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Letter

Immune response to three doses of mRNA SARS-CoV-2 vaccines in CD19-targeted chimeric antigen receptor T cell immunotherapy recipients

Pierre Sesques,[1] Emmanuel Bachy,[1] Emmanuelle Ferrant,[1] Violaine Safar,[1] Morgane Gossez,[1] Florence Morfin-Sherpa,[1] Fabienne Venet,[1] and Florence Ader[1,*]
[1]Lyon University Hospital, Lyon, France
*Correspondence: florence.ader@chu-lyon.fr
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Anti-SARS-CoV-2 vaccine response in patients with B cell lymphopenia is low compared to the general population. Here, we investigated humoral and cellular responses in 43 adult anti-CD19 chimeric antigen receptor (CAR) T cell recipients who received one (n = 11) or two (n = 22) booster doses of SARS-CoV-2 mRNA vaccine and 10 COVID-19 survivors in comparison to adult controls. The seroconversion rate was less than 20% in vaccinated recipients or COVID-19 survivors. T cell SARS-CoV-2-specific proliferation was detected in 42.4% and 57% of vaccinated recipients and COVID-19 survivors, respectively. Among the recipients tested consecutively after the first and second booster doses, no gain in specific humoral and cellular responses was observed. In responders, peripheral $CD4^+$ T cell and naive and central memory T cell counts were significantly higher. Cellular proliferative response was dependent on the timing of primary immunization; there were significantly more responders in the patients receiving primary immunization at least 6 months after CAR T cell infusion.

Severe cases of COVID-19 have been reported in recipients of autologous CAR T cells targeting CD19 (Busca et al., 2021; Hensley et al., 2021; Spanjaart et al., 2021) Not much is known about the immune response to mRNA vaccines against SARS-CoV-2 in recipients of CAR T cells. Small series have shown low seroconversion rates (<15%) after a single booster dose, particularly if vaccines were administrated within 6 months after CAR T cell infusion (Dhakal et al., 2021; Parvathaneni et al., 2022). Regarding the T cell repertoires, a study has reported that the frequency of Spike-specific memory $CD4^+$ T cell responses measured before and 1 month after the primary and booster vaccinations was not different in 12 CAR T cell-treated patients and eight healthy controls (Parvathaneni et al., 2022). French National Authority for Health has recommended the use of a second booster dose in immunosuppressed patients (Santé, 2022).

Here, we report the humoral and cellular responses after one or two booster doses of SARS-CoV-2 mRNA vaccine (n = 33) or after developing COVID-19 (n = 10) in a prospective observational single-center cohort of adults (≥18-year-old) who received commercial CAR T cells in comparison to control groups of mRNA-vaccinated adults (n = 5) or patients who developed mild to moderate ambulatory COVID-19 (n = 5). SARS-CoV-2-specific immunoglobulin (Ig) G was measured in sera harvested from CAR T cell recipients and control individuals (Supplemental information). Cellular response was assessed by $CD3^+$ T cell proliferation assay measured under antigenic peptide stimulation covering Spike, nucleocapsid, and the membrane of original SARS-CoV-2 ancestral strain.

In vaccinated CAR T cell recipients, 11 received one booster dose and 22 received two booster doses of either BNT162b2 (Pfizer/BioNTech) (n = 26) or mRNA-1273 (Moderna) (n = 7) (Figure S1A). The median age at primary dose or COVID-19 onset was 65 (interquartile range, IQR: 52–72) years, and sex ratio female/male was 0.48 (Table S1). The primary dose was administered either before (n = 8) or after (n = 25) CAR T cell infusion at a median time of 97 days (IQR: 68.5–141.2) and 257 days (IQR: 133–609), respectively. When primary dose was administered before CAR T cell infusion, the booster dose schedule was continued after infusion. The first booster dose was given 1 month apart from the primary dose, and the second booster dose was administered at a median time of 98.5 days (IQR: 61.2–146) after the first booster dose.

