Neurological Sciences (2021) 42:3893–3895
https://doi.org/10.1007/s10072-021-05357-1

LETTER TO THE EDITOR

Rituximab- and ocrelizumab-induced early- and late-onset neutropenia in a multiple sclerosis patient

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Received: 22 March 2021 / Accepted: 28 May 2021 / Published online: 1 June 2021

Dear Editor-in-Chief,

Increasing evidence suggests B cells play a key role in multiple sclerosis (MS) pathogenesis. Ocrelizumab (OCR), a humanized anti-CD20 IgG1 mAb, significantly suppresses acute inflammatory disease activity in relapsing–remitting cases, by selective depletion of $CD20^+$ B cells. Likewise, rituximab (RTX), an IgG1 mouse/human chimeric mAb, with a similar mechanism of action but targeting a different binding epitope, has also been used off-label to treat MS.

Adverse events reported with RTX include late-onset neutropenia (LON), defined as an unexplained absolute neutrophil count below 1.5×10^9/L, 4 weeks after termination of RTX therapy. By contrast, early-onset neutropenia (EON; within 4 weeks of treatment initiation) is rare. Incidence of LON linked to RTX treatment for lymphoma and certain autoimmune diseases, alone or in combination with other drugs, varies between 5.6 and 27.3% [1].

We report the case of a patient with MS who presented EON and LON induced by RTX and OCR and review the potential pathophysiological mechanisms that could be involved.

A 32-year-old man diagnosed with MS in 2012 failed initial treatment with interferon β-1a and was switched to fingolimod after 7 months. Due to persistent lymphopenia, this treatment was also discontinued and dimethyl fumarate prescribed. One year later, the patient presented a clinical relapse with a significant increase in MRI lesion load. John Cunningham virus antibody was detected on serology testing, and therefore, the use of natalizumab was excluded. Rituximab (375 mg/m^2) was started in January 2018. Repeated infusions every 6 months were well tolerated for 20 months. Two days after the 4th infusion, the patient developed fever and ulcers in the oral cavity associated with severe neutropenia (total white blood cells (WBC) 1×10^9/L, neutrophils 0.038×10^9/L) and was hospitalized. Levels of IgG, IgM, IgA, complement, antinuclear antibodies, anti-dsDNA antibodies, and anti-neutrophil antibodies were normal. IgM and IgG for HSV I were positive and IV acyclovir treatment was indicated for 14 days. Concomitantly the patient received 6 consecutive doses (300 mcg per dose) of granulocyte colony-stimulating factor (G-CSF) to recover non-critical neutrophil levels (over 1×10^9/L). Two months later, he developed multiple episodes of neutropenia requiring re-administration of G-CSF (Fig. 1). Bone marrow aspirate (BMA) was normal. After 8 months of clinical and hematologic stability, different treatment options were discussed with the patient, who refused to receive alentuzumab due to the risk of side effects. He was switched to OCR considering that OCR binds to a different epitope and it is a fully humanized anti-CD20 mAb. One month after the initial infusion, the patient presented neutropenia again (2.4×10^9/L WBC and 0.240×10^9/L neutrophils) requiring 3 consecutive doses of G-CSF. Levels of IgG, IgM, IgA, antinuclear antibodies, anti-dsDNA antibodies, complement levels, anti-neutrophil antibodies, B-cell activating factor (BAFF), and stromal-derived factor-1 (SDF-1) were normal, as were large granular lymphocytes (LGLs) percentage. Genetic testing for single-nucleotide polymorphisms (SNPs) 158 V/F (rs396991) in FCγR3A, 131H/R (rs1801274) in FCγR2A, and in FCGγ2B 232I/T (rs1050501), as well as BAFF – 871C/T (rs9514828) genes, was negative. The patient presented no further episodes of neutropenia after 2 additional cycles of OCR (Fig. 1).

In MS and other autoimmune disorders, RTX- and OCR-induced LON has been anecdotally reported. In clinical trials

