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### ► To cite this version:

Roch Houot, Ronald Levy, Guillaume Cartron, Philippe Armand. Could anti-CD20 therapy jeopardise the efficacy of a SARS-CoV-2 vaccine?. *European Journal of Cancer*, 2020, 136, pp.4-6. 10.1016/j.ejca.2020.06.017 . hal-02929021

**HAL Id: hal-02929021**

**<https://hal.science/hal-02929021>**

Submitted on 22 Aug 2022

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

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**Running title:** SARS-CoV-2 vaccine and anti-CD20 therapy

**Text word count:** 675

**Figures:** 0

**Tables:** 0

**References:** 19

**Key words:** COVID-19, SARS-CoV-2, vaccine, anti-CD20 antibody, rituximab

## **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 jeopardize the efficacy of such a vaccine. This is regrettable because patients receiving anti-CD20 therapy (*i.e.* those with hematologic 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.

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 neutralizing antibodies (Nabs) play a dominant role in the protection against coronaviruses, as previously demonstrated with SARS and MERS.[3,4] The role of humoral 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 patients with COVID-19.[6,7] Thus, it will be critical that future COVID-19 vaccines generate a protective humoral immune response, including Nabs.

Recent data suggest that patients with cancer, notably those with hematologic 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 hematologic malignancies and autoimmune disorders, including B-cell lymphoma, chronic lymphocytic leukemia, immune thrombocytopenia, rheumatoid arthritis, antineutrophil 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 to 9 months after the completion of therapy, and normal levels are obtained after 9 to 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 humoral immune responsiveness to vaccination. Indeed, B cells are required for the development of humoral immune responses to neoantigens, and depletion of B cells following rituximab seems to reduce humoral 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 humoral 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 disclosure**

RH received honoraria from Bristol-Myers Squibb, MSD, Gilead, Kite, Roche, Novartis, Janssen, and Celgene. RL received honoraria from Apexigen, Beigene, Forty-Seven, Tenebio, Sutro, Checkmate, Nurix, Dragonfly, Quadriga, GigaGen, Abpro, Spotlight, Xcella, Immunoscore, and Walking Fish. GC received honoraria from Roche, Celgene, Abbvie, Sanofi, Gilead, and Janssen. PA received honoraria from Merck, BMS, Pfizer, Affimed, Adaptive, Infinity, ADC Therapeutics, Celgene, Morphosys, Daiichi Sankyo, Miltenyi, Tessa, GenMab, C4, Enterome; and research funding from Genentech, Merck, BMS, Affimed, Adaptive, Roche, Tensha, and IGM.

