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Effects of the BTN162b2 mRNA COVID-19 vaccine in humoral and cellular immunity in patients with chronic lymphocytic leukemia

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Abstract

Chronic lymphocytic leukemia (CLL), the most common leukemia in the western countries, is characterized by immunosuppression due to disease itself and cytotoxic treatments. Since the beginning of COVID-19 pandemic, patients with CLL appear to be a vulnerable population. In addition, phase III mRNA vaccine trials did not provide information about the efficacy in immunocomprised population. In CLL, the antibody-mediated response to SARS-CoV-2 vaccine is impaired. The goal of this study was to evaluate the effects of SARS-CoV-2 vaccination on humoral immune response and on cellular immunity in CLL patients. Humoral immune response to BNT162b2 messenger RNA COVID-19 vaccine was evaluated in 44 CLL patients comprising 20 treatment-naïve, 14 under treatment with ibrutinib and 10 in follow-up after completion of therapy. A positive serological response to SARS-CoV-2 vaccination with IgG titers higher than 13 UA/ml was detected in 54.6% of CLL patients with a higher response in patients who obtained remission after treatment. Reduced antibody response was detected in patients under ibrutinib treatment. T-cell response to overlapping pool of peptides representing the spike region was assessed in paired CLL samples collected before and after 1 month from the second dose of COVID-19 vaccine in treatment-naïve and ibrutinib-treated CLL patients using cytokine secretion assay. Both CD3+ CD4+ and CD3+ CD8+ T cells are able to mount a cellular response to spike peptides with secretion of IFNγ and TNFα before and after vaccination in both treatment naïve and ibrutinib-treated patients and this cellular immune response is independent by COVID-19 vaccination. Collectively, T cell response to spike peptides appeared more blunted in CLL patients under treatment with ibrutinib compared to untreated ones. Our study supports the need for optimization of vaccination strategy to achieve an adequate immune response keeping strict preventive measures by CLL patients against COVID-19.

KEYWORDS
chronic lymphocytic leukemia, COVID-19, immunity, vaccine

1 | INTRODUCTION

COVID-19 pandemic is nowadays the main healthcare issue with high grade of transmission affecting millions of people in the world. In the past months, COVID-19 vaccines based on mRNA or adenovirus have been approved by international and national medicines agencies. In particular, BNT162b2 (Pfizer–BioNTech) is a lipid nanoparticle-encapsulated mRNA-based vaccine encoding the spike glycoprotein that has shown rapid and robust immunogenicity profile in immunocompetents patients.[1] Interferons (IFNs) are involved in the antiviral immunity. In particular, immune cells from several and critical COVID-19 patients have impaired type I IFN response (including IFNα, IFNβ, IFNω) and increased levels of TNFα and IL-6.[2] IFNγ is a key cytokine for several antiviral response. BNT162b2 stimulates an immune response with SARS-CoV-2 S-specific neutralizing antibodies and specific CD4+ and CD8+ T cells. Antibodies neutralize free virus, CD8+ T cells remove the intracellular virus and CD4+ T cells promote memory generation and cytotoxic activity through IFNγ.[3]

Advanced age, hypogammaglobulinemia and immune dysregulation put patients with chronic lymphocytic leukemia (CLL) as a high-risk group for COVID-19 infection. Immunodeficiency in CLL includes defects in humoral and cellular immune responses that is exacerbated by prolonged action of therapeutic agents. Predisposition to infection in CLL patients is related to the leukemia itself and the result of cumulative immunosuppression caused by treatments.[4] Of note, immune response to vaccines for influenza, varicella zoster or pneumococcus, was severely impaired in patients with CLL compared with the general population. This suboptimal response to vaccination is even worsen in CLL patients during treatment with Bruton's tyrosine kinase (BTK) inhibitors, such as ibrutinib and acalabrutinib, that seem to decrease antibody production in response to novel antigens.[5–7] Nowadays this evidence of lack of seroconversion for different vaccinations opened several questions related to the efficacy and protective effect of vaccination against COVID-19.[8] Phase III mRNA vaccine trials excluded immunocompromized patients as their immune response to vaccination is usually blunted. Recent studies showed that antibody-mediated response to SARS-CoV-2 vaccine in patients with CLL is consistently impaired by disease activity and treatments.[9–11] After 6 months post vaccination antibodies were still detectable, but titers were significantly decreased overtime in particular in CLL patients under active treatments.[12,13] In addition, the third vaccine dose is not able to increase the humoral response in CLL patients who had developed antibodies after the second dose.[14] CLL patients exhibit functional SARS-CoV-2 specific cellular immunity, but T cell response to COVID-19 vaccination is lower than healthy controls.[15,16]

In this study, we evaluated the SARS-CoV-2 specific antibody response in treatment-naïve, ibrutinib-treated and off-therapy CLL patients after 1 month from the second dose of BNT162b2 COVID-19 vaccine. In addition, we examined the T cell response to spike peptides in CLL patients before and after 1 month from the second dose of vaccine in treatment-naïve and ibrutinib-treated CLL patients.

