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CASE REPORT / ПРИКАЗ БОЛЕСНИКА

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

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SUMMARY

Introduction Ocrelizumab is a recombinant humanized monoclonal antibody that selectively depletes CD20-expressing B cells, which is approved for the treatment of the relapsing and primary progressive multiple sclerosis (MS). It is extremely rarely associated with late-onset neutropenia (LON), as an adverse event.

Case outline We describe a case, from the Treatment Registry of the Clinic of Neurology, University Clinical Center of Serbia, Belgrade, of a transient, asymptomatic LON detected in a naïve relapsing–remitting MS patient, six-months after treatment with ocrelizumab.

Conclusion Having in mind all the presently available data, which indicate that rarely occurring LON on ocrelizumab is asymptomatic and transient in the majority of cases, we assume that it may be suggested that only in patients with complaints suggesting the presence of possible infection, additional complete blood count monitoring should be mandatory, exclusively at that moment, apart from the precisely defined regular follow-up.

Keywords: late-onset neutropenia; ocrelizumab; multiple sclerosis

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 United States Food and Drug Administration, and in January 2018 by the European Medicines Agency, 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 × 10^9/L that develops in more than four weeks after the last drug administration, preceded by a normal neutrophils count, without other identifiable causes [2, 3, 4]. In the postmarketing surveillance period, ocrelizumab-induced late-onset neutropenia (LON) was rarely reported [2–6]. LON was transient in all of those patients, and they all continued with ocrelizumab treatment after neutropenia resolved.

We describe a case of a 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. The diagnosis was based on brain MRI that revealed a large number of T2-weighted supra- and infratentorial lesions, with one gadolinium-enhancing lesion, and oligoclonal bands present exclusively in the cerebrospinal fluid. The patient had autoimmune thyroiditis, without other illnesses or use 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 abnormalities in the bone marrow aspirate. On August 6, 2020, she started the treatment with the first two doses of intravenous infusions of ocrelizumab (600 mg in total). Preinfusion blood counts were normal and the patient did not have any signs or symptoms of infection. Six months later, on February 3, 2021, isolated neutropenia (ANC = 1.3 × 10^9/L) was observed in the laboratory results, without other changes in the blood count (hemoglobin 128 g/l, MCV 9.6 fL, white blood cells 3.6 × 10^9/l, platelets 191 × 10^9/l). Routine biochemical analysis, test

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Table 1. Previously reported cases of ocrelizumab associated with late-onset neutropenia

Reference	Age (years) sex	MS phenotype	Previous MS therapy	Date of the I/II dose of OCR	Date of the III dose of OCR	Date, laboratory results	Clinical presentation at time of LON	Treatment related to neutropenia	Date of recovery
[2]	35 F	RRMS	GA, INF-ß-1a, DMF	/	January, 2018	April 3, 2018 WBC = 3.5 ALC = 0.3 ANC = 0	mucositis, lethargy, fever	cefepime acyclovir MP filgrastim	April 6, 2018 WBC = 19 ALC = 14.8 ANC = 1.1
[3]	26 F	RRMS	/	October, 2018	April, 2019	August 1, 2019 WBC = 1.1 ALC = 0.3 ANC = 0 AMC = 0.8	aphthous stomatitis, headache, fever, lethargy	ceftriaxone acyclovir	August 3, 2019 WBC = 4.6 ALC = 1.8 ANC = 1.3 AMC = 1.3
[4]	21 F	RRMS	DMF, RTX (April 2016, January 2017)	March, 2019	/	July 8–12, 2019 ANC = 0.3 > 0.1	/	Lidaprim acyclovir MP	July 19, 2019 ALC = > 1.5 September, 2019 ALC = 5.6
[5]	34 M	PPMS	/	N/A	N/A	42 days post initial infusion of ocrelizumab	fever, abdominal tenderness – neutropenic enterocolitis	broad-spectrum of intravenous antibiotics G-CSF	in 5 days
[6]	38 M	PPMS	/	3.5 years before LON	N/A	January 29, 2020 WBC = 3.7 ALC = 0.8 ANC = 0 AMC = 2.8	fever, chills, painful swelling of the left great toe, generalized weakness, vesicular lesions in the mouth	broad-spectrum of intravenous antibiotics, acyclovir, G-CSF	January 31, 2020 WBC = 8 ALC = 1 ANC = 2.7 AMC = 3.9
Current case, 2021	25 F	RRMS	/	August, 2020	February 26, 2021	February 3, 2021 WBC = 3.6 ALC = 1.4 ANC = 1.4 AMC = 0.2	/	/	February 24, 2021 WBC = 5.6 ALC = 2.3 ANC = 2.7 AMC = 0.6

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 – interferon beta 1a; LON – late-onset neutropenia; MP – methylprednisolone; OCR – ocrelizumab; RTX – rituximab; WBC – white blood cells

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 by 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 – such as relevant data in the 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 with the registered level of LON as ANC = 1.3×10^9/L, close monitoring of blood count twice weekly was indicated without application of granulocyte colony-stimulating factor. After three weeks of follow-up, the patient was asymptomatic with complete recovery of LON (ANC = 2.7×10^9/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 anti-CD20 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 sex and RRMS were the most common demographic and clinical characteristics in these patients. In line with our case, three reported patients, one with RRMS and two with PPMS, were treatment-naïve [3, 5, 6]. In the two remaining cases, disease-modifying therapy had 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]. Cohen [2], 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 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 patients' neutropenia was transient, without associated infection [1]. Reported untreated cases resolved spontaneously within 6–20 days [2]. Only three patients with LON due to ocrelizumab, published to date, received human granulocyte colony-stimulating factor [2, 5, 6]. Ocrelizumab administration was continued in all cases, except in the patient with neutropenic enterocolitis, where 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 the aforementioned in mind, we suggest that blood count monitoring should be mandatory immediately only in patients on ocrelizumab with complaints suggesting possible infection.

Conflict of interest: None declared.

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Неутропенија касног почетка удружена са применом окрелизумаба код болеснице са мултиплом склерозом – приказ болесника и преглед литературе

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САЖЕТАК

Увод Окрелизумаб је рекомбинантно хуманизовано моноклонско антитело које доводи до селективне деплеције лимфоцита *CD-20 B*, и које је одобрено за лечење релапсне и примарно прогресивне мултипле склерозе. Касна неутропенија је изузетно ретко удружена са окрелизумабом, као нежељени догађај.

Приказ болесника Приказана је болесница из Терапијског регистра Клинике за неурологију Универзитетског клиничког центра Србије, у Београду, са транзиторном, асимптоматском неутропенијом касног почетка, која је детектована код претходно нелечене болеснице са релапсно ремитентном мултипле склерозом, шест месеци после примене окрелизумаба.

Закључак На основу досадашњих доступних података који указују на то да је неутропенија касног почетка индукована окрелизумабом, у већини случајева асимптоматска и транзиторна, могло би се закључити да је додатно праћење крвне слике, ван стандардизованог протокола, неопходно само у случају сумње на постојање инфекције.

Кључне речи: неутропенија касног почетка; окрелизумаб; мултипла склероза