## References

- [1] Chandrashekar A, Liu J, Martinot AJ, McMahan K, Mercado NB, Peter L, et al. SARS-CoV-2 infection protects against rechallenge in rhesus macaques. *Science* (80- ) 2020. <https://doi.org/10.1126/SCIENCE.ABC4776>.
- [2] Yu J, Tostanoski LH, Peter L, Mercado NB, McMahan K, Mahrokhian SH, et al. DNA vaccine protection against SARS-CoV-2 in rhesus macaques. *Science* (80- ) 2020. <https://doi.org/10.1126/SCIENCE.ABC6284>.
- [3] Du L, Tai W, Zhou Y, Jiang S. Vaccines for the prevention against the threat of MERS-CoV. *Expert Rev Vaccines* 2016;15:1123–34. <https://doi.org/10.1586/14760584.2016.1167603>.
- [4] Padron-Regalado E. Vaccines for SARS-CoV-2: Lessons from Other Coronavirus Strains. *Infect Dis Ther* 2020. <https://doi.org/10.1007/s40121-020-00300-x>.
- [5] Corey BL, Mascola JR, Fauci AS, Collins FS. A strategic approach to COVID-19 vaccine R&D. *Science* 2020;5312. <https://doi.org/10.1126/science.abc5312>.
- [6] Li L, Zhang W, Hu Y, Tong X, Zheng S, Yang J, et al. Effect of Convalescent Plasma Therapy on Time to Clinical Improvement in Patients With Severe and Life-threatening COVID-19. *JAMA* 2020. <https://doi.org/10.1001/jama.2020.10044>.
- [7] Shen C, Wang Z, Zhao F, Yang Y, Li J, Yuan J, et al. Treatment of 5 Critically Ill Patients With COVID-19 With Convalescent Plasma. *JAMA* 2020;323:1582. <https://doi.org/10.1001/jama.2020.4783>.
- [8] Williamson E, Walker AJ, Bhaskaran KJ, Bacon S, Bates C, Morton CE, et al. OpenSAFELY: factors associated with COVID-19-related hospital death in the linked electronic health records of 17 million adult NHS patients. *MedRxiv* 2020:2020.05.06.20092999. <https://doi.org/10.1101/2020.05.06.20092999>.
- [9] Mehta V, Goel S, Kabarriti R, Cole D, Goldfinger M, Acuna-Villaorduna A, et al. Case Fatality Rate of Cancer Patients with COVID-19 in a New York Hospital System. *Cancer Discov* 2020. <https://doi.org/10.1158/2159-8290.CD-20-0516>.
- [10] McLaughlin P, Grillo-López AJ, Link BK, Levy R, Czuczman MS, Williams ME, et al. Rituximab chimeric anti-CD20 monoclonal antibody therapy for relapsed indolent lymphoma: half of patients respond to a four-dose treatment program. <https://doi.org/10.1200/JCO.1998.16.8.2825>.
- [11] Yri OE, Torfoss D, Hungnes O, Tierens A, Waalen K, Nordøy T, et al. Rituximab blocks protective serologic response to influenza A (H1N1) 2009 vaccination in lymphoma patients during or within 6 months after treatment. *Blood* 2011;118:6769–71. <https://doi.org/10.1182/blood-2011-08-372649>.
- [12] Bedognetti D, Zoppoli G, Massucco C, Zanardi E, Zupo S, Bruzzone A, et al. Impaired Response to Influenza Vaccine Associated with Persistent Memory B Cell Depletion in Non-Hodgkin's Lymphoma Patients Treated with Rituximab-Containing Regimens. *J Immunol* 2011;186:6044–55. <https://doi.org/10.4049/jimmunol.1004095>.
- [13] Takata T, Suzumiya J, Ishikawa T, Takamatsu Y, Ikematsu H, Tamura K. Attenuated antibody reaction for the primary antigen but not for the recall antigen of influenza vaccination in patients with non-Hodgkin B-cell lymphoma after the administration of rituximab-CHOP. *J Clin Exp Hematop* 2009;49:9–13. <https://doi.org/10.3960/jslrt.49.9>.
- [14] Van Der Kolk LE, Baars JW, Prins MH, Van Oers MHJ. Rituximab treatment results in impaired secondary humoral immune responsiveness. *Blood* 2002;100:2257–9. [https://doi.org/10.1182/blood.v100.6.2257.h81802002257\\_2257\\_2259](https://doi.org/10.1182/blood.v100.6.2257.h81802002257_2257_2259).
- [15] Bingham CO, Looney RJ, Deodhar A, Halsey N, Greenwald M, Coddling C, et al. Immunization responses in rheumatoid arthritis patients treated with rituximab: Results from a controlled clinical trial. *Arthritis Rheum* 2010;62:64–74. <https://doi.org/10.1002/art.25034>.
- [16] Kim W, Kim SH, Huh SY, Kong SY, Choi YJ, Cheong HJ, et al. Reduced antibody formation after influenza vaccination in patients with neuromyelitis optica spectrum disorder treated with

- rituximab. *Eur J Neurol* 2013;20:975–80. <https://doi.org/10.1111/ene.12132>.
- [17] Eisenberg RA, Jawad AF, Boyer J, Maurer K, McDonald K, Prak EL, et al. Rituximab-Treated Patients Have a Poor Response to Influenza Vaccination\*. *J Clin Immunol* 2013;33:388. <https://doi.org/10.1007/S10875-012-9813-X>.
- [18] Nazi I, Kelton JG, Larché M, Snider DP, Heddle NM, Crowther MA, et al. The effect of rituximab on vaccine responses in patients with immune thrombocytopenia. *Blood* 2013;122:1946–53. <https://doi.org/10.1182/blood-2013-04-494096>.
- [19] Omarini C, Maur M, Luppi G, Narni F, Luppi M, Dominici M, et al. Cancer treatment during the coronavirus disease 2019 pandemic: Do not postpone, do it! *Eur J Cancer* 2020;133:29–32. <https://doi.org/10.1016/j.ejca.2020.04.034>.