

# Managing patients with late-onset neutropenia during treatment with ocrelizumab

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Beigneux et al. reported three cases of recurrent symptomatic late-onset neutropenia (LON) following ocrelizumab treatment in patients with relapsing remitting multiple sclerosis (MS). Although the first case of symptomatic LON associated with ocrelizumab in MS was reported in 2019,<sup>1</sup> these are the first reported cases of recurrent LON associated with continuation of ocrelizumab treatment.

LON has been well documented following rituximab treatment in non-neurological autoimmune diseases and haematological malignancies, defined as an absolute neutrophil count of  $<1.5 \times 10^9/L$  four weeks after the last dose of rituximab. The largest series of non-neurological LON reported incidence of 5%–6%, and a minority (11%,  $n = 2/17$ ) with symptomatic LON recurrence on rituximab.<sup>2</sup> Similarly, cases of symptomatic LON in MS treated with rituximab did not develop LON recurrence.<sup>3</sup> No predisposing host factors are yet recognised in MS, although in non-neurological diseases, a higher risk of LON was seen with previous chemotherapy, multiple rituximab courses and autologous stem cell transplantation and is not associated with hypogammaglobulinemia. The OPERA and ORATORIO trials reported similar rates of neutropenia at ~4.5%, and only seven patients had infective sequelae.<sup>4</sup> The cause of LON is not understood, but hypotheses include neutrophil autoantibody production, myeloid progenitor cells and IgG Fc receptor polymorphisms – promyelocyte maturation arrest was seen on bone marrow biopsy in a case of ocrelizumab LON.<sup>5</sup>

The answer to the key clinical question as to whether it is safe to rechallenge patients with symptomatic LON remains unclear due to the risk of neutropenic sepsis. A larger cohort of symptomatic LON is required to understand the long-term safety and risk of recurrence. In conclusion, the underlying effect of anti-CD20 on neutrophil function is not well understood, and as demonstrated in this case report, it is highly probable that recurrent symptomatic LON could recur on rechallenge. Further studies are required to understand the effect of anti-CD20 on neutrophil function, whether the risk of LON differs with the route of administration or dose (such as subcutaneous ofatumumab) and if there are predisposing host factors.

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