

Ofatumumab Interruption Results in Disease Reactivation: A Case Report

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ABSTRACT

Multiple sclerosis (MS) specialists are increasingly using highly effective anti-CD20 therapies to quickly and successfully achieve disease control. We present the case of a 30-year-old Black woman with relapsing MS who did well on ofatumumab for several years before her treatment was interrupted, leading to a relapse 4 months later. Her symptoms improved with intravenous steroid treatment. After restarting ofatumumab, she remained clinically and radiologically stable. To our knowledge, this is the first case report on disease activity following the interruption of ofatumumab in a person with MS. Our case highlights a real-world clinical scenario that may have clinical implications for people with MS treated with ofatumumab, an anti-CD20 therapy with a shorter half-life, after stopping treatment or attempting to become pregnant.

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Multiple sclerosis (MS) is one of the most common chronic neurological diseases of the central nervous system affecting young adults, most often women (female to male ratio: 3:1) aged 20 to 50 years.^{1,2} MS specialists are increasingly turning to anti-CD20 therapies, mainly due to the growing literature supporting the early use of high-efficacy treatments to quickly and effectively achieve disease control.^{2,3} Findings from some studies have demonstrated that the depleting effects of intravenous anti-CD20 therapies such as rituximab and ocrelizumab may last longer than the 6-month dosing schedule.^{4,5} For instance, the median time to B-cell repopulation was 72 weeks after the last ocrelizumab infusion in a phase 2 trial.^{3,6} Additionally, low rates of increased disease activity have been reported 12 to 18 months after discontinuing rituximab and ocrelizumab.^{3,7,8} In contrast, subcutaneous ofatumumab has a shorter half-life (approximately 16 days) and time to B-cell repopulation, and there are no data about disease reactivation associated with its discontinuation.^{4,6} Here, we present the case of a 30-year-old Black woman with relapsing MS who experienced a relapse 4 months after ofatumumab cessation.

Case Presentation

A 30-year-old Black woman was in her usual state of health until 2015, when she experienced double and blurred vision for 3 days, prompting her to visit the local hospital. The neurological examination results were remarkable for bilateral internuclear ophthalmoplegia. MRI of the brain and orbits demonstrated multiple white matter lesions, many of which were associated with open-ring enhancement. Her serological workup results for MS mimickers were negative/normal. She was treated with 1 g intravenous methylprednisolone (IVMP) for 7 days, with improvement in her symptoms.

Following steroid treatment, she was evaluated in the outpatient clinic and had normal neurological examination results except for brisk reflexes in the lower extremities bilaterally. She was diagnosed with relapsing MS and started on natalizumab infusions. After 9 months of natalizumab treatment, she

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PRACTICE POINTS

Although intravenous anti-CD20 therapies have shown benefits beyond their standard dosing schedule, the long-term effects of ofatumumab, an anti-CD20 therapy with a shorter half-life, are less understood.

Health care professionals should engage in regular discussions with people with multiple sclerosis to optimize treatment strategies when disease-modifying therapies may need to be paused or discontinued, such as family planning. ■

remained neurologically stable and had negative results for anti-John Cunningham virus antibody. Unfortunately, she was lost to follow-up until 2021.

During this absence, she was hospitalized twice for an MS relapse. In mid-2018, after more than 1 year off treatment, she developed left optic neuritis with visual acuity of 20/20 OD and 20/200 OS. Brain and orbits MRI demonstrated new and enhancing brain lesions and enhancement of the left optic nerve. She received IVMP for 5 days, with improved vision. In 2021, she was readmitted to a local hospital with complaints of memory, hearing, and gait difficulties. MRI of the brain and cervical spine showed multiple new and active supratentorial and infratentorial lesions, including enhancement of the lesions at C2 and C5. She was treated with IVMP for 5 days, with a good response.

After 2 MS relapses while off treatment, she reestablished care in 2021. Her neurological examination results were remarkable for sustained nystagmus on left lateral gaze, bilateral end-point dysmetria, impaired heel-to-shin bilaterally, decreased pinprick in the left hemibody, urinary urgency, cognitive complaints, and abnormal tandem gait (estimated Expanded Disability Status Scale [EDSS] score of approximately 3.5). We discussed the importance of restarting treatment and recommended she begin an anti-CD20 therapy. She was started on subcutaneous ofatumumab 20-mg injections every 4 weeks. The treatment was well tolerated, and she remained neurologically stable throughout therapy. Laboratory monitoring demonstrated sustained B-cell depletion, with CD19-positive (CD19+) cell counts less than 20 cells (normal range, 56-561 cells/mm³) and 0% (normal range, 4%-27%). At her last visit in 2024, before discontinuing ofatumumab, her estimated EDSS score was 1.5 (visual: 1; bladder/bowel: 1).

Four months later, she was admitted to the hospital due to left arm and leg weakness, tingling in the left leg, and knee buckling

for several days, resulting in difficulties ambulating (estimated EDSS score of approximately 6.0). MRI of the brain and cervical spine revealed an enhancing lesion at the C5 level. She was treated with IVMP for 5 days, with significant improvement. After discharge, a follow-up visit revealed that she had missed 4 injections due to insurance issues. Repeat laboratory test results from 4 months off ofatumumab showed partially repopulated B cells, with a CD19+ cell count of 16 and 1%.

