Ocrelizumab associated late-onset neutropenia in the patient with multiple sclerosis – case report and literature review

Neutropenija kasnog početka udružena sa primenom okrелизумаба код пацијенткиње са мултиплом склерозом – приказ случаја и преглед литературе

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INTRODUCTION

Ocrelizumab is a recombinant humanized monoclonal antibody that selectively depletes CD20-expressing B cells [1]. The precise mechanisms of action of ocrelizumab are not fully elucidated, but it has been demonstrated that this molecule has no influence on plasma cells or neutrophils [2]. In March 2017, it has been approved by the FDA, and in January 2018 by EMA, for the treatment of both, relapsing (R) and primary progressive (PP) multiple sclerosis (MS). Until May 2021, more than 200,000 people have been treated globally with ocrelizumab [1]. The most commonly reported adverse effects in clinical trials were infusion-related reactions, infections and in a small proportion of subjects, malignancies [1].
Late onset neutropenia (LON), is defined as an absolute neutrophils count (ANC) < 1.5 × 10⁹/L that develops in > four weeks after the last drug administration, preceded by a normal neutrophils count, without other identifiable causes [2, 3, 4]. In the postmarketing period ocrelizumab induced late-onset neutropenia (LON) was rarely reported [2, 3, 4, 5, 6]. LON was transient in all of those patients, and they all continued with ocrelizumab treatment after neutropenia resolved.

We describe a case of the transient, asymptomatic, LON which developed in a naïve relapsing-remitting (RR) MS patient after treatment with ocrelizumab.

**CASE REPORT**

A 25-year-old female patient was diagnosed with RRMS, after second, severe, motor relapse, in December 2019. Diagnosis was based on brain MRI that revealed high number of T2 weighted supra and infratentorial lesions, with one gadolinium enhancing lesion, and oligoclonal bands present exclusively in the cerebrospinal fluid. She had autoimmune thyroiditis, and no other illnesses, without usage of other drugs. Several years prior to establishing MS diagnosis, she suffered from Epstein–Barr virus infection. At that time, because of the abnormal complete blood count, sternal puncture was performed which did not indicate any abnormality in the bone marrow aspirate. On August 6, 2020, she started the treatment with the two first doses of intravenous infusions of ocrelizumab (600 mg, in total). Preinfusion blood counts were normal and she didn’t have any signs or symptoms of infection. Six months later, on February 3, 2021, in the laboratory results isolated neutropenia (ANC = 1.3 × 10⁹/L) was observed, without other changes in the blood count (hemoglobin 128g/l, MCV 9.6fL, white blood cells 3.6x10⁹/l, platelets 191 x 10⁹/l). Routine biochemical analysis, test panel for autoimmune diseases including autoimmune thyroiditis, did not reveal any pathological findings. Due to the above-mentioned data from medical history, on February 10th,
2021, sternal puncture was repeated and analysis of the bone marrow aspirate indicated normal bone marrow characterized with normal cellularity and appearance of granulocytic lineage, as well as the absence of dysplastic features or interrupted differentiation. Based on the finding of the bone marrow aspirate, and absence of other proven causes of neutropenia as: relevant data in patient's medical history, absence of any other complaints or physical findings; lack of other laboratory deviations; or concomitant medication possibly causing abnormalities in the blood count, diagnosis of LON was established. In accordance to the registered level of LON as ANC = $1.3 \times 10^9$/L, close monitoring of blood count twice weekly was indicated without application of granulocyte colony-stimulating factor (G-CSF). After three weeks of follow-up, patient was asymptomatic with complete recovery of LON (ANC = $2.7 \times 10^9$/L) and ocrelizumab administration was continued as previously scheduled on February 26, 2021.

The study was done in accordance with the institutional Committee on Ethics.

**DISCUSSION**

Ocrelizumab is a recombinant antiCD-20 monoclonal antibody, that has proven its efficacy and safety in pivotal controlled clinical trials (OPERA I, OPERA II, ORATORIO) for RMS and PPMS [1]. In the OPERA I and II, neutropenia in the RMS patients treated with ocrelizumab (14.7%), occurred significantly less frequently compared to interferon beta-1a patients (40.9%) [1]. Comparison of PPMS ocrelizumab patients (13%) with patients on placebo (10%), related to the development of neutropenia, did not demonstrate major differences [1]. In all of those patients, neutropenia was transient, and thus the ocrelizumab administration was continued.

We present the first case of LON associated with ocrelizumab at the Clinic of Neurology of the University Clinical Center of Serbia, in Belgrade. The diagnosis, follow-up and treatment of LON were conducted in accordance with the current recommendations for the diagnostics
and treatment of neutropenia. As of March 30, 2021, 139 patients with RMS and PPMS have been included in the Treatment Registry for highly effective disease modifying therapies for MS, established at the Clinic of Neurology. Until now, in the postmarketing surveillance, there are five reported cases of LON associated with ocrelizumab (Table 1). Female gender and RRMS were the most common demographic and clinical characteristics in these patients. In line with our case, three reported patients [3, 5, 6], one with RRMS and two with PPMS, were treatment naive. In the two remaining cases, disease modifying therapy has been already administered prior to ocrelizumab. Therefore, this interaction may have contributed to the development of LON [2, 4]. At least three to six months from the last dose of ocrelizumab was necessary for LON to be developed. Bone marrow biopsy performed in our patient, and one recently reported case, did not suggest any primary bone marrow dysfunction [6]. Cohene, Zanetta et al. [3] and Rauniyar et al. [6] have described symptoms of possible infection due to LON in their MS patients, which completely resolved after treatment with antibiotics, acyclovir [2, 3] and human granulocyte colony stimulating factor [6]. Additionally, a reported case of a 34-year-old male who developed neutropenic enterocolitis, treated with administration of broad-spectrum of intravenous antibiotics, had a complete recovery [5]. It has been described that with rituximab, B cell-depleting drug with very similar mechanism of action, rates of infections due to LON ranged 0–20% [7].

Our patient had no complaints, and thus the antibiotics were not applied. In the clinical trials with ocrelizumab, in 13% of patient’s neutropenia has transient, without associated infection [1]. Reported untreated cases resolved spontaneously within 6–20 days [2]. Only three patients with LON due to ocrelizumab, published until now, received human granulocyte colony stimulating factor [2, 5, 6]. Ocrelizumab administration was continued in all cases, except in the patient with neutropenic enterocolitis, were ocrelizumab was not scheduled at the moment of publication [5].
LON associated with ocrelizumab has unpredictable time of appearance, transient course and low prevalence. Therefore, the treatment with ocrelizumab does not necessitate the development of the new guidelines for regular complete blood count monitoring during therapy. Currently available data suggest that LON may be asymptomatic and, extremely rarely, associated with severe clinical manifestations. Having all above mentioned in mind, we suggest that only in patients on ocrelizumab with complaints suggesting possible infection, blood count monitoring should be mandatory at that moment.

**Conflict of interest:** None declared.
REFERENCES

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MS – multiple sclerosis; RRMS – relapsing remitting multiple sclerosis; PPMS – primary progressive multiple sclerosis; ALC – absolute lymphocyte count; AMC – absolute monocyte count; ANC – absolute neutrophil count; all values are $\times 10^3/\mu$L (10^9/L); DMF – dimethyl fumarate; F – female; GA – glatiramer acetate; G-CSF – granulocyte colony stimulating factor; INF-ß-1a – interferone beta 1a; LON – late onset neutropenia; MP – methylprednisolone; OCR – ocrelizumab; RTX – rituximab; WBC – white blood cells