratogenic abnormalities are expected.[5,7,9,10,14]

This placental transmission of antibodies starts after the 22nd week of gestation and increases throughout the pregnancy, so that foetal levels exceed maternal levels of IgG. In that way, also TNFi are transported across the placenta to the infant where they can be detected in their serum up to twelve months after birth.[1-5,7,8,10,11] Cessation of IFX at the end of the second trimester or early in the third trimester may help to reduce transportation of IFX across the placenta and therefore lower the levels of IFX in the serum of the newborn.[3,5,10,11] Maternal use of TNFi during breastfeeding is considered safe because only a very small concentration of the drug is detectable in the breast milk.[2,5,6,13]

Several cases of severe neutropenia in children exposed to IFX were reported.[3,8,14] Severe neutropenia or agranulocytosis (absolute count < $0.5x10^9$/L) in an infant always requires further investigation and has a broad differential diagnosis, with amongst others SCN, sepsis/infection, autoimmune neutropenia and drug-induced destruction. In drug-induced immune neutropenia, drug-dependent antibodies against neutrophil membrane glycoprotein are produced, causing neutrophil destruction.[8,14] Considering the maternal intake of IFX during gestation in this case, a drug-induced destruction cannot be excluded as the possible cause.

Presumably, TNFi also have a direct toxic effect on the bone marrow with agranulocytosis as a known side effect.[8] The bone marrow result of our case was normocellular with left-shifted myelopoiesis and a relative stop at the band stage but no agranulocytosis.

As a result of the placental transfer, it is assumed that treatment with TNFi during pregnancy leads to neonatal immunosuppression with increased risk of neonatal infections.[7] However, until now, studies could not identify an increased risk of infections in the first year of life of infants exposed to TNF inhibitors during pregnancy.[1,3,10] It also has been hypothesised that foetal TNFi exposure potentially may alter the development of their immune system.[2,4,7,10] In a clinical immunology study, Esteve-Solé *et al.* examined seven infants exposed to either IFX or ADA during gestation. These children presented more immature B and T helper cells than non-exposed children, but these findings normalised within twelve months, with normal immunoglobulin production and vaccine responses. A decreased number of T regulatory cells (Tregs) was also observed and was inversely correlated with maternal peripartum TNFi levels. It is possible that a Treg decrease facilitates hypersensitivity leading to atopy. Furthermore, a decreased response after mycobacterial challenge was noted. It is hypothesised that defects in interleukin 12/interferon-gamma pathways might place the infant at risk of intracellular infections.[4,7,10]

Life-attenuated vaccines should be avoided in infants exposed to TNFi in utero for at least six months unless drug clearance is documented. However, TNFi exposed new-borns have a normal response to non-living vaccines, so inactive vaccinations can be administered as scheduled in the vaccination program.[1,4,5,7,10]

CONCLUSION

Here, we described a 7-month-old girl with severe neutropenia born to a mother treated for UC with IFX until the 24th week of pregnancy. Retrospectively, an autoimmune neutropenia is the most probable diagnosis in this child considering the presence of anti-granulocyte antibodies. However, severe congenital neutropenia and auto-antibodies developed as a result of the treatment with IFX have to be included in the differential diagnosis of exposed infants with severe neutropenia.

For every woman with IBD, the consideration has to be made between the benefit of TNFi administration to maintain stable disease and to minimise the risk of pregnancy complications due to flare-ups on one side, and foetal exposure on the other.[1,3,12] Because of the inconclusive results about the effect on the developing immune system, it may be better to err on the side of caution and, in women with quiescent disease, consider discontinuing TNFi at the end of the second trimester or the start of the third trimester to limit foetal exposure.[1,3,10-12] However, despite the recommendation of using TNFi only in the first and second trimester, significant levels of TNFi in offspring are possible.[5,14]

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KEY MESSAGES FOR CLINICAL PRACTICE

1. **Besides SCN and autoimmune neutropenia, drug-induced neutropenia should be considered in the differential diagnosis of severe neutropenia in infants that were exposed to TNFi in utero.**
2. **For pregnant women with IBD in remission, consider discontinuing TNFi at the end of the second trimester or the start of the third trimester.**
3. **Foetal exposure to TNFi during the second/third trimester leads to higher levels of TNFi in cord blood than in serum of the mother and the drug remains detectable till six months to one year after birth.**
4. **Breastfeeding is safe, regardless of TNFi treatment of the mother.**
5. **Life-attenuated vaccinations should be avoided for at least six months after birth or until TNFi is undetectable in serum.**

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