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COMMENTARY

Can B cell-deficient patients rely on COVID-19 vaccine-induced T-cell immunity?

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Summary

Anti-CD20 antibody treatments prevent humoral responses to vaccines against severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) vaccines, but the nature of T-cell responses in this setting is less well understood. Riise et al. assess vaccine-induced epitope-specific CD8 T cell responses in patients with lymphoma recently treated with rituximab and find a wide range of responses, with the most recently treated patients frequently failing to respond, while others exhibit responses stronger than healthy controls. They suggest these epitopes among others could be used in a T cell-targeted vaccine, and such strategies are indeed in clinical trials now.

Commentary on: Riise J, et al. Rituximab-treated patients with lymphoma develop strong CD8 T-cell responses following COVID-19 vaccination. Br J Haematol. 2022;197:697-708

KEYWORDS
B cell-deficient patients, coronavirus disease 2019 (COVID-19), T-cell immunity

During the coronavirus disease 2019 (COVID-19) pandemic, those with compromised immune systems have suffered from a higher risk of severe infection and a lower response to vaccines. Anti-CD20 antibodies, commonly used for B cell malignancies, autoimmune conditions, and post-transplant immune suppression, are particularly strong inhibitors of de novo vaccine responses. Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) vaccine seroconversion rates are around 10% or less in individuals vaccinated within 6 months of receiving an anti-CD20 antibody.[1–3] Poor vaccine responses in anti-CD20-treated patients likely contribute to the greater incidence of COVID-19 infection, hospitalisation, and death in vaccinated patients with haematological malignancies compared to vaccinated healthy individuals.[4,5]

Whether the current vaccines efficiently induce T cell responses in B cell-deficient patients and whether such responses can provide meaningful protection against infection has been an open question. Emerging evidence is encouraging and suggests that a substantial proportion of patients without antibody responses to SARS-CoV-2 vaccines develop T cell responses. There is conflicting data on whether these responses are blunted,[6–9] equivalent,[10,11] or enhanced[12–14] compared to healthy controls. Blunted immune responses may arise from broader immune dysfunction induced by the underlying disease or by treatments, while enhanced T cell responses may arise from a depletion of regulatory B cells or from increased antigen availability due to lack of antibody-mediated clearance.

In their paper Riise et al.[15] further our understanding of T cell responses in B cell-deficient patients. They studied patients with B cell lymphoma who had received two doses of COVID-19 vaccination and all of whom had received rituximab within the past 8 months. The dismal seroconversion rates previously reported in this population were again confirmed, with only 6% of 110 patients developing anti-spike receptor-binding domain antibodies 3–6 weeks after their second vaccine dose. They then evaluated CD8 T cell responses in 29 patients with B-cell lymphoma and 16 controls. T cell vaccine responses are commonly evaluated by ex vivo stimulation of peripheral T cells with spike protein peptide pools to identify SARS-CoV-2-specific T cells by cytokine production

or upregulation of cell surface activation markers. Riise et al.[15] applied a different approach. They evaluated vaccine-induced CD8 T cell responses to defined immunogenic spike epitopes identified in convalescent patients[16] and quantified responding cells using fluorescently tagged peptide-bound HLA multimers. This bypassed the need for peptide antigen presentation by autologous cells present in the patients' blood, which may be deficient in number or quality, and directly evaluated whether a T cell response had been generated, although did not provide evidence of T-cell functionality.

They observed that epitope-specific CD8 T cell responses in this B cell-deficient cohort were equivalent to controls, even after adjustment for HLA distribution. Although further conclusions are limited by the small sample size, it is interesting to note that individuals with the lowest and highest T cell responses were both present within the B cell-deficient cohort. T cell responses were more often absent in patients on active treatment, while the strongest T cell responses were also seen in patients rather than controls. Strong T cell responses were concentrated among patients who had completed treatment with rituximab and chemotherapy. Thus, determinants of vaccine-induced T cell responses in B cell-deficient individuals are likely complex and may depend on time elapsed since treatment, the specific treatments received, and the nature of the underlying disease, among other factors.

The finding that many patients with B cell deficiency can develop vaccine-induced T cell responses provides a rationale for developing T cell-focused vaccine strategies, e.g., by including prevalent immunogenic T cell peptides from spike and non-spike viral proteins in a messenger RNA vaccine. As T cells recognise intracellular peptides presented on major histocompatibility complex (MHC) molecules after a cell has been infected by virus, there is not a direct mechanistic basis for preventing infection by cellular immunity alone. However, it may be possible for T cells to clear virus-infected cells before a clinical infection is established, and it is very likely that a robust T cell memory response would lead to a milder course of COVID-19 upon infection. Indeed, although T cells may contribute little in the setting of high titre neutralising antibodies,[17] in at least two animal models where T cell-targeted vaccines against coronaviruses were employed, protection from infection challenge was seen in the absence of neutralising antibodies.[18,19]

T cell-directed SARS-CoV-2 vaccines are already in clinical trials (NCT05113862, NCT04776317, NCT04885361, NCT05069623), including in B cell-depleted patients (NCT04954469), with preliminary evidence of induced responses.[20] Interestingly, several of these include only T cell epitopes without the ability to induce neutralising antibodies, and thus would likely function best as boosters, even in B cell-deficient patients, some of whom may still generate antibody responses. The observation that T cell epitopes may suffer less from mutational escape by variants[21–23] is a potential benefit of vaccines targeting T cells, and Riise et al.[15] demonstrate this to be true for the epitopes they studied. In designing vaccines with T cell epitopes, it will be crucial to incorporate peptides covering HLA types prevalent in as much of the global population as possible, either in one pool or in specific pools for specific populations.

