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Current Perspective

# Could anti-CD20 therapy jeopardise the efficacy of a SARS-CoV-2 vaccine?

Roch Houot [a,b,*], Ronald Levy [c], Guillaume Cartron [d], Philippe Armand [b]

[a] *Department of Hematology, CHU Rennes, University of Rennes, INSERM U1236, Rennes, France*
[b] *Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA, USA*
[c] *Department of Medical Oncology, Stanford University School of Medicine, Stanford, CA, USA*
[d] *Department of Hematology, CHU Montpellier University Hospitality, University of Montpellier, Institut de Génétique Moléculaire de Montpellier, CNRS UMR 5535, Montpellier, France*

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**Abstract** A vaccine against SARS-CoV-2 might represent the most promising approach to halt durably the current COVID-19 pandemic. We believe that anti-CD20 therapy may jeopardise the efficacy of such a vaccine. This is regrettable because patients receiving anti-CD20 therapy (i.e. those with haematologic malignancies or autoimmune disorders) are particularly at risk of severe COVID-19 and, as such, are the most in need of a vaccine. Here, we review the reasons why anti-CD20 therapy may abrogate or diminish the efficacy of a vaccine against SARS-CoV-2 and we draw physicians' attention towards this potential risk so that it can be considered when evaluating the risk/benefit ratio of anti-CD20 therapy during the current pandemic.
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Vaccination against SARS-CoV-2 might represent the most promising approach to halt durably the current COVID-19 pandemic. Although it is still uncertain whether COVID-19 generates post-infection immunity in patients, preliminary data in animal models suggest that infection and vaccination confer immune protection [1,2]. It is generally accepted that neutralising antibodies (Nabs) play a dominant role in the protection against coronaviruses, as previously demonstrated with SARS and MERS [3,4]. The role of humoural immunity is further supported by (i) the relatively high levels of antibody responses to the surface (spike) protein that mediates entry into host cells [5] and (ii) the therapeutic efficacy of passive infusion of convalescent plasma in

* *Corresponding author*: CHU Rennes, Department of Hematology, F-35000 Rennes, France.
*E-mail address:* roch.houot@chu-rennes.fr (R. Houot).

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patients with COVID-19 [6,7]. Thus, it will be critical that future COVID-19 vaccines generate a protective humoural immune response, including Nabs.

Recent data suggest that patients with cancer, notably those with haematologic malignancies, are more susceptible to suffer severe complications from SARS-CoV-2 infection [8,9]. It is assumed that immunocompromised patients generally are also at increased risk of severe COVID-19. Thus, it will be of particular importance for these patients to benefit from an effective vaccine as soon as it becomes available. Yet some of them may also be less likely to benefit from such a vaccine, especially those treated with anti-CD20 monoclonal antibodies. These antibodies (including rituximab, obinutuzumab, ofatumumab and ocrelizumab) are widely used in patients with haematologic malignancies and autoimmune disorders, including B-cell lymphoma, chronic lymphocytic leukaemia, immune thrombocytopaenia, rheumatoid arthritis, anti-neutrophil cytoplasmic antibody-associated vasculitis, systemic sclerosis and systemic lupus erythematosus. Anti-CD20 antibodies induce rapid and prolonged B-cell depletion. The half-life of rituximab is 20.8 days, but recovery of B cell counts usually starts only 6–9 months after the completion of therapy, and normal levels are obtained after 9–12 months [10]. The prolonged period of rituximab-induced B-cell depletion might compromise the immune system, which may be the mechanism of action of anti-CD20 antibodies in antibody-mediated autoimmune diseases. Consistent with the immunosuppressive effect of anti-CD20 antibodies, rituximab has been associated with a risk of reactivation of latent viruses, especially hepatitis B virus infection and progressive multifocal leukoencephalopathy caused by reactivation of latent JC virus. Anti-CD20 treatments also result in impaired secondary humoural immune responsiveness to vaccination. Indeed, B cells are required for the development of humoural immune responses to neoantigens, and depletion of B cells following rituximab seems to reduce humoural immune responses to neoantigens, of which COVIDS-19 is one. Several studies showed a blunted vaccine response after vaccination in patients with lymphoma [11–14] or autoimmune disorders [15–18] treated with rituximab. Both T cell–dependent and independent responses have been shown to be significantly impaired for at least 6 months after rituximab treatment [18]. Thus, anti-CD20 therapy may dramatically and durably impair the humoural response to vaccination. For these reasons, most guidelines recommend to wait for at least 6 months after rituximab infusion to perform vaccination.

Given the above considerations, and acknowledging that this remains purely theoretical at this point, there is a significant plausible risk that anti-CD20 therapies may abrogate or diminish the future efficacy of a vaccine against SARS-CoV-2. Unfortunately, the patients receiving anti-CD20 therapies are also those who are the most in need of a protective immunity against COVID-19. Therefore, although life-saving anticancer treatments should be maintained [19], we suggest that physicians carefully weigh the risk/benefit ratio of anti-CD20 therapy in patients currently considering or receiving such treatment, especially patients in whom anti-CD20 therapy is not expected to improve overall survival (for example, maintenance therapy for follicular lymphoma). If a timeframe of 6 months is necessary after the last infusion of anti-CD20 before effective vaccination, and if a vaccine is expected to become available early 2021, it will soon be time to consider discontinuing anti-CD20 therapy for patients who may tolerate this interruption. This is particularly true if anti-CD20 therapy is not urgent, potentially dispensable or replaceable with alternative therapies, or if the clinical benefit does not outweigh the risk of COVID-19 infection in these high-risk patients. Further insights regarding this potential risk may come from studies evaluating the rate of seroconversion in patients who experienced COVID-19 after receiving anti-CD20 therapy.

## Author contribution

All authors wrote and reviewed the manuscript.

## Conflict of interest statement

R.H. reports receiving honoraria from Bristol-Myers Squibb, MSD, Gilead, Kite, Roche, Novartis, Janssen, and Celgene. R.L. reports receiving honoraria from Apexigen, Beigene, Forty-Seven, Teneobio, Sutro, Checkmate, Nurix, Dragonfly, Quadriga, GigaGen, Abpro, Spolight, Xcella, Immunoscore, and Walking Fish. G.C. reports receiving honoraria from Roche, Celgene, Abbvie, Sanofi, Gilead, and Janssen. P.A. reports receiving honoraria from Merck, BMS, Pfizer, Affimed, Adaptive, Infinity, ADC Therapeutics, Celgene, Morphosys, Daiichi Sankyo, Miltenyi, Tessa, GenMab, C4, Enterome; has received research funding from Genentech, Merck, BMS, Affimed, Adaptive, Roche, Tensha, and IGM.

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