

**Late onset absolute neutropenia associated with ocrelizumab treatment in multiple sclerosis:
A case report and review of the literature**

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Dear Editor,

Ocrelizumab is a recombinant humanized monoclonal antibody approved for the treatment of multiple sclerosis (MS) directed against CD20, a membrane glycosylated protein expressed on B-lymphocytes, but not plasma cells or neutrophils. Ocrelizumab structure and mechanism of action are related to rituximab, which has been used for years in the treatment of rheumatoid arthritis. The precise mechanisms through which ocrelizumab exerts its therapeutic clinical effects are not fully elucidated but, likely, CD20 binding leads to antibody-dependent cellular cytotoxicity and complement-mediated lysis of CD20 expressing cells [1].

In January 2018, ocrelizumab has been approved in Europe for the treatment of both relapsing remitting (RRMS) and primary progressive MS (PPMS) and it is administered intravenously every six months. Infusion reactions, infections and a small proportion of malignancies are the main side effects that have been reported in clinical trials [2].

We describe a case of absolute neutropenia in a naïve patient affected by RRMS treated with ocrelizumab.

A 26-year old naïve woman was diagnosed with RRMS in August 2018 and started ocrelizumab 600 mg, administered as two separate infusions over a period of two weeks, on October 2018. She had no other medical illness and did not take any concomitant medications.

She received her third cycle of ocrelizumab, the first as a single 600 mg infusion, on April 15th 2019. Pre-infusion biochemical analysis, immunoglobulin A (IgA), G (IgG), M (IgM) and blood counts were normal and she did not experience any infections prior to the infusion.

On July 30th 2019 she reported pain in her mouth, headache and fever with chills evolving over a 2-day period and presented to the Emergency Room (ER) on August 1st 2019 for transient loss of consciousness. On physical examination, she had aphthous stomatitis on tongue and pharynx and a normal neurologic examination except for mild lethargy. She had no evidence of organomegaly or skin rash.

On August 1st, body temperature was 39 °C, white blood cell count, absolute lymphocyte count (ALC), absolute neutrophil count (ANC) and absolute monocyte count (AMC) were $1.1 \times 10^9/L$ (normal range $4.0\text{--}10.0 \times 10^9/L$), $0.3 \times 10^9/L$ (normal range $1.5\text{--}3.5 \times 10^9/L$), $0 \times 10^9/L$ (normal range $2.0\text{--}6.0 \times 10^9/L$), and $0.8 \times 10^9/L$ (normal range $0.1\text{--}0.9 \times 10^9/L$), respectively. C-reactive protein (CRP) and procalcitonin (PCT) were 36 U/L (normal value < 5 U/L) and 1.0 U/L (normal value < 0.5 U/L). Red blood cell count was within the normal range. Full blood examinations are summarized in Table 1.

In the ER, an otorhinolaryngology evaluation was performed and it demonstrated aphthous lesions on left margin of the tongue and epi- glottis and white spots on palatine tonsils. Brain computed tomography and investigations for infections as chest x-ray, abdominal ultrasounds, cultures of blood and urine were negative. Considering the presence of headache, high body temperature and lethargy, she subsequently underwent a lumbar puncture: physical-chemical analysis of cerebrospinal fluid was normal and molecular tests for viruses, including Epstein Barr Virus, Cytomegalovirus, Human Herpes Simplex 1 and 2 and Varicella-zoster virus, were negative.

She was hospitalized and empirically treated with acyclovir at the dosage of 10 mg/kg three times a day and ceftriaxone 2 g/day, intravenously, starting from August 1st 2019. Symptoms started improving two days after treatment started and ANC, ALC and CRP returned to normal. She was discharged on August 6th 2019: headache and fever were completely resolved and patient displayed exclusively a mild stomatitis. Blood tests performed 14 days after discharge were normal (Table 1).

Late-onset neutropenia (LON) is defined as an ANC of $< 1.5 \times 10^9/L$ that develops > 4 weeks after last drug administration, preceded by a normal neutrophil count, without other identifiable causes. LON has emerged as a possible adverse event of rituximab treatment and its incidence, as calculated from various studies, ranges from 3% to 27% [3]. Causes of LON following rituximab are poorly understood and many mechanisms such as infectious etiology, antibody-mediated destructions, neutrophil apoptosis triggered by the FAS/FAS ligand pathway, low granulocytic progenitor cell reserve and abnormal localization of immature precursors in the bone marrow have been postulated [3].