Ultimately, relying on a vaccine-induced T-cell response for protection against COVID-19 may or may not prove to be sufficient. We should note that while CD20-targeted agents have proven to be an Achilles heel for vaccine-induced de novo B cell responses, other agents may preferentially impair T cell responses, as has been suggested for sphingosine-1-phosphate (S1P) receptor modulators,[8,24] bendamustine,[25] and corticosteroids.[26] Optimal immune responses against SARS-CoV-2 are generated by successful B- and T cell co-operation.[17] Thus, ensuring the best possible protection for immunosuppressed patients requires working on all fronts: maximising B cell responses by decreasing exposure to B cell-depleting therapies and vaccinating prior to treatment whenever possible,[3,27] as well as specifically targeting T cell responses if this proves beneficial. But this also includes continuing appropriate personal and public health measures to reduce virus spread. The best way for us to protect vulnerable populations is still to ensure low community prevalence of the virus.

REFERENCES

1. Perry C, Luttwak E, Balaban R, Shefer G, Morales MM, Aharon A, et al. Efficacy of the BNT162b2 mRNA COVID-19 vaccine in patients with B-cell non-Hodgkin lymphoma. Blood Adv. 2021;5:3053–61.
2. Gurion R, Rozovski U, Itchaki G, Gafter-Gvili A, Leibovitch C, Raanani P, et al. Humoral serologic response to the BNT162b2 vaccine is abrogated in lymphoma patients within the first 12 months following treatment with anti-CD2O antibodies. Haematologica. 2022;107:715–20. https://doi.org/10.3324/haematol.2021.279216
3. Shree T, Shankar V, Lohmeyer JJK, Czerwinski DK, Schroers-Martin JG, Rodriguez GM, et al. CD20-targeted therapy ablates De novo antibody response to vaccination but spares Preestablished immunity. Blood Cancer Discov. 2022;3:95–102. https://doi.org/10.1158/2643-3230.BCD-21-0222
4. Mittelman M, Magen O, Barda N, Dagan N, Oster HS, Leader A, et al. Effectiveness of the BNT162b2mRNA Covid-19 vaccine in patients with hematological neoplasms in a Nationwide mass vaccination setting. Blood. 2021;139:1439–51. https://doi.org/10.1182/blood.2021013768
5. Pagano L, Salmanton-García J, Marchesi F, Busca A, Corradini P, Hoenigl M, et al. COVID-19 infection in adult patients with hematological malignancies: a European Hematology Association survey (EPICOVIDEHA). J Hematol Oncol. 2021;14:1–15.
6. Moor MB, Suter-Riniker F, Horn MP, Aeberli D, Amsler J, Möller B, et al. Humoral and cellular responses to mRNA vaccines against SARS-CoV-2 in patients with a history of CD20 B-cell-depleting therapy (RituxiVac): an investigator-initiated, single-Centre, open-label study. Lancet Rheumatol. 2021;3:e789–97.
7. Liebers N, Speer C, Benning L, Bruch PM, Kraemer I, Meissner J, et al. Humoral and cellular responses after COVID-19 vaccination in anti-CD20-treated lymphoma patients. Blood. 2022;139:142–7.
8. Tortorella C, Aiello A, Gasperini C, Agrati C, Castilletti C, Ruggieri S, et al. Humoral- and T-cell–specific immune responses to SARS-CoV-2 mRNA vaccination in patients with MS using different disease-modifying therapies. Neurology. 2022;98:e541–54.
9. Marasco V, Carniti C, Guidetti A, Farina L, Magni M, Miceli R, et al. T-cell immune response after mRNA SARS-CoV-2 vaccines is frequently detected also in the absence of seroconversion in patients with lymphoid malignancies. Br J Haematol. 2022;196:548–58.
10. Marty PK, van Keulen VP, Erskine CL, Shah M, Hummel A, Stachowitz M, et al. Antigen specific Humoral and cellular immunity following SARS-CoV-2 vaccination in ANCA-associated Vasculitis patients receiving B-cell depleting therapy. Front Immunol. 2022;13:834981.