She decided to restart ofatumumab injections, and a few months later, she reported feeling well, her gait returned to baseline, and she was ambulating without an assistive device. MRI of the brain did not reveal any new or active lesions. She gave written informed consent to publish the details of her medical case.

DISCUSSION

To our knowledge, this is the first case report on MS disease reactivation following an interruption of ofatumumab. This young woman with active relapsing MS at diagnosis responded well to 9 months of IV natalizumab. However, she discontinued therapy and was lost to follow-up, during which she experienced 2 relapses requiring hospitalization. Upon reestablishing care, she initiated treatment with ofatumumab and remained clinically stable for 3 years. Insurance issues led to a 4-month interruption of therapy, during which she experienced a relapse requiring hospitalization, IV steroids, and physical therapy for gait impairment and weakness. At the time of relapse, her CD19+ B cells were partially repopulated. After restarting treatment with ofatumumab, her MS disease activity stabilized.

This case illustrates increased MS disease activity following a 4-month interruption of ofatumumab therapy. Notably, the timing of this relapse aligns with the known pharmacokinetics of ofatumumab, which is characterized by a shorter elimination half-life and an earlier B-cell repopulation than other IV anti-CD20 therapies. This observation provides insight into a real-world clinical scenario regarding the potential clinical implications of discontinuing ofatumumab.

Several publications have reported that patients with MS who discontinued IV rituximab or ocrelizumab had B-cell repopulation exceeding the 6-month dosing regimen. In addition, the treatment effect remained for more than 12 months after the last infusion, given the low rates of disease activity in patients who were off treatment.^{3,7,8} Findings from other studies reported that early B-cell reconstitution varied and was not associated with an increased risk of relapse or disease progression in patients with relapsing MS or progressive MS.^{4,5}

Although this case does not directly address family planning, it represents a clinical scenario that MS clinicians frequently encounter. The optimal washout period to discontinue anti-CD20 therapies, particularly ofatumumab, before attempting pregnancy remains uncertain. Emerging evidence suggests that the washout interval may be shortened to 2 months rather than the 6 months currently recommended by the US Food and Drug Administration (FDA).⁹ This issue is of growing clinical importance in managing high-efficacy anti-CD20 therapies for women of childbearing potential and other clinical situations where clinicians must balance treatment interruption, the timing of B-cell

repopulation, and the potential risk of MS disease reactivation.

Because of the long treatment effect, the high efficacy, and to reduce the risk of relapse, IV anti-CD20 therapy is often recommended to young women with MS who desire to become pregnant.^{3,4,10} Although the current guidelines from the FDA, European Medicines Agency, and Health Canada recommend that women do not conceive for 6 to 12 months after their last dose, many clinicians recommend waiting only 3 months before attempting to conceive, as rituximab and ocrelizumab are fully cleared after approximately 19 weeks and ofatumumab after 12 weeks.^{3,4,11,12} Based on the elimination period, the anti-CD20 therapies would minimally cross the placenta during the first trimester.^{2,3,12} Further, the results of several studies show that exposure to ofatumumab during pregnancy was not associated with maternal toxicity, embryotoxicity, or birth defects.^{6,10,13} Another study's findings did not show a significant impact on B-cell levels in infants exposed to rituximab, ocrelizumab, and ofatumumab during the first trimester of pregnancy.¹² However, exposure during the second or third trimester of pregnancy did result in neonatal B-cell depletion.^{10,12}

CONCLUSIONS

The efficacy and convenient dosing of anti-CD20 therapies have led to their increased use by MS specialists, particularly rituximab and ocrelizumab infusions for young women of childbearing potential, as the suppression of disease activity often exceeds the 6-month dosing regimen. When combined with the naturally reduced relapse risk during pregnancy, especially in the second and third trimesters, this strategy offers a reassuring approach to minimizing relapse risk during planned treatment interruptions for family planning purposes.¹⁴ Although ofatumumab has an efficacy similar to that of other anti-CD20 therapies, there is still much to learn about it regarding treatment cessation, especially for family planning, due to its shorter elimination half-life and median B-cell repopulation time of approximately 24 weeks to baseline or the lower limit of normal.¹⁵ Moreover, study findings have reported a more rapid B-cell reconstitution following IV anti-CD20 therapy in Black and African American patients.¹⁶ Considering ofatumumab's half-life and the lack of significant placental transfer during the first trimester, some experts have proposed an alternative approach for patients planning pregnancy. This involves timing their monthly injection with their menstrual cycle to minimize fetal exposure during early gestation or utilizing a shorter washout period to prevent disease activity before conception.^{9,14} It should be noted that this single case report does not directly address family planning practices for people receiving ofatumumab; rather, it emphasizes the need for further data to guide clinical practice. It is still unclear whether ofatumumab may have a prolonged treatment effect comparable to IV B-cell therapies and how it may impact our current strategies for treatment interruption in clinical scenarios such as family planning, therapy transitions, and other individualized care decisions. ■

Conflicts of Interest: Jeffrey Hernandez, DNP, APRN, reports relationships with Amgen, Banner Life Sciences, Can Do MS, the Consortium of Multiple Sclerosis Centers, EMD Serono, Novartis Pharmaceuticals, Sanofi, and

TG Therapeutics that include consulting or advisory and/or speaking and lecture fees. Silvia Delgado, MD, FAAN, reports receiving research support unrelated to this case report from EMD Serono and Novartis.

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