B-Cell depletion with rituximab in the COVID-19 pandemic: where do we stand?
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The COVID-19 pandemic has presented several challenges owing to insufficient evidence to guide clinical practice. Many patients with severe, refractory rheumatic disease (including vasculitis, systemic lupus erythematosus (SLE) and rheumatoid arthritis) depend on B-cell depletion with anti-CD20 monoclonal antibodies, such as rituximab. In the current crisis, some clinicians and patients have elected to delay maintenance rituximab therapy due to safety concerns [A: as a result of that they believe it may cause harm?]. Pausing rituximab therapy carries a risk of destabilising disease control and may increase the requirement for corticosteroids, which could ironically worsen outcomes. Initial results of the EULAR registry suggest poor outcomes in patients receiving prednisolone ≥10mg (n=64), but not in the small numbers (n=37) treated with rituximab\(^1\). Clinical-decision making is further complicated by other observations, however, such as a severe COVID-19 phenotype being reported in a patient treated with rituximab for ANCA-associated vasculitis\(^2\). Here we discuss the position of B-cell-mediated adaptive immunity and rituximab therapy in the current pandemic and consider a potential role for rituximab to treat specific COVID-19 complications.

The safety of rituximab in the context of COVID-19 is unclear. B-cell depletion could affect anti-viral immunity, the risk of re-infection, and vaccine efficacy (when available) [A: ok as edited?]. The potential risks of hypogammaglobulinemia secondary to rituximab need due consideration and the results of clinical trials evaluating convalescent sera are awaited. Positive sera trials may suggest that neutralising antibodies could be a potential therapeutic option for patients with immunodeficiency (hypogammaglobulinemia) secondary to rituximab who develop severe COVID-19, whereas rituximab therapy may compromise anti-viral immunity, including anti-SARS-CoV-2 antibodies. [A: what are the implications of sera trials with regards to rituximab? Your point isn’t entirely clear to me here].

COVID-19-associated thromboses, severe lung pathology, and hyperinflammation contribute to poor outcomes. These manifestations bear some similarities to those observed in rheumatic disease, such as antiphospholipid syndrome\(^3\), rheumatic-associated lung disease\(^4\) and macrophage activation syndrome\(^5\) secondary to SLE, respectively: diseases for which B-cell depletion with rituximab has been effective [A: correct as edited?]. Antiphospholipid antibodies have been reported in COVID-19 patients with thromboses, although it is unclear whether these [A: antibodies?] antibodies are pathogenic in this context\(^3\) and lung CT features in some patients with COVID-19 resemble those of fibrotic organising pneumonia e.g. anti-MDA5 anti-synthetase syndrome\(^6\) [A: is rituximab used in these contexts? Link]
It is plausible that anti-SARS-CoV-2 antibodies and/or immune complexes may potentially evoke monocyte or alveolar macrophage activation contributing to sustained secretion of proinflammatory cytokines and the development of pulmonary disease. Therefore, could adaptive immunity contribute to poor outcomes in COVID-19, signalling a role for rituximab? Immunomodulation might improve outcomes in patients with COVID-19-associated hyperinflammation. Although rituximab appears effective in targeting hyperinflammation in Epstein-Barr (EBV)-associated haemophagocytic lymphohistiocytosis, by reducing the viral (EBV) driver, but unlike EBV, SARS-CoV-2 is not known to reside in B-cells. Therefore, B-cell depletion is not appropriate for COVID-19-associated hyperinflammation. However, rituximab may be useful in specific scenarios in COVID-19 to target chronic adaptive host immune responses, e.g. when thrombotic or inflammatory lung complications persist beyond the acute infection, when viral loads are negative or low and anti-SARS-CoV-2 antibodies are positive.

In the context of COVID-19, we call for dedicated research regarding B-cell depletion to better understand the impact and timing of rituximab on patient outcomes and to explore the potential therapeutic utility in the management of specific complications of COVID-19, to facilitate the judicious use of rituximab in the pandemic.

References

**Author contribution:**

PM and VR drafted the manuscript. All authors contributed to discussions, revised and approved the manuscript.

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