# When timing is more important than quantity in COVID-19 vaccination

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In this issue of *Haematologica*, Kohn *et al.* report the results of a prospective, single-center, non-randomized study,[1] shedding more light on the efficacy of vaccination against coronavirus disease 2019 (COVID-19) in patients with non-Hodgkin lymphoma (NHL) or chronic lymphocytic leukemia (CLL) who have received prior treatment with anti-CD20 antibody-containing therapies and/or have low levels of serum immunoglobulins. Patients with hematologic malignancies may suffer from impairments of primary immunity due to biological features of the disease but also from secondary immunodeficiencies related to therapies. These patients are at higher risk of severe infections, which may result in a worse survival.[2] One of the best examples is CLL, in which infections are a main contributor to morbidity and mortality driven by an impaired immune system. Moreover, treatment initiation is likely to induce a more profound immune dysfunction that further increases the risk of severe infections.[3] With regard to infection by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), patients with NHL or CLL are at higher risk of developing severe and/or prolonged forms of COVID-19.[4,5] In the EPICOVIDEHA study, one of the largest registries of COVID-19 in patients with hematologic diseases published so far, patients with NHL and CLL showed a mortality rate of 31.8% and 28.3%, respectively.[6]

It is known that the seroconversion rate after SARS-CoV-2 infection is low in these groups of patients after recent treatment with anti-CD20 monoclonal antibodies. The same poor serological response has been shown after two doses of mRNA SARS-CoV-2 vaccination, with a rate of 5% in patients with CLL recently treated with anti-CD20 antibodies[7] and 3% in NHL patients vaccinated within 45 days after administration of the last dose of monoclonal antibody, although the rate reached up to 80% in patients vaccinated more than 1 year after this therapy.[8] One burning question is whether a third dose of mRNA SARS-CoV-2 vaccine may enhance the serological response in this group of poor responders.

The study by Kohn *et al.* analyses the outcome of 100 patients with NHL or CLL who received a third dose of mRNA SARS-CoV-2 vaccine at the discretion of each physician in a non-randomized study. Serology was performed at least 2 weeks after the last vaccination, with a median interval between serology and the last vaccine injection of 47 days. Half of the patients did not show a serological response to vaccination. Patients who did not have a serological response had significantly lower lymphocyte counts, B-cell counts and IgG levels than those patients with a demonstrated serological response. These factors may, therefore, be considered for further vaccination strategies in these groups of patients. Patients who had received any treatment within the year before their first vaccine injection were at higher risk than other patients of not developing a serological response, with anti-CD20 therapy being strongly associated with the risk of absence of a serological response. Among the patients in whom the last anti-CD20 administration was within 1 year prior to their first vaccine injection, 74% did not seroconvert despite 16 out of 25 patients having received a third dose. In this study, Kohn *et al.* did not find an association between the number of vaccine injections and seroconversion rate, with an absence of serological response in 58.3% and 46.9% of patients who received three or two doses, respectively. Regardless of the number of vaccine administrations, patients who did not receive anti-CD20 antibodies within 1 year prior to their first vaccine injection had higher levels of anti-spike IgG levels. These findings are supported by those of another study which included patients with CLL given a third dose of mRNA SARS-CoV-2 vaccine and showed a moderate increase in SARS-CoV-2 anti-spike IgG levels after the third dose in patients treated for CLL, although the increase in IgG levels had a limited impact on the prevalence of anti-spike IgG ≥30 BAU/mL in patients treated for CLL, which rose from 5% after two doses to 45% after receiving the third dose.[9] Administration of a third dose of mRNA SARS-CoV-2 vaccine seems not to overcome the poor serological response observed in patients who had anti-CD20 treatment within 1 year prior to their first vaccine injection or low IgG levels.

## Disclosures

*No conflicts of interest to disclose.*

# References


1. Kohn M, Delord M, Chbat M, et al. A third anti-SARS-CoV-2 mRNA dose does not overcome the pejorative impact of anti-CD20 therapy and/or low immunoglobulin levels in patients with lymphoma or chronic lymphocytic leukemia Haematologica. 2022;107(6):1454-1459.
2. Jolles S, Smith BD, Vinh DC, et al. Risk factors for severe infections in secondary immunodeficiency: a retrospective US administrative claims study in patients with hematological malignancies. Leuk Lymphoma. 2022;63(1):64-73.
3. Langerbeins P, Eichhorst B. Immune dysfunction in patients with chronic lymphocytic leukemia and challenges during COVID-19 pandemic. Acta Haematol. 2021;144(5):508-518.
4. Duléry R, Lamure S, Delord M, et al. Prolonged in-hospital stay and higher mortality after Covid-19 among patients with non-Hodgkin lymphoma treated with B-cell depleting immunotherapy. Am J Hematol. 2021;96(8):934-944.
5. Mato AR, Roeker LE, Lamanna N, et al. Outcomes of COVID-19 in patients with CLL: a multicenter international experience. Blood. 2020;136(10):1134-1143.
6. Pagano L, Salmanton-García J, Marchesi F, et al. COVID-19 infection in adult patients with hematological malignancies: a European Hematology Association Survey (EPICOVIDEHA). J Hematol Oncol. 2021;14(1):168.
7. Benjamini O, Rokach L, Itchaki G, et al. Safety and efficacy of the BNT162b mRNA COVID-19 vaccine in patients with chronic lymphocytic leukemia. Haematologica. 2022;107(3):625-634
8. Gurion R, Rozovski U, Itchaki G, et al. Humoral serologic response to the BNT162b2 vaccine is abrogated in lymphoma patients within the first 12 months following treatment with anti-CD20 antibodies. Haematologica. 2022;107(3):715-720.
9. Marlet J, Gatault P, Maakaroun Z, et al. Antibody responses after a third dose of COVID-19 vaccine in kidney transplant recipients and patients treated for chronic lymphocytic leukemia. Vaccines (Basel). 2021;9(10):1055.