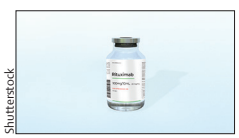
Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Rituximab during the COVID-19 pandemic: time to discuss treatment options with patients



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Published Online
December 23, 2021
https://doi.org/10.1016/
S2665-9913(21)00418-5

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Accumulating data suggest that treatment with anti-CD20 therapy, such as rituximab and ocrelizumab, puts patients at considerably increased risk of developing severe outcomes from COVID-19 (risk ratios ranging from 1·7 to 5·5 have been reported).[1,2] This reported risk emphasises how important it is that these patients develop protective immunity via COVID-19 vaccinations, but, unfortunately, studies have shown that humoral immune responses after COVID-19 vaccination are poor in patients with rheumatic diseases or multiple sclerosis who are taking anti-CD20 agents, even after two doses.[3,4] T-cell immunity after COVID-19 vaccination might be relatively unaffected by rituximab, but results from studies have varied,[5,6] and whether cellular immunity in the absence of humoral immunity provides sufficient protection against severe COVID-19 remains uncertain. Results of a 2021 case series of fully vaccinated patients with rheumatic diseases who became infected with breakthrough SARS-CoV-2 suggest that treatment with rituximab still increases the risk of a worse COVID-19 outcome.[7] Therefore, it is highly relevant to investigate the effects of a third COVID-19 vaccine dose in patients receiving rituximab and critically discuss the place of rituximab in treatment strategies for patients with rheumatic diseases.

In *The Lancet Rheumatology*, Ingrid Jyssum and colleagues[8] evaluated the development of humoral and cellular immunity against SARS-CoV-2 after two and three COVID-19 vaccine doses in 87 patients with rheumatoid arthritis and 1114 healthy controls. All patients were treated with rituximab, and concomitant treatment with conventional synthetic disease-modifying antirheumatic drugs was paused 1 week before until 2 weeks after each vaccination. Classification of antibody respose (no response, weak response, and response) was based on immunoglobulin G antibody levels found in healthy controls. Only patients with a weak or absent antibody response after two vaccine doses received a third dose (n=49); healthy controls did not receive a third dose. Cellular analyses to evaluate $CD4^+$ and $CD8^+$ T-cell responses were done in a subset of randomly chosen participants (19 patients and 20 healthy controls after the second vaccine dose, and 12 patients after the third vaccine dose). In line with previous studies,[3,4] Jyssum and colleagues[8] observed that the majority of rituximab-treated patients (54 [62·1%] of 87) had no serological response after two vaccine doses, compared with four (0·4%) of 1114 controls. A third dose only marginally improved seroconversion rates; 29 (59·2%) of 49 patients had no response and 12 (24·5%) had a weak antibody response. By contrast, T-cell responses after two vaccine doses were similar for patients and controls, and a third vaccine dose slightly increased SARS-CoV-2-specific $CD4^+$ and $CD8^+$ T-cell counts.

Altogether, Jyssum and colleagues[8] showed that the effects of a third dose of COVID-19 vaccine on humoral and cellular immunity in patients with rheumatoid arthritis receiving rituximab are marginal and therefore unlikely to considerably improve humoral protection against severe COVID-19. Hence, now that the negative impact of rituximab on COVID-19 severity, even after vaccination, is becoming increasingly clear,[1,2] the data from Jyssum and colleagues further emphasise that physicians should be cautious when prescribing rituximab during the ongoing COVID-19 pandemic. Physicians always need to carefully weigh the benefits against the risks before prescribing immunosuppressive treatment, and normally this balance is in favour of benefit due to low absolute risk of becoming infected with a dangerous pathogen. During the COVID-19 pandemic, however, people are constantly at a substantial risk of becoming infected with SARS-CoV-2, which means that the risks of rituximab treatment become considerably more important. Because of this altered risk–benefit evaluation, it could be argued that physicians should discuss the necessity of rituximab with their patients, and, when possible, prescribe other treatments. Shared decision making will be of utmost importance in this process. Choosing alternative therapies while maintaining adequate rheumatic disease control is more challenging for diseases with less effective alternative treatment options to rituximab (eg, anti-neutrophil cytoplasmic antibody-associated vasculitis) than for diseases for which several alternatives with comparable effectiveness are available (eg, rheumatoid arthritis). Decisions to continue or discontinue rituximab treatment should

therefore always be made individually and in consultation with the patients themselves, who should be made aware of the additional risks that rituximab treatment poses during the current COVID-19 pandemic.

In addition to implications for treatment strategies regarding rituximab itself, the data from Jyssum and colleagues also have important implications for therapeutic strategies when patients receiving rituximab become infected with SARS-CoV-2. Data from the RECOVERY trial[9] show that therapeutic monoclonal SARS-CoV-2 antibody infusions significantly reduced mortality in patients with severe COVID-19 who had no detectable SARS-CoV-2 antibodies before infection. As the majority of patients treated with rituximab do not develop detectable SARS-CoV-2 antibodies after vaccination,[3,4] even after receiving a third vaccine dose,[8] monoclonal antibody infusions could be an important therapeutic component for these patients. Moreover, because the risks of COVID-19 in patients receiving rituximab are substantial,[1,2] we believe that therapeutic monoclonal antibody infusions should be considered for all these patients shortly after diagnosis of COVID-19 and before the development of severe disease manifestations. However, the neutralising efficacy of monoclonal antibody infusions, and thus subsequently the clinical efficacy, might decrease with the rise of new SARS-CoV-2 variants such as the omicron variant (B.1.1.529).[10]

In conclusion, the current literature suggests that treatment with rituximab during the ongoing COVID-19 pandemic puts patients at an increased risk of COVID-19-related hospitalisation and death, even after vaccination. Because the results from Jyssum and colleagues indicate that a third COVID-19 vaccination does not substantially improve humoral protection, physicians should discuss alternative therapies with patients who receive or would start treatment with rituximab, at least for the remainder of the COVID-19 pandemic. In addition, patients receiving rituximab should be actively advised to contact a physician as soon as they test positive for COVID-19, so that early treatment with monoclonal SARS-CoV-2 antibodies and antiviral therapy can be considered.

GJW received funding from ZonMw for COVID-19 research (project number 10430022010020) outside the committed work. LB declares no competing interests.

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Wider considerations following evaluation of the STAR care pathway for patients with painful knee replacement

In *The Lancet Rheumatology*, Vikki Wylde and colleagues[1] present the results of a randomised controlled trial (RCT) investigating the clinical and cost-effectiveness of the Support and Treatment After Replacement (STAR) care pathway compared with usual care on pain severity and pain interference after total knee replacement. The first point of note for this new RCT is the research question and design—the trial is an excellent example of

Published **Online** January 27, 2022 https://doi.org/10.1016/S2665-9913(22)00003-0

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