2 | MATERIAL AND METHODS

2.1 | Patients

CLL patients, followed at the Hematology Unit of Modena Hospital, were vaccinated through the national Italian vaccination program. Blood samples were collected from CLL patients fulfilling standard clinical, morphological and immunophenotypic criteria with a protocol approved by the local Institutional Review Board and complied with Declaration of Helsinki. This study was performed on 44 samples isolated from CLL patients who have not experienced COVID-19 infection accordingly to their medical history. Blood serum and peripheral blood mononuclear cells (PBMC) of patients with CLL were collected before vaccination and after 1 month after administration of the second dose of BNT162b2 vaccine. Relevant data were extracted from the medical records and included age, sex, mutational status of the immunoglobulin heavy chain variable (IGHV) gene, analyses of genomic aberrations by fluorescent in situ hybridization (FISH) and laboratory parameters. Data are reported in Table 1.

2.2 | Serology

Blood serum samples were drawn at given timepoints. Serum samples were tested for the detection of IgG anti-S1/S2 antibodies to SARS-CoV-2 and were analyzed by chemiluminescent immunoassay IgG (CLIA) with a cut-off of 13 UA/ml.

2.3 | Cytokine secretion assay (CSA)

PBMC were collected before vaccination and after 1 month from the second dose and cryopreserved until use. PBMC were stimulated with SARS-CoV-2 Spike S, S1, S+ peptides (Miltenyi Biotech) for 6 h and T cell populations (CD3+ CD4+ and CD3+ CD8+) were analyzed using TNFα, IFNγ and IL-4 cytokine secretion assay according to manufacturer's instructions (CSA Detection kit; Miltenyi Biotec). Events were acquired using a BD Accury cytometer (Becton Dickinson) and then analyzed by FlowJo software.

TABLE 1 Patient demographic and disease characteristics

Parameter	Patients with CLL ($n = 44$)
Age, median, years	74.0 (41–86)
Age ≤60, *N* (%)	6 (13.6%)
Male sex, *N* (%)	26 (59%)
Disease/treatment status, *N* (%)	
Treatment-naïve	20 (45.5%)
Ibrutinib-treated	14 (31.8%)
Off-therapy in follow-up	10 (22.7%)
IGHV mutational status, *N* (%)	
Mutated	20 (45.5%)
Unmutated	21 (47.7%)
Missing	3 (6.8%)
FISH, *N* (%)	
Normal	10 (22.7%)
del(13q)	18 (40.9%)
Trisomy 12	7 (15.9%)
del(11q)	4 (9.1%)
del(17p)	6 (13.6%)
Laboratory parameters, median	
Before vaccination	
White blood cell count (10^9/L)	17.02 (1.1–217.6)
Lymphocyte count (10^9/L)	11.31 (0.5–20.6)
Neutrophil count (10^9/L)	4.01 (0.3–9.5)
Monocyte count (10^9/L)	0.55 (0.1–3.5)
Eosinophil count (10^9/L)	0.15 (0–1.1)
Basophil count (10^9/L)	0.06 (0–2.2)
Platelet count (10^9/L)	166 (17–609)
Hb (g/dl)	13.8 (8.8–17.1)
Gamma globulin (mg/dl)	690 (330–2240)
After vaccination	
White blood cell count (10^9/L)	15.8 (0.9–22.8)
Lymphocyte count (10^9/L)	11.7 (0.5–21.9)
Neutrophil count (10^9/L)	3.9 (0.25–11.1)
Monocyte count (10^9/L)	0.6 (0.1–3.5)
Eosinophil count (10^9/L)	0.2 (0–1.3)
Basophil count (10^9/L)	0.05 (0–0.3)
Platelet count (10^9/L)	152.5 (11–540)
Hb (g/dl)	13.3 (8.3–17.7)

Abbreviations: CLL, chronic lymphocytic leukemia; FISH, fluorescent in situ hybridization; IGHV, immunoglobulin heavy chain variable.