Humoral response in CAR T cell recipients showed that 6/33 (18%) and 1/7 (14%) tested positive for specific SARS-CoV-2 IgG in the vaccinated group and the COVID-19 survivor group, respectively, while 100% of controls were positive (Figure S1B). T cell spike-specific proliferation was observed in 14/33 (42.4%) of vaccinated patients (among whom 8 had received two booster doses) and in 100% of controls (Figure S1B). Among the COVID-19 survivor group, 4/7 (57%) had a positive T cell SARS-CoV-2 antigen-specific proliferation in response to at least one recall antigen (1/4 responded to all three, 1/2 responded to the Spike and nucleocapsid antigens, 1/4 responded to the Spike antigen, and 1/4 responded to the nucleocapsid antigen). Among the 16 patients tested consecutively after the first and second booster doses, no significant gain in humoral response or lymphocyte proliferation was observed ($p = 0.12$ and $p = 0.15$, respectively) (Figure S1C). Peripheral absolute $CD4^+$ T cell counts were significantly higher in responders than in non-responders, whether after one or two booster doses ($p = 0.021$ and $p = 0.016$, respectively) (Figure S1B). $CD8^+$ T cell, B cell, NK cell, and $CD19^+$ CAR T cell absolute counts were not different in responders and non-responders (Figure S1D).

When further investigating $CD4^+$ T cell subsets, responders had significantly more naive and central memory T cells and significantly less effector memory and terminally differentiated memory T cells than non-responders, whether after one or two booster doses ($p = 0.0160$ and $p < 0.0001$, respectively) (Figure S1B). When comparing responders and non-responders, receiving

the primary dose after CAR T cell infusion rather than before was the only factor significantly associated with a Spike-specific cellular response ($p = 0.049$) (Table S2). The number of responders was significantly lower if primary immunization was initiated within 6 months rather than beyond 6 months post-infusion ($p = 0.025$) (Table S2). Response was not different according to mRNA vaccine type ($p = 0.97$) (Table S2).

Overall, 82% of vaccinated CAR T cell recipients did not mount a humoral response, which is consistent with previous reports (Dhakal et al., 2021; Parvathaneni et al., 2022). In addition, we found that developing COVID-19 or receiving a second booster dose did not enhance specific IgG production in CAR T cell recipients. When considering the T cell response, studies conducted in healthy volunteers showed that both mRNA vaccines elicited systematically a Spike-specific $CD4^+$ and $CD8^+$ T cell response, although the responses varied inter-individually in magnitude and did not seem to be dose dependent (Jackson et al., 2020; Sahin et al., 2020). Here, specific T cell response was decreased by more than half (57.6%) in vaccinated recipients, indifferently of the number of booster dose, and by 43% in COVID-19 survivors who developed a response to at least one of the SARS-CoV-2 recall antigenic peptide. This suggests that developing COVID-19 generates a stronger and broader T cell response. Our results suggest a time-dependent efficacy of mRNA SARS-CoV-2 vaccines in inducing a specific cellular response after CAR T cell infusion. In addition, among peripheral $CD4^+$ lymphocyte subsets, naive $CD4^+$ lymphocyte count may be a predictive biomarker of appropriate cellular response. The present results are limited by the small sample size, and further studies are required. In the meantime, CAR T cell immunotherapy recipients must be advised to strictly maintain barrier measures, and vaccination of relatives must be strongly encouraged, particularly in the context of the new epidemiological landscape of Omicron takeover.

SUPPLEMENTAL INFORMATION

Supplemental information can be found online at https://doi.org/10.1016/j.ccell.2022.01.010.

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AUTHOR CONTRIBUTIONS

F.A., P.S., F.V., and E.B. were involved in the design, implementation, and day-to-day management of the study. P.S., E.F., V.S., E.B., and F.A. included participants in the study. F.M.-S. was responsible for the virological analyses. M.G. and F.V. were responsible for the immunological analyses. P.S., F.A., and F.V. were involved in the statistical analyses. F.A. and F.V. wrote the original draft of the manuscript, which was reviewed and edited by P.S., E.F., V.S., M.G., F.M.-S., and E.B. All authors have read and approved the manuscript. The corresponding author had full access to all the data and had final responsibility for publication.

DECLARATION OF INTEREST

P.S. declares Honoraria and Advisory/Consultancy from BMS, Novartis, and Kite/Gilead; E.F. declares Honoraria and Advisory/Consultancy from Kite/Gilead, Janssen, BMS, and Abbvie; V.S. declares Honoraria from Roche; E.B. declares Honoraria and Consultancy from Gilead, Novartis, Roche, Amgen, Janssen, Sanofi, and Abbvie. All other authors declare no conflicts of interest.

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