Successful switch to Ofatumumab after loss of efficacy of Ocrelizumab in multiple sclerosis: a case report.

Fabbri S, Gazzola P, Bedognetti M, Bandini F
Centro Sclerosi Multipla Asl3 Genovese

BACKGROUND

Anti-CD20 monoclonal antibodies are a cornerstone in the treatment of relapsing-remitting multiple sclerosis (RRMS), due to their ability to selectively deplete CD20+ B cells and suppress inflammatory disease activity [1,2]. Ocrelizumab and Ofatumumab share this common mechanism of action, though they differ in structure, route of administration (intravenous for Ocrelizumab, subcutaneous for Ofatumumab), and pharmacokinetic/pharmacodynamic profiles [3,4].

CASE PRESENTATION

We report the case of a 38-year-old woman with a diagnosis of RRMS, established in 2018. Her medical history is also significant for a prior diagnosis of bipolar disorder. Clinically, the patient reported a history of fixed diplopia successfully treated with steroid therapy and subsequent onset of gait disorders with ataxia. She was investigated with serological tests of autoimmunity, including serum anti-AQP4 and anti-MOG, with negative results. Magnetic resonance imaging (MRI) demonstrated multiple T2-hyperintense lesions in brain areas typically involved in MS, along with two spinal cord lesions. Cerebrospinal fluid analysis revealed no oligoclonal bands. Initially treated with teriflunomide in 2019, therapy was quickly discontinued due to poor compliance and worsening psychiatric symptoms. Clinical deterioration characterized by dysarthria and gait worsening was observed in January 2020. MRIs performed in February 2020 and February 2021 confirmed the presence of new cerebellar lesions. Ocrelizumab therapy was initiated in August 2022, resulting in initial clinical and radiological stability. In April 2023, the patient experienced a psychiatric exacerbation with a depressive episode and auditory hallucinations requiring hospitalization. A MRI performed in May 2023 remained stable, and Ocrelizumab was continued. However, in May 2024, the patient reported new neurological symptoms, including fatigue, vertigo and worsening gait, requiring assisted ambulation. The assessment revealed internuclear ophthalmoplegia, left lower limb hyposthenia, and gait ataxia. Additionally, iatrogenic extrapyramidal signs were present. MRI revealed new lesions in the brainstem and enlargement of previously documented supratentorial lesions (*Figure 1*). We retrospectively analysed the lymphocyte subpopulations collected throughout 2023 and 2024 and noted a poor persistence of B cell depletion with an early CD19+ lymphocyte repopulation (*Table, Figure 2*). Given persistent MS activity under Ocrelizumab, poor venous access complicating intravenous administration, and the pharmacokinetic and pharmacodynamic differences between Ocrelizumab and Ofatumumab, therapy was switched to subcutaneous Ofatumumab in August 2024. The patient tolerated the therapeutic switch well, achieving sustained clinical and radiological stability. Lymphocyte typification from August 2024 to August 2025 consistently demonstrated complete depletion of CD19+ B cells (*Table, Figure 2*).

Table. Ocrelizumab infusions performed in August and February, 2023 and 2024. Ofatumumab start in August 2024

	Lymphocytes count (cells/µL)	CD19 cell %	CD19 cell counts (cells/µL)
January 2023	1800	3.7	69
May 2023	2100	0	1
August 2023	1791	0.7	54
Novembre 2023	2419	0.1	2
February 2024	2482	6.3	161
May 2024	2240	0	0
August 2024	2317	5.4	125
September 2024	2510	0	0
November 2024	2176	0	0
February 25	2283	0	0
April 2025	2294	0	0
May 2025	1995	0	0
August 2025	2187	0	0