2.4 | Statistical analysis

The Pearson chi-square test was used to test for associations between categorical variables. To determine statistical significance Wilcoxon or Mann–Whitney *U* tests were used (GraphPad v6, GraphPad Software Inc.). Statistical significance was determined at $\alpha < 0.05$.

3 | RESULTS

3.1 | Serologic response to SARS-CoV-2 vaccination in CLL patients

In 2021, a total of 44 patients with CLL patients were included in this study. Patient demographic and disease characteristics are included in Table 1. In our cohort, median age at time of vaccination was 74 (range 41–86) and 41% were female ($n = 18$). Half of patients were hypogammaglobulinemic (cut-off 700 mg/dl). Twenty patients were untreated (45.4%), 14 were actively treated with ibrutinib monotherapy (31.8%) and 10 were off-therapy in follow-up (22.7%). CLL-directed therapy was not modified prior of vaccination. Serology was tested 1 month following second vaccine dose. Firstly, a positive serological response (IgG > 13 UA/ml) was detected in 24 of 44 (54.6%) CLL patients analyzed. We detected a positive response in 60% of treatment-naïve CLL patients ($n = 12$ of 17). Among the ibrutinib-treated patients only 28.6% showed production of IgG after vaccination ($n = 4$ of 14), conversely 80% of CLL patients in follow-up after completion of treatment as chemoimmunotherapy (FCR or bendamustine and rituximab regimen) or target therapies (ibrutinib treatment) showed high antibody response (Figure 1A,B, Table 2 and Table S1, $p < 0.05$). We found that CLL patients off-therapy were more likely to produce anti-SARS-CoV-2 antibodies and production of antibodies was less common in patients under ibrutinib regimen. In addition, 8/44 (18%) CLL patients contracted COVID-19 infection after vaccination. Among these, five patients (5/8, 62.5%) had developed a positive serological response suggesting that presence of antibodies did not correlated with a higher protection to infection. Moreover, among the patients that have experience COVID-19 infection, 3/8 (37.5%) have developed severe illness and were actively treated with ibrutinib and two (2/3, 66.6%) of them have not a positive serological response.

3.2 | T-cell responses after SARS-CoV-2 vaccination in CLL patients

Definition of mechanisms involved in the protection against COVID-19 is still to be fully determined, but it is known that both neutralizing antibodies and antigen-specific T cells play important role. In CLL, T cell population is dysfunctional showing features of pseudo-

