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Impact of Continuous Ofatumumab Exposure During Pregnancy in Multiple Sclerosis

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Abstract

Objectives

Anti-CD20 therapies are highly effective treatment options for patients with multiple sclerosis (MS), an inflammatory disorder of the CNS commonly affecting women of childbearing age. Anti-CD20 therapies are however unlicensed for use in pregnancy. Belonging to the IgG1 family, anti-CD20 monoclonal antibodies are likely to cross the placenta, especially after the 20th week of gestation. Our objective was to analyze the impact of ofatumumab (OFA), a subcutaneous anti-CD20 monoclonal antibody, during pregnancy.

Methods

We present the case of a woman with MS who accidentally administered OFA every 4 weeks until delivery. In addition to detailing the clinical and laboratory outcomes of both mother and child, we provide a summary of the available evidence regarding anti-CD20 treatment during pregnancy and breastfeeding.

Results

Our patient gave birth to a healthy girl between estimated gestational weeks 32–35. Notably, at 3 months postpartum and 4 months after the last OFA administration, the mother remained fully B-cell depleted while the B-cell counts of the child were within the normal range.

Discussion

Further data are necessary to confirm that OFA treatment during pregnancy does not affect neonatal B cells.

PRACTICAL IMPLICATIONS

We observed no B-cell depletion in the child despite ofatumumab exposure during pregnancy.

Introduction

Multiple sclerosis (MS) is an inflammatory disorder of the CNS that commonly affects women of childbearing age. Anti-CD20 therapies, including ofatumumab (OFA), are effective treatment options frequently used for highly active MS, but they are not licensed for use during pregnancy. The subcutaneous (SC) administration of OFA allows for lower dosing at monthly intervals compared with intravenous (IV) anti-CD20 drugs and is associated with faster B-cell recovery rates.[1,2] Although IV anti-CD20 administration can lead to neonatal B-cell depletion,[3,4] the effect of OFA during pregnancy is unclear.

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Methods

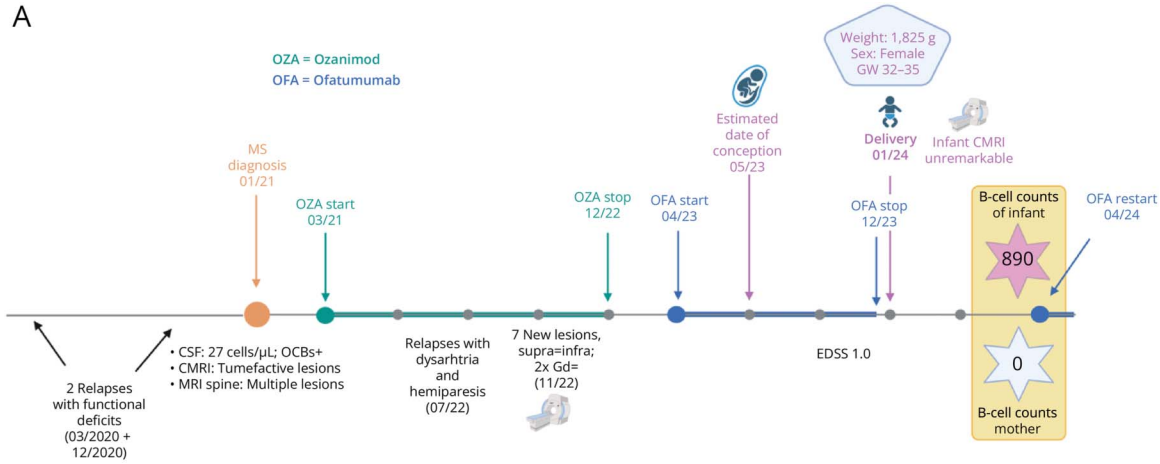
We present the case of a women with MS accidentally administering OFA every 4 weeks until delivery. We provide clinical and laboratory outcomes of both mother and child and a summary of the available evidence regarding anti-CD20 treatment during pregnancy and breastfeeding.

Standard Protocol Approvals, Registrations, and Patient Consents

Written consent was obtained from the mother of the infant.