Clinical issues following LON, including infectious risk and rituximab re-treatment, are of outstanding importance as they may affect treatment strategy and final patient outcome. Individual rates of infections in literature range from 0 to 20% and they usually are mild and self-limited [4]. The use of granulocyte colony-stimulating factor, filgrastim, seems to minimally affect the course of LON, speeding rather than altering LON resolution [3].

In the RRMS clinical trial, neutropenia was found in 14.7% of ocrelizumab patients, compared to 40.9% of interferon beta-1a patients. In the PPMS trial, neutropenia occurred in 13% of ocrelizumab-treated patients compared to 10% in placebo. The majority of decreased neutrophil counts were transient and ANC were between $1.5 \times 10^9/L$ and $1.0 \times 10^9/L$. Only 1% of patients displayed an ANC $< 1.0 \times 10^9/L$ and none of those cases was associated with infections. Only two patients who respectively displayed $0.5 < ANC < 1.0 \times 10^9/L$ and $ANC < 0.5 \times 10^9/L$ needed a specific treatment with filgrastim. All of those patients continued with ocrelizumab treatment after neutropenia resolved [2].

Some insight about continuation of ocrelizumab treatment after LON could be driven by rheumatologic literature. Wolach et al. reported that re-challenging a patient with rituximab following LON could lead to recurrent episodes [3]. On the contrary, Monaco et al. described a case series of patients with rheumatic disease who developed LON following rituximab administration and stated that rituximab re-treatment after recovery from LON appears safe. Specifically, authors described 25 patients who were re-treated with rituximab with only two reported cases of LON, who experienced complete recovery without adverse events while neutropenic [5]. Overall, taking into account the possibility of recurrence of LON and the unclear implications of re-treatment, it seems reasonable to evaluate whether to administer further doses of ocrelizumab on a case-by-case basis.

Currently, available data are insufficient to establish guidance for timing of blood count monitoring. One of the difficulties in characterizing LON is that very diverse and heterogeneous populations have been assessed in most studies. Rissanen et al., who described a case of absolute neutropenia after rituximab treatment in a multiple sclerosis patient, suggest monitoring of white blood cell count during the first five months following rituximab administration, as this is when the risk is expected to be the highest [6]. Dunleavy et al., who reported a case series of 153 patients treated with rituximab for B-cell lymphoma, mantle cell lymphoma and Burkitt lymphoma, suggest evaluation of complete blood cell count every three months for the first year [7].

There is only one reported case of LON developing 73 days after ocrelizumab infusion in an MS patient, who was previously treated with glatiramer acetate, interferon- β -1a and dimethyl fumarate [8]. Patient developed fever, mild lethargy and mucositis and her ANC and ALC were 0.0 and $0.3 \times 10^9/L$, respectively. She was treated with cefepime and acyclovir and she was given a single dose of filgrastim 300 μ g and methylprednisolone 1000 mg with net improvement of both ANC and ALC, which returned to normal values.

In our case, absolute neutropenia could be directly correlated with ocrelizumab action, likely through an immune-mediated mechanism that could resemble the one involved in rituximab LON, or, alternatively, could be a consequence of a viral infection such as Human Herpes Virus, which we were not able to detect.

Overall, this case highlights the importance of serial monitoring of blood count after ocrelizumab, raises questions regarding the continuation of ocrelizumab use, and prompts further investigations in order to unravel underneath causes.

Acknowledgement

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Patient gave informed consent for personal and clinical data publication.

Disclosures

Dr. Zanetta, Dr. Nozzolillo and Dr. Sangalli have nothing to disclose. Dr. Robotti received fundings from Novartis.

Dr. Liberatore reported travel grants to attend scientific meetings from CSL Behring and Kedrion.

Prof. Eduardo Nobile-Orazio reported personal fees for Advisory or Scientific Board from Kedrion, Italy, Baxter, Italy, Novartis, Switzerland, CSL-Behring, Italy, LFB, France, Astellas, the Netherlands, outside the submitted work and travel grants to attend Scientific Meeting from Baxter, Grifols, Kedrion, and Novartis, Italy.

Dr. Moiola received compensation for speaking activities, and/or consulting services from Merck, Biogen, Novartis, Roche, Sanofi, and TEVA.

Prof. Filippi is Editor-in-Chief of the Journal of Neurology, received compensation for consulting services and/or speaking activities from Biogen Idec, Merck-Serono, Novartis, Teva Pharmaceutical Industries; and receives research support from Biogen Idec, Merck-Serono, Novartis, Teva Pharmaceutical Industries, Roche, Italian Ministry of Health, Fondazione Italiana Sclerosi Multipla, and ARiSLA (Fondazione Italiana di Ricerca per la SLA).

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