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Severe Late-Onset Neutropenia in a Pregnant Patient with Multiple Sclerosis after Ocrelizumab

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Abstract
Introduction: Ocrelizumab is a recombinant humanized anti-CD20 monoclonal antibody used to treat multiple sclerosis. Late-onset neutropenia, absolute neutrophil count <1.5 × 10^9/L that develops >4 weeks after last drug administration, is a known adverse event associated with anti-CD20 monoclonal antibodies, including rituximab and ocrelizumab. ***Case Presentation:*** We present the case of a 27-year-old woman who developed severe late-onset neutropenia during her third trimester of pregnancy after treatment with ocrelizumab 6 months prior. ***Conclusion:*** Neurologists should be aware of this risk and consider additional hematologic monitoring for pregnant patients who received anti-CD20 therapy as therapies such as G-CSF are available to help prevent serious infections.

Introduction

Ocrelizumab is a recombinant humanized anti-CD20 monoclonal antibody that was approved in the USA for the treatment of primary progressive or relapsing forms of multiple sclerosis (MS) in March 2017. Common adverse events include upper respiratory reactions and infusion reactions, but the full adverse event profile is still being determined through post-marketing surveillance and case reports. Late-onset neutropenia (LON), defined as an absolute neutrophil count (ANC) <1.5 × 10^9/L that develops >4 weeks after last drug

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administration and is preceded by a normal neutrophil count without other identifiable causes, is a known adverse event associated with anti-CD20 therapy, including both rituximab and ocrelizumab. Here, we present the case of a 27-year-old woman who developed severe LON during her third trimester of pregnancy after treatment with ocrelizumab 6 months prior.

Case Report

A previously healthy 20-year-old woman was diagnosed with relapsing-remitting MS in December 2016 after presenting to the ER with bilateral lower extremity numbness. MRI brain and total spine were notable for multiple enhancing lesions including subcortical, deep, periventricular white matter lesions, right cerebellar hemisphere lesions, upper cervical spine demyelinating lesions, and multifocal thoracic intramedullary cord lesions. Given the fulminant onset and significant lesion burden throughout her brain and cord at her young age, she was initially treated with natalizumab in January 2017.

Due to positive JC virus seroconversion in November 2019, natalizumab was discontinued and ocrelizumab started. When her first pregnancy was confirmed, therapy with ocrelizumab was paused and subsequently resumed postpartum. Records are limited, but there were no blood count derangements noted during this period. Similarly, ocrelizumab was paused after confirmation of her second pregnancy via transvaginal ultrasound on September 2, 2023 with estimated gestational age of 5 weeks 0 days with her last infusion on January 26, 2023.

In July 2023, routine third trimester blood work demonstrated severe neutropenia with ANC of 0.0×10^9/L. ANC was normal 5 months earlier (3.7×10^9/L). She was sent to the ER for a repeat CBC which showed WBC 1.3×10^9/L, stable anemia of pregnancy with Hgb 11.4 g/dL, platelets 187×10^9/L, and ANC of 0.0×10^9/L. Upon initial presentation, she was asymptomatic. Hematologic workup was notable for normal vitamin B12, folate, and copper levels. ANA, hepatitis panel, HIV, CMV, EBV, and autoimmune neutrophil antibody were all negative. Granulocyte colony-stimulating factor (G-CSF) was deferred given her asymptomatic presentation.

On hospital day 2, she developed chills, tender right submandibular lymphadenopathy, and severe mucositis. G-CSF was recommended. Prior to initiation of G-CSF, bone marrow biopsy showed hypocellular bone marrow with granulocytic maturation arrest and expanded monocytes. Cytogenetics and flow cytometry were normal. After 3 doses of G-CSF, ANC improved to 3.4×10^9/L on hospital day 8, and she was discharged. Post-discharge CBCs were collected weekly for 1 month and demonstrated resolution of neutropenia. Two months after discharge, ANC was again normal at 5.4×10^9/L. Duffy antigen testing was positive for Fy^a and negative for Fy^b. It was determined that ocrelizumab toxicity was the most likely cause of her unexplained neutropenia.

Discussion

B-cell depletion with anti-CD20 therapy is an effective treatment strategy for MS, but it can lead to unwanted side effects such as hypogammaglobulinemia and neutropenia. In the ocrelizumab phase III clinical trials, near-complete depletion of B cells was observed within 2 weeks [1]. Patients at higher risk of development of hypogammaglobulinemia include those with lower baseline immunoglobulin levels and those who have trialed more DMTs in the past [2]. Extended interval dosing has been shown to lead to less of a progressive decline in IgG, IgA, and IgM [2]. There is growing evidence that LON is a rare adverse event of

ocrelizumab [3–10]. While neutropenia was a recognized adverse reaction in the placebo-controlled clinical trial for ocrelizumab, less than 1% of the patients in the ocrelizumab group had neutrophil counts less than 1.0×10^9/L, and these were not associated with infection [11]. However, a 2022 systematic review of neutropenia complicating anti-CD20 treatment in patients with MS, which included both rituximab and ocrelizumab, found that most patients with symptomatic severe neutropenia were treated with both antibiotics and G-CSF [3]. This study had several limitations including retrospective nature, small sample size, and lack of data regarding immediate monitoring with full blood counts to determine onset of neutropenia. A separate review of safety data of patients treated with ocrelizumab from the US Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS) found most neutropenic events (19/25) were listed as life-threatening or requiring hospitalization [12]. It is not known what factors are associated with the development of future neutropenia [13].

Currently, the only prospective study examining LON following anti-CD20 therapy for inflammatory disorders of the central nervous system found that such neutropenia was rare, asymptomatic, and short-lasting [4]. However, this study was limited by short duration of follow-up and underestimation of the long-term frequency of this possibly life-threatening adverse event. A retrospective study examining the incidence and risk factors of serious infections in patients receiving ocrelizumab versus rituximab showed there was no difference in neutropenia between rituximab and ocrelizumab, but that ocrelizumab had fewer immunogenic and immunosuppressive risks [14]. Larger prospective studies are needed to determine the prevalence and consequences of LON.

It is unclear if pregnancy confers an additional risk of severe LON [15]. In the absence of larger prospective studies, it may be reasonable to perform additional hematologic monitoring for patients who become pregnant while on ocrelizumab. Interventions such as G-CSF, a safe and well-tolerated therapy in pregnancy [16], may help prevent major bacterial infections.

Conclusion

This is the first reported case of a patient who developed severe LON on ocrelizumab while pregnant. Neurologists should be aware of this possible risk and counsel their patients on the need to present to medical attention if infectious symptoms arise. While larger prospective studies are still needed to determine the true prevalence and clinical relevance of ocrelizumab-associated LON, pregnant patients may warrant additional hematologic monitoring as interventions such as G-CSF are available to help prevent major infections.

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Statement of Ethics

This retrospective review of patient data did not require IRB or other ethical approval in accordance with local/national guidelines. Written informed consent was obtained from the patient to publish this case report.

Conflict of Interest Statement

The authors declare that there is no conflict of interest.

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Author Contributions

C.J.F. drafted the initial manuscript. M.N.R.-N., M.J.L.A., and S.D.G. contributed to and revised the manuscript.

Data Availability Statement

All data generated or analyzed during this study are included in this article. The CARE Checklist for this case report is available as online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000544749). Further inquiries can be directed to the corresponding author.

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