11. Candon S, Lemee V, Leveque E, Etancelin P, Paquin C, Carette M, et al. Dissociated humoral and cellular immune responses after a three-dose schema of BNT162b2 vaccine in patients receiving anti-CD20 monoclonal antibody maintenance treatment for B-cell lymphomas. Haematologica. 2022;107:755–8. https://doi.org/10.3324/haematol.2021.280139
12. Apostolidis SA, Kakara M, Painter MM, Goel RR, Mathew D, Lenzi K, et al. Cellular and humoral immune responses following SARS-CoV-2 mRNA vaccination in patients with multiple sclerosis on anti-CD20 therapy. Nat Med. 2021;1–12:1990–2001. https://doi.org/10.1038/s41591-021-01507-2
13. Gadani SP, Reyes-Mantilla M, Jank L, Harris S, Douglas M, Smith MD, et al. Discordant humoral and T cell immune responses to SARS-CoV-2 vaccination in people with multiple sclerosis on anti-CD20 therapy. EBioMedicine. 2021;73:103636.
14. Madelon N, Lauper K, Breville G, Sabater Royo I, Goldstein R, Andrey DO, et al. Patients treated with anti-CD20 therapy can mount robust T cell responses to mRNA-based COVID-19 vaccines. medRxiv 2021.07.21.21260928. 2021; ciab954. https://doi.org/10.1101/2021.07.21.21260928
15. Riise J, Meyer S, Blaas I, Chopra A, Tran TT, Delic-Sarac M, et al. Rituximab-treated patients with lymphoma develop strong CD8 T-cell responses following COVID-19 vaccination. Br J Haematol. 2022;197:697–708.
16. Meyer, S, Blaas I, Bollineni RC, Delic-Sarac M, Tran TT, Knetter C, et al. *Beyond Spike: Identification of nine highly prevalent SARS-CoV-2-specific CD8 T-cell epitopes in a large Norwegian cohort*. http://biorxiv.org/lookup/doi/10.1101/2021.10.13.463911 (2021) https://doi.org/10.1101/2021.10.13.463911.
17. Israelow B, Mao T, Klein J, Song E, Menasche B, Omer SB, et al. Adaptive immune determinants of viral clearance and protection in mouse models of SARS-CoV-2. Science Immunology. 2021;6:eabl4509. https://doi.org/10.1126/sciimmunol.abl4509
18. Matchett WE, Joag V, Stolley JM, Shepherd FK, Quarnstrom CF, Mickelson CK, et al. Cutting edge: Nucleocapsid vaccine elicits spike-independent SARS-CoV-2 protective immunity. J Immunol. 2021;207:376–9.
19. Zhao J, Zhao J, Mangalam AK, Channappanavar R, Fett C, Meyerholz DK, et al. Airway memory CD4+ T cells mediate protective immunity against emerging respiratory coronaviruses. Immunity. 2016;44:1379–91.
20. Heitmann JS, Bilich T, Tandler C, Nelde A, Maringer Y, Marconato M, et al. A COVID-19 peptide vaccine for the induction of SARS-CoV-2 T cell immunity. Nature. 2022;601:617–22.
21. Geers D, Shamier MC, Bogers S, den Hartog G, Gommers L, Nieuwkoop NN, et al. SARS-CoV-2 variants of concern partially escape humoral but not T cell responses in COVID-19 convalescent donors and vaccine recipients. Sci Immunol. 2021;6:eabj1750.
22. Madelon N, Heikkilä N, Sabater Royo I, Fontannaz P, Breville G, Lauper K, et al. Omicron-specific cytotoxic T-cell responses after a third dose of mRNA COVID-19 vaccine among patients with multiple sclerosis treated with Ocrelizumab. JAMA Neurol. 2022;79:399–404. https://doi.org/10.1001/jamaneurol.2022.0245
23. Tarke A, Coelho CH, Zhang Z, Dan JM, Yu ED, Methot N, et al. SARS-CoV-2 vaccination induces immunological T cell memory able to cross-recognize variants from alpha to omicron. Cell. 2022;185:847–859.e11.
24. Achiron A, Mandel M, Dreyer-Alster S, Harari G, Magalashvili D, Sonis P, et al. Humoral immune response to COVID-19 mRNA vaccine in patients with multiple sclerosis treated with high-efficacy disease-modifying therapies. Ther Adv Neurol Disord. 2021;14:17562864211012836.
25. Lim SH, Stuart B, Joseph-Pietras D, Johnson M, Campbell N, Kelly A, et al. Immune responses against SARS-CoV-2 variants after two and three doses of vaccine in B-cell malignancies: UKPROSECO study. Nat Can. 2022;1–13. https://doi.org/10.1038/s43018-022-00364-3
26. Ehmsen S, Asmussen A, Jeppesen SS, Nilsson AC, Østerlev S, Vestergaard H, et al. Antibody and T cell immune responses following mRNA COVID-19 vaccination in patients with cancer. Cancer Cell. 2021;39:1034–6.
27. Moser T, Otto F, O'Sullivan C, Hitzl W, Pilz G, Harrer A, et al. Recall response to COVID-19 antigen is preserved in people with multiple sclerosis on anti-CD20 medications – a pilot study. Mult Scler Relat Disord. 2022;59:103560.

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