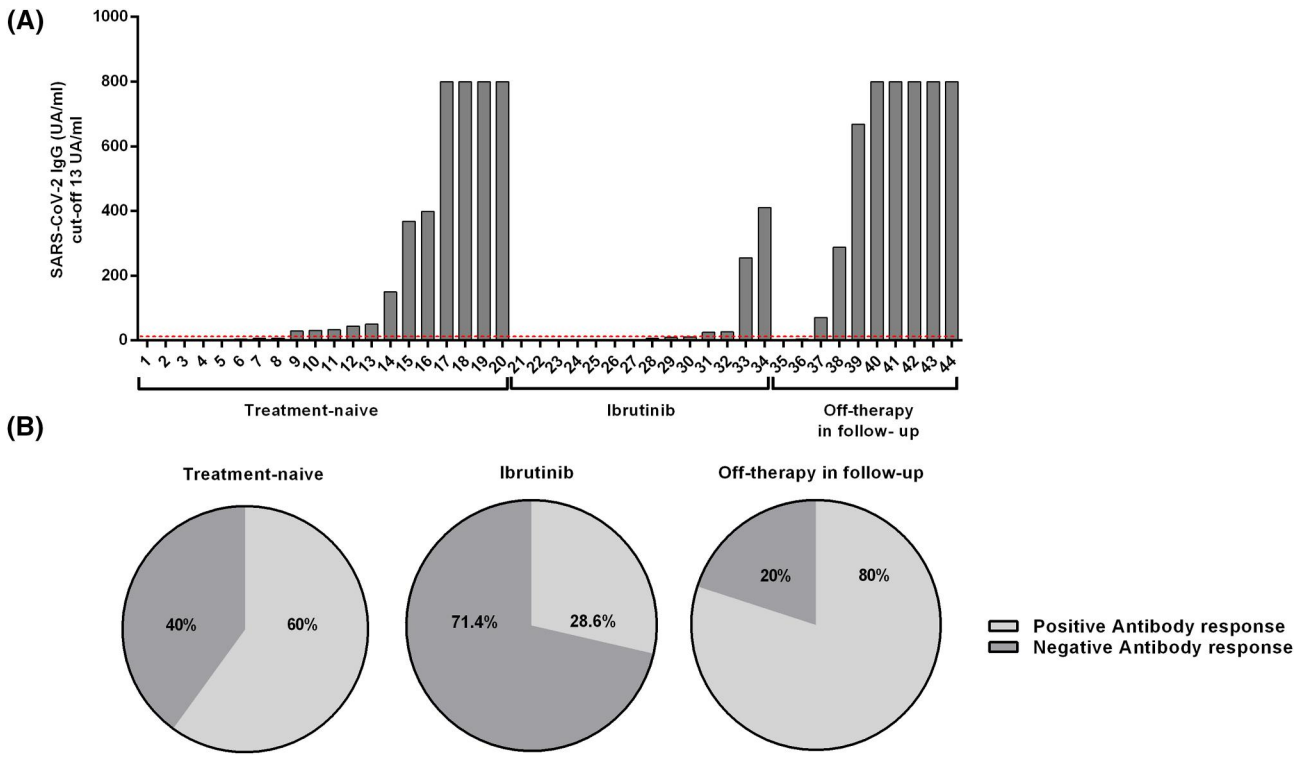

FIGURE 1 Antibody response to BNT162b2 mRNA COVID-19 vaccine in CLL patients. (A) Distribution of individual response in patients with CLL ($n = 44$). Patients were dividing according to treatment-naïve ($n = 20$), ibrutinib treatment ($n = 14$) and off-therapy in follow-up ($n = 10$). Each column represents the level of antibodies for each single patient. Serum samples were analyzed by chemiluminescent immunoassay IgG (CLIA) with a cut-off of 13 UA/ml. (B) Pie charts represent the antibody response rate according to the disease status: treatment-naïve, ibrutinib-treated and off-therapy in follow-up CLL patients. Light grey region represents a positive antibody response and dark gray region a negative antibody response. All data are presented as mean ± SEM. CLL, chronic lymphocytic leukemia

exhaustion with significant upregulation of checkpoint molecules and exhaustion markers.[17] In addition, ibrutinib irreversibly inhibits interleukin-2-inducible kinase (ITK) leading to normalization of T cell number in CD4 and CD8 populations and inducing polarization of T cells towards a Th1 predominant phenotype. This Th1 polarization is accompanied by an increase in Th1-mediated cytokines (IFNγ, TNFα) while Th2-mediated cytokines (IL-2, IL-4, IL-5, IL-10) are significantly reduced.[18] For this reason, we wondered to determine the secretion of immune-modulatory cytokines upon activation of CD4+ and CD8+ T cells with specific SARS-CoV-2 Spike. CD4+ and CD8+ T cell responses were characterized in CLL patients before priming vaccination and after 1 month from the second dose vaccination with BNT162b2. Stimulation with overlapping pool of peptides representing the spike region determined a significant induction of IFNγ and TNFα secretion by CD3+ CD4+ T cells in both treatment-naïve and ibrutinib treated CLL samples before and after SARS-CoV-2 vaccination (Figure 2A,B, $^{*}p < 0.05$ and $^{**}p < 0.01$). In addition, higher levels of IFNγ and TNFα secretion by CD3+ CD4+ T cells were detected in treatment naïve patients compared to ibrutinib ones before vaccination, but no significant difference between these two groups was measured after SARS-CoV-2 vaccination. In treatment naïve and ibrutinib-treated CLL samples, we detected a significant induction of IFNγ and TNFα secretion following stimulation with spike peptides either before and after vaccination (Figure 2C,D, $^{*}p < 0.05$ and $^{**}p < 0.01$), but no significant differences between samples collected before and after vaccine. In addition, we detected a significant higher response to spike peptides pool by CD3+ CD8+ with increased IFNγ secretion in treatment naïve CLL patients compared to ibrutinib treated ones before and after SARS-CoV-2 vaccination (Figure 2C, $^{*}p < 0.05$). Lastly, we analyzed IL-4 secretion by CD3+ CD4+ T cells measuring a significant induction determined by Spike peptides pool in both CLL patient groups (Figure 2E, $^{*}p < 0.05$ and $^{**}p < 0.01$). In treatment naïve CLL patients, we observed a significant induction of IL-4 secretion triggered by stimulation compared to ibrutinib treated ones after SARS-CoV-2 vaccination. Altogether our results display a functional T cell response both in treatment naïve and ibrutinib-treated CLL patients to SARS-CoV-2 spike peptides highlighting an impaired cellular response during treatment with ibrutinib compared to the others.