Figure 1

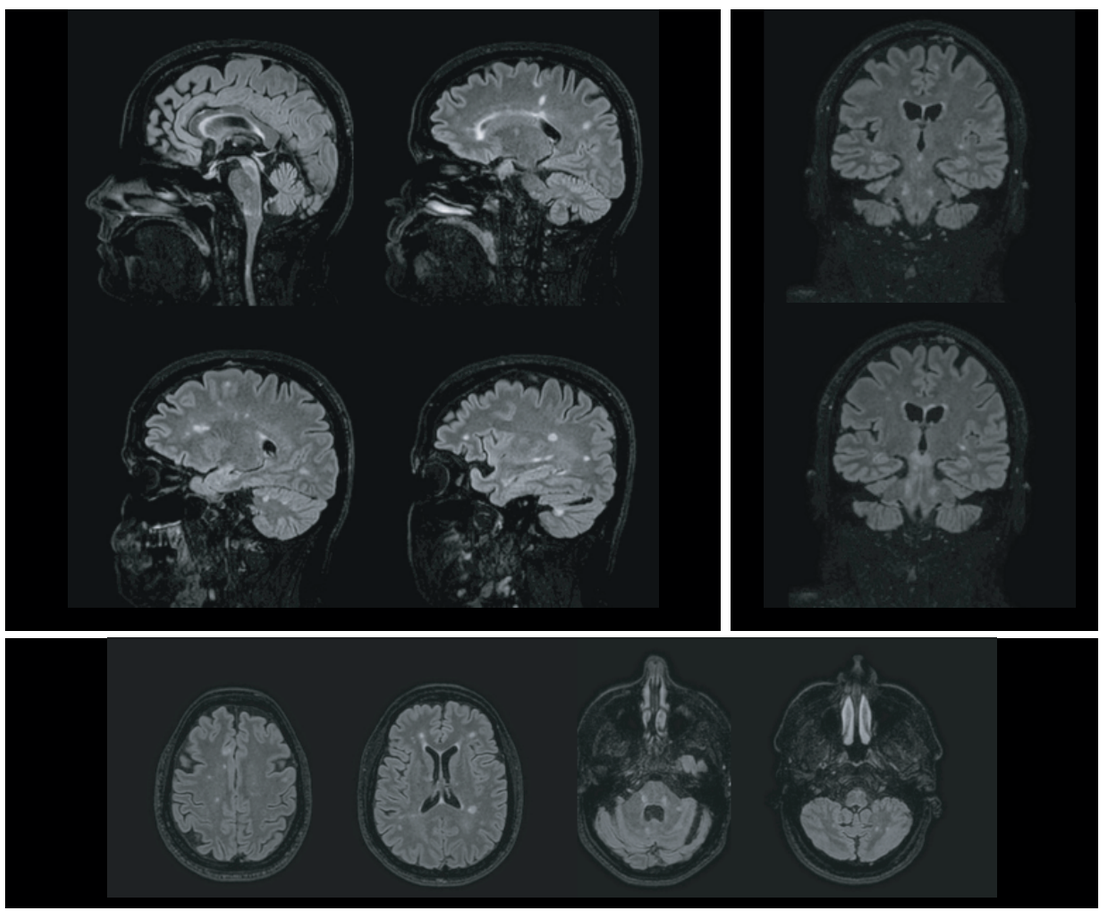
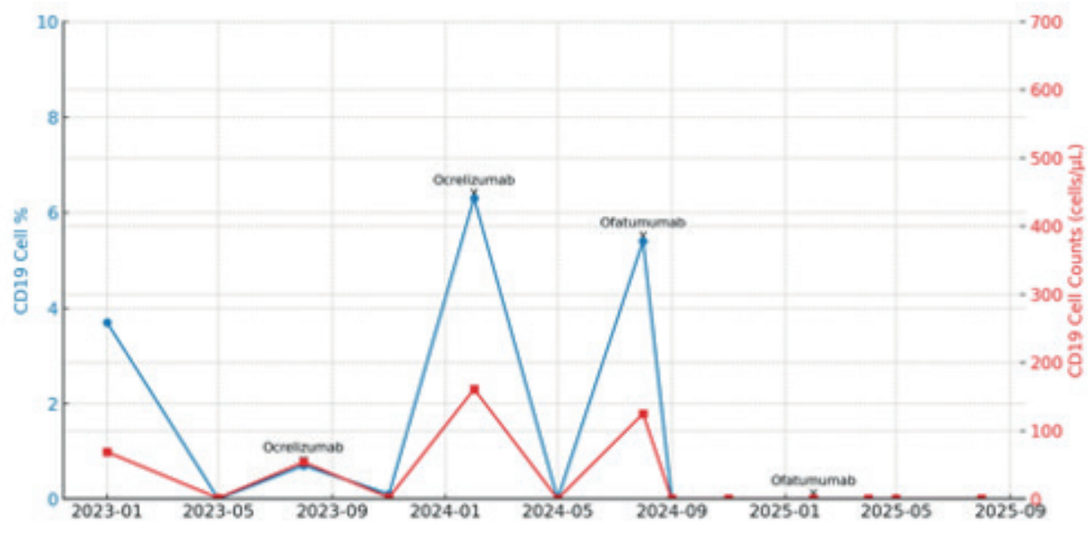


