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Letter

COVID-19 vaccines elicit robust cellular immunity and clinical protection in chronic lymphocytic leukemia

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B cell chronic lymphocytic leukemia (CLL) is the most common subtype of adult leukemia and is associated with profound secondary immunodeficiency. SARS-CoV-2 infection has been a significant cause of morbidity and mortality (Mato et al., 2020; Pagano et al., 2021), and immunological responses against SARS-CoV-2 vaccines are impaired (Fendler et al., 2021) in patients with CLL. In particular, reduced rates of seroconversion and antibody titer have been reported (Parry et al., 2021; Greenberger et al., 2021; Herishanu et al., 2022) and associate with reduced serum immunoglobulin level or use of medication such as Bruton tyrosine kinase inhibitors or anti-CD20 antibodies (Parry et al., 2021; Herishanu et al., 2022). However, questions regarding optimal immune protection remain unresolved, and these include the potential for additional vaccine doses to increase seroconversion rate, potential humoral and cellular immune protection against Omicron, and the impact of vaccine delivery on breakthrough infection rate and clinical outcome.

We determined antibody and cellular immune responses after third and fourth vaccine dose in participants in the CLL-VR study together with age-matched healthy donor controls (n = 93). Blood samples were taken from 404 patients at a median time of 20 days following the third dose. Of those patients, 161 (40%) had received the BNT162b2 vaccine (Pfizer/BioNTech) as primary series and 243 (60%) had received the ChAdOx1 vaccine (Oxford/AstraZeneca). Almost all patients (393/404) received an mRNA vaccine for their third dose (375 received BNT162b2 and 18 received mRNA-1273). Samples were also collected from 186 patients following the fourth vaccine dose (Table S1). Patients with clinical or serological evidence of prior natural SARS-CoV-2 infection were excluded from analysis.

Spike-specific antibody responses have previously been reported to develop in 66% (322/486) of patients within the CLL-VR study following the first two vaccine doses compared to 100% of controls (Parry et al., 2021). This response rate improved to 80% following the third vaccine dose (298/374) ($p < 0.0001$) (Figure S1A). Analysis of vaccine subtype received during the first two doses showed no difference in seroconversion rate following a heterologous or homologous third dose (ChAdOx1/mRNA response rate 81% [187/230] vs. BNT162b2/mRNA response rate 77% [111/144], $p = 0.28$).

However, the seroconversion rate was not increased further after a fourth vaccine (77%; 132/171), and this indicates that the proportion of patients who develop a spike-specific antibody response following COVID-19 vaccination plateaus after the third vaccine (Figure S1A). Three seronegative patients became available for study following breakthrough infections, and natural infection also failed to generate spike-specific antibodies; this indicates that patients in the seronegative subgroup are broadly refractory to seroconversion. Regardless of vaccine dose number, a low serum IgM, current BTKi therapy, or imminent planned treatment were independent predictors of poor response with an 81% ($p = 0.003$), 90% ($p = 0.021$), and 96% ($p = 0.027$) reduction in odds of response respectively after the fourth dose.

In those patients who had a positive antibody response following vaccination, titers increased by 4.5-fold after the third vaccine dose (Geometric mean [GM] 404 arbitrary units [AU]/ml [95% confidence interval (CI) 311–526] vs. 1,820 AU/ml [95% CI 1,340–2,480], $p < 0.0001$) and became comparable to values seen within healthy controls following primary series dual vaccination (GM 2,317 [95% CI 1,191–4,508] AU/ml) (Figure S1B). No difference in antibody titer was observed following heterologous or homologous vaccination (ChAdOx1/mRNA GM 2,580 [95% CI 1,150–,5780] vs BNT162b2/mRNA 1,830 [95% CI 526–6,340], $p = 0.72$).

Cellular responses were initially assessed through the use of IFNγ-QuantiFERON after the second (n = 19) and third vaccine dose (n = 70). These responses were robust and comparable with values seen in control donors after two vaccine doses (CLL for two doses, 0.25 [interquartile range (IQR) 0.08–0.46] IU/mL and for three doses, 0.15 [IQR 0.03–0.3] IU/mL vs. controls for two doses, 0.14 [IQR 0.06–0.36] IU/mL) (Figure S1C). Response was found to be markedly higher after the third dose in patients who had a heterologous vaccine course (ChAdOx1/mRNA 0.22 [IQR 0.06–0.55] IU/mL vs mRNA/mRNA 0.04 [IQR 0.02–0.25] IU/mL; $p = 0.009$).