4 | DISCUSSION

Nowadays, different studies have demonstrated low rates of seroconversion to the SARS-CoV-2 vaccines in CLL patients either untreated and those receiving targeted therapies compared with the general population.[19–21] Our results confirm that the anti-SARS-CoV-2 antibody response rate in CLL patients is generally low with

TABLE 2 Patients characteristics

Characteristic	Anti-SARS-CoV-2 serological response, *N* (%)		Total	*p* value
	Positive 24 (54.6%)	Negative 20 (45.5%)		
Age at vaccination				
Median (range)			74 years (41–86)	0.5211
≤60	4 (66.7%)	2 (33.3%)	6	
>60	20 (52.6%)	18 (47.4%)	38	
Sex				
Male	14 (53.8%)	12 (46.2%)	26	0.9109
Female	10 (55.6%)	8 (44.4%)	18	
CLL treatment history				
Treatment-naïve	12 (60.0%)	8 (40.0%)	20	0.0357
Ibrutinib-treated	4 (28.6%)	10 (71.4%)	14	
Off-therapy in follow-up	8 (80.0%)	2 (20.0%)	10	
IGHV				
Mutated	12 (60.0%)	8 (40.0%)	20	0.6623
Unmutated	10 (47.6%)	11 (52.4%)	21	
Missing	2 (66.7%)	1 (33.3%)	3	
FISH test				
Normal	6 (60.0%)	4 (40.0%)	10	0.0808
del(13q)	13 (72.2%)	5 (27.8%)	18	
Trisomy 12	4 (57.1%)	3 (42.9%)	7	
del(11q)	0 (0.0%)	4 (100.0%)	4	
del(17p)	2 (33.3%)	4 (66.7%)	6	
Previous treatment, *n*				
Yes	12 (50%)	12 (50%)	24	
No	12 (60%)	8 (40%)	20	
Off-therapy in follow-up patients ($n = 10$)				
Previous treatment lines, *N*				
1	7 (100%)	0 (0%)	7	0.02
≥1	1 (50%)	2 (50%)	3	

Abbreviations: CLL, chronic lymphocytic leukemia; FISH, fluorescent in situ hybridization; IGHV, immunoglobulin heavy chain variable.

a detrimental response to SARS-CoV-2 vaccine in those patients receiving ibrutinib but better response in patients who completed treatment and in remission. This impaired response is mainly linked to the disease itself and to the immunosuppressive effect of administered therapies. Hypogammaglobulinemia is typically evident in CLL patients affecting all subclasses of immunoglobulins (IgA, IgG, and IgM). Ibrutinib has a variable effect on the Ig classes with IgA that increases and remains above baseline levels during treatment and that IgG decrease with longer duration on drug.[22] In addition, our data are in line with multiple studies showing a suboptimal humoral response to vaccinations in CLL in particular in response to novel immunogens and a suppression of vaccine response in patient who are undergoing treatment with BTK inhibitors for pathogens in which pre-existing immunity is not present.[7,23]

Protective immune response to vaccines emerges from combination between humoral and cellular immune systems. T cell responses after SARS-CoV-2 vaccination is not been completely studied until now. In healthy controls, BNT162b2 induces a broad immune response with SARS-CoV-2-specific neutralizing antibodies and specific CD4+ and CD8+ T cells.[3] In CLL, SARS-CoV-2 vaccination induces a functional T cell response that appears inferior compared to healthy donors. In addition, most patients showed a discordant response with only either detectable humoral or cellular response.[15,16,24,25] This may be due to disease burden as leukemic B