Figure 2



DISCUSSION

This case highlights a loss of therapeutic efficacy of Ocrelizumab despite initial clinical and radiological stability. During treatment, the patient exhibited incomplete and transient B-cell depletion, along with early repopulation of CD19+ lymphocytes. These events are associated with suboptimal disease control and increased risk of relapse and wearing off phenomenon [5,6]. Although no universally accepted threshold for therapeutic B-cell depletion exists, expert consensus suggests targets of <10 cells/µL or <1% of total lymphocytes [3,4,7].

Prior to the fifth planned infusion of Ocrelizumab, the patient experienced clinical worsening and MRI revealed new demyelinating lesions. These findings prompted a reasoned change in therapy based on the patient's evolving disease activity and individual characteristics. The choice of switching to Ofatumumab was primarily based on the following considerations:

- Evidence of MS activity despite ongoing Ocrelizumab therapy
- The need to maintain a highly effective disease-modifying therapy
- The know differences in structure, pharmacokinetic and pharmacodynamic between Ocrelizumab and Ofatumumab
- Subcutaneous route of administration, more feasible for this patient

Ofatumumab achieved rapid, sustained, and complete CD19+ B-cell depletion, eliminating the lymphocyte oscillation observed with Ocrelizumab and halting further disease activity, findings consistent from the ASCLEPIOS I/II trails and MIRROR study.

In this case, Ofatumumab eliminated the phenomenon of lymphocyte oscillation and B cell repletion between dosing observed during the months of Ocrelizumab therapy. The achievement of complete CD19+ B-cell depletion supports the continued use of this highly effective therapy, thereby reducing the risk of clinical and neuroradiological relapses.

1. Hauser SL, Bar-Or A, Comi G, et al. Ocrelizumab versus interferon beta-1a in relapsing multiple sclerosis. N Engl J Med. 2017;376(3):221–234.
2. Hauser SL, Bar-Or A, Cohen JA, et al. Ofatumumab versus teriflunomide in multiple sclerosis. N Engl J Med. 2020;383(6):546–557.
3. Massacesi L, Mariottini A, Nicoletti F. Relevance of pathogenetic mechanisms to clinical effectiveness of B-cell-depleting monoclonal antibodies in multiple sclerosis. J Clin Med. 2022;11:4288.
4. Bar-Or A, Freedman MS, Kappos L, et al. Rapid and sustained B-cell depletion with subcutaneous ofatumumab in relapsing multiple sclerosis: APLIOS, a randomized phase 2 study. Mult Scler J. 2022;28(6):910–924.
5. Monteiro C, et al. The ocrelizumab wearing-off phenomenon is associated with reduced immunomodulatory response and increased neuroaxonal damage in multiple sclerosis. J Neurol. 2024;271:5012–5024.
6. Marian ML, et al. The patient-reported wearing-off phenomenon with monoclonal antibody treatments for multiple sclerosis. Mult Scler J Exp Transl Clin. 2024;10(2):1–8.
7. Zecca C, et al. Treatment of multiple sclerosis with rituximab: a multicentric Italian-Swiss experience. Mult Scler J. 2020;26(12):1519–1531.