We next assessed the quality of humoral and cellular vaccine-induced immunity against the Omicron variant that has become globally dominant since its original description in November 2021. Neutralizing antibody titers after the third vaccine dose were markedly reduced against Omicron compared to the ancestral variant, but they were equivalent in patients and controls (ancestral, CLL GM 1,780 [95% CI 969–3,280] U/ml vs controls 2,600 [95% CI 1,423–4,738] U/ml; Omicron, CLL 122 [95% CI 88–170] vs controls 215 U/ml [95% CI 99–465]) (Figure S1D). In contrast, ELISpot analysis of peptide-specific pools for ancestral and Omicron showed no difference in the magnitude of the cellular responses amongst vaccinated CLL patients, with a median 246 SFC/10^6 peripheral blood mononuclear cells (PBMCs) (IQR 85–679) against ancestral peptides compared to 238 SFC/10^6 against Omicron peptides (IQR 71–725; p = 0.33) (Figure S1E). As such, vaccine-induced cellular responses in patients with CLL may provide strong cross-protection against the Omicron variant.

Clinical data on breakthrough infection were collected from the whole cohort on February 21, 2022. At that point, 491 participants remained in the study (seven participants had withdrawn and two participants had non-COVID-related mortality). Data were obtained on 486 participants (99%), and the remaining five were confirmed to be alive. 79/486 (16%) reported a confirmed COVID-19 infection at least once since the pandemic started. A further eight donors were found to be nucleocapsid-specific antibody positive without a history of infection, and together, 18% (87/486) of participants experienced SARS-CoV-2 infection.

We next obtained information on vaccine breakthrough infection in order to assess if correlates of protection might be observed within the CLL-VR cohort. 66 of 486 patients (14%) reported a COVID-19 infection during the 14 months since the first vaccine dose was administered and, of those, three also had a reinfection. Five infections (7.6%) occurred between January and June 2021, when the Alpha variant was dominant, 22 (33%) between July and December 2021 during the Delta wave, and 39 cases (59%) in the last 3 months during Omicron transmission. The proportion of patients who required hospitalization during these three phases was 20% (1/5), 32% (7/22), and 7.7% (3/39) respectively (Figure S1F).

Somewhat unexpectedly, patients who were seropositive after the second dose showed a 79% increase in infection rate (n = 471; hazard ratio (HR) 1.79 [95% CI 1.0–3.1]; p = 0.046) during the median follow-up time of 46 (IQR 43–54) weeks. Younger age (p = 0.001) and low total serum IgM (p = 0.03) were independent predictors for breakthrough infection by multivariate analysis.

These findings reveal the utility and limitations of current COVID-19 vaccines in patients with CLL. Although three vaccine doses increase the rate of seroconversion to 80%, this represents a plateau that is not overcome by further vaccine doses or natural infection. As a result, 20% of patients continue to lack any detectable anti-spike response, and this reflects the inherent immunodeficiency created by CLL and the immunosuppressive impact of CLL-directed therapy. Indeed, hypogammaglobulinaemia and BTKi therapy were also associated with failure of seroconversion in patients following breakthrough infection. This patient group appears resistant to improvement in humoral immunity and will require alternative approaches, such as prophylactic monoclonal antibody treatment, for immune protection.

However, there were also encouraging findings. Antibody titers after three vaccine doses in those patients who did develop an antibody response were comparable with those seen in healthy donors after primary series vaccination. Furthermore, cellular immune responses were also comparable. Homologous and heterologous vaccination protocols elicited comparable humoral responses, although cellular immunity was stronger following the ChAdOx1 primary series. A similar finding has been reported in healthy elderly donors and patients with other hematologic malignancies, and this suggests that adenoviral-based vaccines may be particularly effective in generating cellular immunity in patients with immune suppression (Collier et al., 2021; Lim et al., 2022). Furthermore, we found that neutralization of Omicron was low, although values were broadly equivalent in both CLL participants and controls following a third vaccine dose, whereas cellular responses against Omicron were equivalent to those seen against the ancestral strain amongst vaccinated CLL patients.

The most important consideration in SARS-CoV-2 vaccination is clinical efficacy. Vaccine breakthrough infection occurred in 14% of patients but, encouragingly, there were no COVID-19-related deaths in the members of this cohort who were recruited at the time of the vaccination roll out. The observed increased risk of infection in seropositive patients is thought likely to reflect differences in social behavior and population mixing because this group was younger than the group that remained seronegative. Many patients have been markedly limiting social contact and this must be considered in relation to assessment of the rate of breakthrough infection and clinical protection. However, this observation emphasizes that definition of an immune correlate of protection will be challenging in patients with immune suppression, and it indicates a need for caution in predicting individual infection risk on the basis of antibody status in the clinic. Hospitalization rates were high, at 32% for the pre-Omicron variants, although they fell to 7.7% during the Omicron wave. Monoclonal antibody therapy became available in the community in December 2021, and this may have contributed to the reduced rate of hospitalization, although only 36% of those who tested positive during the same period received therapy.

In conclusion, SARS-CoV-2 vaccines are currently providing good clinical protection for patients with CLL, but approximately 20% of patients are refractory to seroconversion and are at increased risk of infection. In contrast, cellular responses after vaccination are comparable with those of healthy donors and may be critical for preventing severe disease.

SUPPLEMENTAL INFORMATION

Supplemental information can be found online at https://doi.org/10.1016/j.ccell.2022.05.001.

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DECLARATION OF INTERESTS

The authors declare no conflicts of interest.

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