Figure Patients' Medical History and Laboratory Assessments of Mother and Child

A



B

	Reference	Mother, no treatment	Mother, on ozanimod	Mother, on OFA	Mother, 3 months after OFA	Infant, at birth (reference)	Infant, at 3 months (reference)
WBC count, x10E9/L	3.50–9.80	6.70	7.44	8.45	8.51	12.66 (5.00–21.00)	10.24 (6.00–17.50)
Hemoglobin, g/dL	12.0–16.0	13.2	13.5	12.8	12.5	15.9 (14.5–23.0)	10.5 (9.5–14.0)
Platelets, x10E9/L	140–400	376	397	402	431	245 (80–500)	501 (355–666)
Neutrophil count abs, X10E9/L	1.60–7.10	3.69	6.03	6.41	5.19	-	0.92 (1.04–7.20)
Lymphocyte count abs, X10E9/L	1.00–2.90	2.28	0.45	1.57	2.30	-	8.09 (2.14–8.99)
CD3 T-cell abs, per µL	754–2,764	1,414	180	1,287	2,024	-	6,877 (2,300–6,500)
CD4 T-cell abs, per µL	404–1,612	1,003	41	722	874	-	5,501 (1,500–5,000)
CD8 T-cell abs, per µL	220–1,129	365	117	518	1,058	-	1,294 (500–1,600)
CD19 B-cell abs, per µL	80–616	160	14	0	0	-	890 (600–3,000)
CD56 NK abs, per µL	84–724	707	257	267	276	-	324 (100–1,300)
IgG, mg/dL	700–1,600	-	597	781	819	-	119 (200–550)
IgG1, mg/dL	405–1,011	-	-	542	-	-	94 (151–792)
IgG2, mg/dL	169–786	-	-	188	-	-	23 (26–136)
IgG3, mg/dL	11–85	-	-	8.4		-	0.7 (9.3–92.0)
IgG4, mg/dL	3–201	-	-	62.4		-	7.0 (0.4–46.4)
IgA, mg/dL	70–500	-	117	137	167	-	<6 (10–34)
IgM, mg/dL	40–280	-	46	68	120	-	<18 (17–66)
Anti-HBs-ab, U/l				19,157			2477
VZV IgG EIA, IE/l	<100			3,738			448 (<100)

(A) Diagram illustrating MS diagnosis, clinical progression, treatment history, pregnancy, and postpartum follow-up. The diagnostic workup revealed multiple MS plaques in the cerebral and spinal MRI, a lympho-monocytic pleocytosis with 27 cells/µL in the CSF and positive oligoclonal bands (OCBs), indicating intrathecal synthesis. In July 2022, the patient suffered from a disabling relapse despite oral therapy with ozanimod and was consequently escalated to OFA in April 2023. Under OFA, an unplanned pregnancy occurred, which was initially not noticed by the patient. During her pregnancy and postpartum period, the mother experienced no MS relapse and no clinical deterioration (EDSS 1.0). (B) Corresponding laboratory values are shown for the mother before therapy, during ozanimod treatment, during OFA treatment, and at 3 months post-OFA and for the infant at birth and at 3 months of age. Values outside of the normal range are indicated in red. The figure was created with biorender.com. Gd+ = gadolinium-enhancing lesions; GW = estimated gestation week; Anti-HBs-ab = hepatitis B-surface-antigen-antibodies; VZV = varicella-zoster virus.

Data Availability

Data not published within this article will be made available by reasonable request.

Case Report

We report the case of a 27-year-old woman diagnosed with active relapsing-remitting MS refractory to oral therapy with ozanimod. The medical history is summarized in Figure, A. The patient was subsequently escalated to OFA and reported no active desire to have children. OFA treatment resulted in complete B-cell depletion, measured at 8 weeks from the first administration. During ongoing therapy with OFA, an unplanned pregnancy occurred, which was initially not noticed by the patient. The conception date was subsequently calculated as May 2023, and OFA was discontinued by the end of December 2023. By this time, she had received 8 doses of OFA during pregnancy. The patient gave birth to a healthy but premature daughter, born early because of premature rupture of the membrane, at around 32 weeks of gestation by the end of January 2024. The birth weight was in the normal range at 1,825 g (66th percentile Fenton). Based on neurologic Ballard signs, the baby was estimated to be rather 34–35 weeks of gestation. After birth, the infant had mild respiratory distress and required respiratory support (continuous positive airway pressure with high-flow nasal cannula) for 4 days. A congenital cytomegalovirus (CMV) infection was diagnosed with positive CMV DNA detection in the first urine of the child. Because of prematurity and the unknown immunologic status from intrauterine OFA exposure, the infant was treated with intravenous ganciclovir for 3 weeks, followed by oral valganciclovir for another 3 weeks. Importantly, the infant showed no clinical symptoms of congenital CMV infection at any time. At the time of delivery, the child's routine laboratory tests yielded normal results. At discharge around the expected date of birth, the infant presented with normal neurologic development except for mild muscular hypotonia.

After delivery, the mother initiated breastfeeding and resumed OFA therapy in April 2024. B-cell counts for both the mother and the child were assessed 3 months after delivery. Surprisingly, the mother maintained complete B-cell depletion 4 months after the last OFA administration, whereas her child's B-cell counts were within the normal range (Figure, B).