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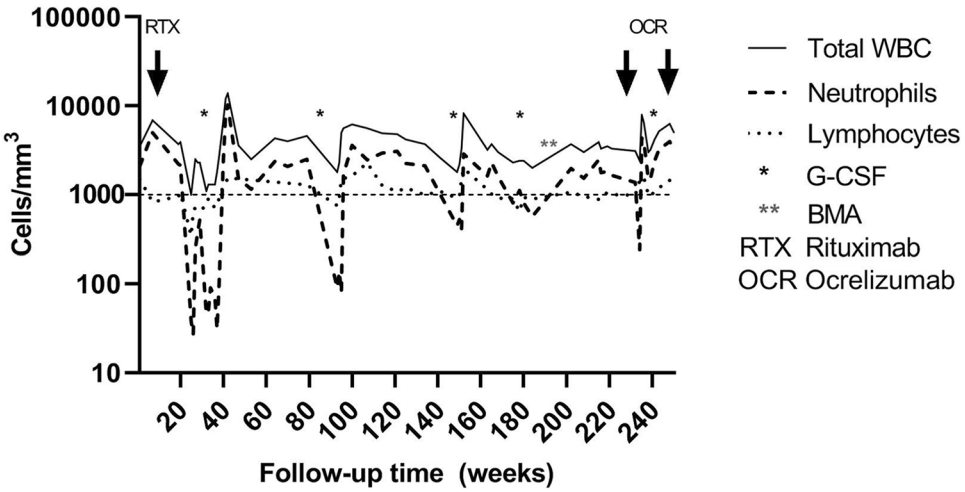

Fig. 1 Total white blood cell, neutrophil, and lymphocyte counts during patient follow-up

evaluating the safety and efficacy of RTX and OCR in MS, less than 1% of patients presented grade III-IV neutropenia [2–6].

After detailed testing, we were unable to identify a specific mechanism indicating either drug had induced neutropenia in this case. Given that neutrophils and their hematopoietic precursors do not express CD20, it is highly unlikely the neutropenia observed had been mediated by a direct toxic effect of RTX or OCR. Different hypotheses have been proposed to explain LON. Some authors have suggested that because lymphopenia and hypogammaglobulinemia were also present in LON, RTX may have induced the production of autoantibodies targeting neutrophils or hematopoietic precursors [7]. However, the absence of anti-neutrophil antibodies and normal levels of immunoglobulins in our case suggest additional factors need to be investigated to explain the neutrophil decline. Another hypothesis has pointed to bone marrow infiltration or increased levels of circulating T-LGLs as linked to neutropenia induced by anti-CD20 mAb, suggesting these cells are associated with neutropenia through neutrophil apoptosis triggered by the Fas/Fas ligand pathway [8]. In this patient, bone marrow aspirate and percentage of T-LGLs cells ($CD3^+CD8^+CD57^+CD28^-$) were both normal. Furthermore, a drop in granulocyte count has been associated with B cell recovery at the time of LON. B cell depletion may induce variations in BAFF and SDF-1/CXCL12 production, which are needed for B-cell lymphopoiesis, triggering cell division and migration of early lineage B cells [9]. B cell recovery could therefore result in disruption of bone marrow SDF-1/CXCL12 gradients, ultimately blocking neutrophil egress from bone marrow [10]. Evidence of adequate granulocyte maturation in this patient and increased neutrophil count with G-CSF would indicate neutrophil egress and myeloid maturation was not affected during LON. Both EON and LON have been associated with single-nucleotide polymorphisms in the IgG receptor, Fcγ RIIIA. These may enhance RTX binding to Fcγ, conferring increased efficacy to antibody-dependent cellular cytotoxicity (ADCC), which in turn leads to B cell depletion, granzyme, and lysozyme release, and ultimately to neutrophil death via bystander effect [11]. No pathogenic polymorphisms were detected in the FCγR genes we examined.

Early-onset neutropenia may go unreported and infection rates range from 0–20% and are usually mild and self-limited. A relevant clinical question is whether it is safe to re-exposing patients with RTX-induced neutropenia, particularly those who have exhausted other treatment options. Individuals with rheumatologic diseases who have been retreated do not regularly experience recurrence, and re-challenge is considered safe [12]. However, since underlying causes of LON are poorly understood, it is difficult to predict the consequences of re-challenging patients with rituximab after the first episode of LON. Likewise, the use of G-CSF remains controversial [12].

In conclusion, mechanisms leading to anti-CD20-induced neutropenia are poorly understood, as are potential predisposing factors, suggesting an idiosyncratic unpredictable event. Although LON is self-limited in most cases, increased monitoring may be necessary to identify and treat infections as early as possible. Infrequent blood sampling after RTX administration can mask asymptomatic EON and LON. Timely treatment with G-CSF in cases of febrile neutropenia and/or when critically low neutrophil levels are detected is recommended, even knowing that G-CSF may exacerbate the underlying demyelinating disease [13].

Data Availability Data and material are available upon request of qualified researchers.

Declarations

Ethics approval Fleni's Institutional Review Board approved the publication of this manuscript.

Consent to participate The patient consented to the publication of this article anonymously.

Conflict of interest The authors declare no competing interest.

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