Discussion

We present a unique case of continuous accidental OFA exposure throughout the entire pregnancy, resulting in birth of a premature, but healthy infant between 32-35 weeks of gestation. Of particular interest are the significant disparities in B-cell counts observed between the mother and child. Despite the persistence of B-cell depletion in the mother at 3 months postpartum (4 months after the last OFA injection), the child's B-cell counts remained within the normal range, implying that OFA did not adversely affect the fetal immune system.

OFA, being an IgG1 monoclonal antibody, is likely transferred across the placenta starting from gestational week 20.[3] Considering the continuous administration of OFA throughout pregnancy, it is reasonable to assume fetal exposure to the drug. Consequently, one would anticipate B-cell reductions in the child akin to those seen in the mother. Normal B-cell counts at age 3 months may either indicate that the neonate has not been B-cell depleted (either because OFA does not reach the site of B-cell depletion in the fetus or because processes inducing B-cell decreases are not fully developed yet) or that B-cell repletion rates are faster in children. In adults, B-cell repletion times are shorter under OFA compared with IV therapy and are estimated to occur after 25 weeks.[1] However, B-cell recovery rates can vary individually,[2] as underscored by the persisting depletion in the mother despite discontinuation of the drug. Rapid B-cell recovery in newborns is supported by findings from 54 individuals exposed to rituximab, within 6 months of conception.[4] Although 39% of the neonates were B-cell depleted at birth, B-cell counts returned to normal levels within 6 months; importantly, B-cell reductions were not associated with infectious complications.[4] Besides the risk of neonatal B-cell depletion, rituximab, administered for various indications, has been associated with hematologic abnormalities involving all cell lines.[5] We did not detect hematologic abnormalities at birth.

In addition to B-cell depletion, anti-CD20 therapies negatively affect pathogen-specific humoral immunity, particularly antibody production against novel antigens.[6] Nonetheless, OFA exposure during pregnancy had no major effects on antibody subclasses of the child. Furthermore, the infant recovered from an early CMV infection, highlighting the absence of significant impairment in the newborn's immune response. Importantly, the CMV infection remained clinically silent, the infant did not display any CNS symptoms, and the cerebral MRI confirmed a normal brain parenchyma.

Besides hematologic and immunologic concerns, the major issues regarding newborns exposed to anti-CD20 therapies are not related to teratogenicity, but rather to the risk of preterm birth.[7] Data on the risk of OFA exposure during pregnancy are limited. A recent study summarized pregnancy outcomes of 281 patients with MS treated with OFA and found no major congenital anomalies or serious infections.[8] Only 3 individuals were exposed to the drug at least temporarily during the third trimester, resulting in either normal live births, pending outcomes, or were lost to follow-up.[8] More data are necessary to evaluate the impact of OFA on the gestational age.

Although the pregnancy label recommends discontinuation of anti-CD20 therapies 6–12 months prior conception, expert opinion and consensus guidelines suggest usage to be safe until shortly before the time of conception.[9,10] According to the half-life, ocrelizumab (IV anti-CD20 therapy) and OFA are cleared from maternal circulation after 19 and 12 weeks, respectively,

therefore before establishment of the IgG placenta transfer, indicating very little risk of direct toxic effects on the fetus.[10]

Restarting of anti-CD20 drugs during breastfeeding appears safe, as transfer of IgG1 in breast milk is minimal, and absorption through the infant's gastrointestinal tract limited.[11] In fact, very low concentrations of the drug were detected in breast milk and therapies were well-tolerated by both mothers and infants.[12] This is particularly noteworthy considering the increase in relapse rate after delivery.[13]

MS disease activity during pregnancy must be carefully balanced with the potential harm to the unborn child, stemming from both direct exposure to medication and the increased susceptibility of an immunocompromised mother.[11] Because there are no high-quality data around anti-CD20 therapy usage in and around pregnancy, our report stands out with continuous OFA treatment and available postpartum clinical and laboratory outcomes, suggesting that administration of OFA may be safe during pregnancy.

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Disclosure

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Tiago Lerda Casaccia, MD	Department of Neurology, Christian-Doppler Clinic, University Hospital of Salzburg, Austria	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
Edda Hofstaetter, MD	Division of Neonatology, Department of Pediatrics and Adolescent Medicine, Paracelsus Medical University, Salzburg, Austria	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
Ferdinand Otto, MD	Department of Neurology, Christian-Doppler Clinic, University Hospital of Salzburg, Austria	Drafting/revision of the manuscript for content, including medical writing for content
Kerstin Hellwig, Prof., MD	St. Josef-Hospital/ Ruhr-University Bochum, Germany	Drafting/revision of the manuscript for content, including medical writing for content
Tobias Moser, MD, PhD	Department of Neurology, Christian-Doppler Clinic, University Hospital of Salzburg, Austria	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data

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