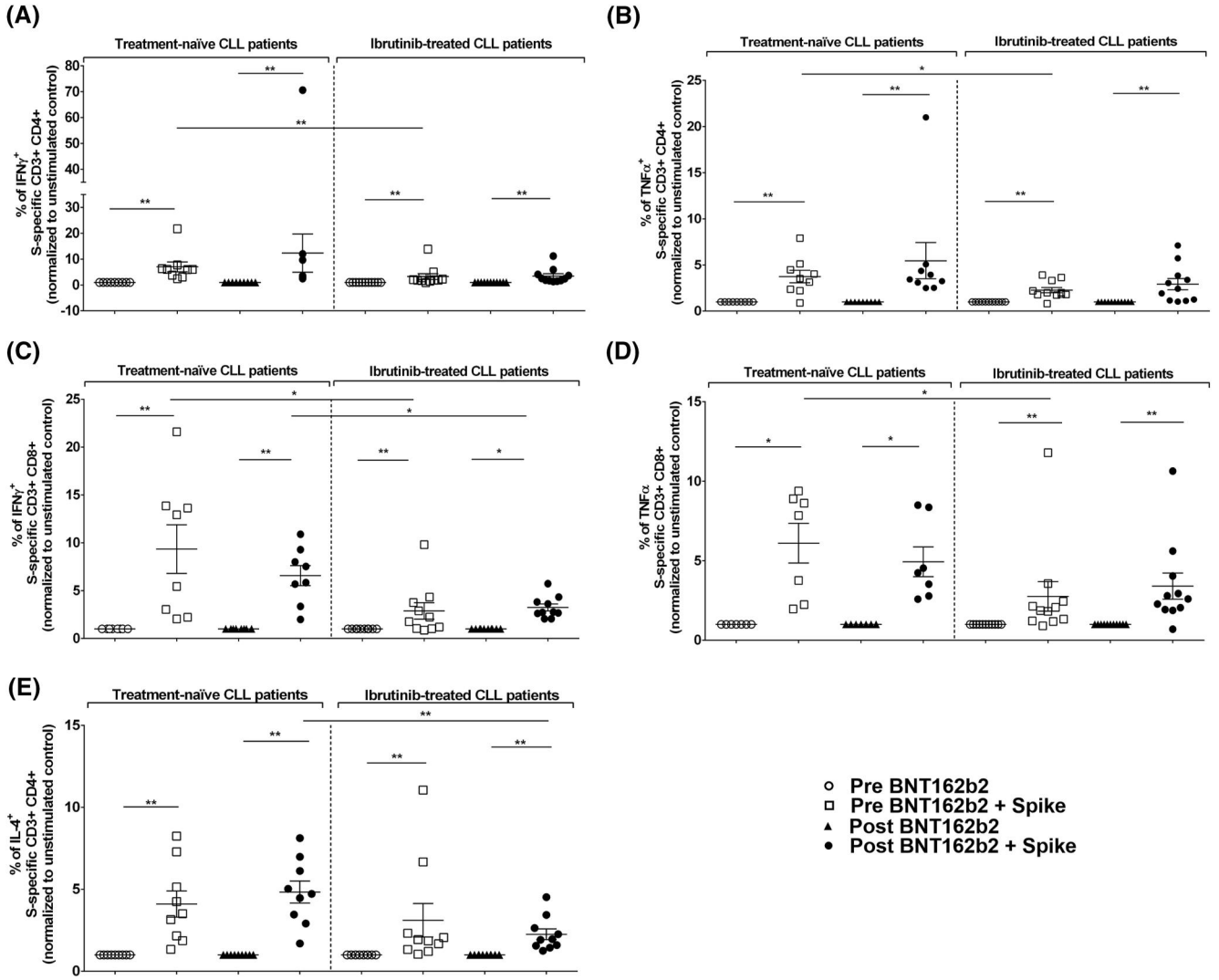

FIGURE 2 CD4+ and CD8+ T-cell response to COVID-19 vaccination in treatment-naïve and in ibrutinib-treated CLL patients. Dot diagrams show the percentage of positive CD3 and CD4 or CD3 and CD8 T cells following in vitro stimulation with SARS-CoV-2 spike pool peptides for 6 h in CLL samples isolated before and after BNT162b2 vaccination. Normalization was performed by dividing the value of the stimulated sample to the value of the corresponding sample unstimulated for the corresponding condition before and after vaccination. Value is expressed as fold change. (A) Diagram show the secretion of IFNγ by CD3+ CD4+ T cells stimulated with S peptides before and after vaccination in treatment-naïve ($n = 9$) and ibrutinib-treated patients ($n = 11$). (B) Diagram show the secretion of TNFα by CD3+ CD4+ T cells stimulated with S peptides before and after vaccination in treatment-naïve ($n = 9$) and ibrutinib-treated patients ($n = 11$). (C) Diagram show the secretion of IFNγ by CD3+ CD8+ T cells stimulated with S peptides before and after vaccination in treatment-naïve ($n = 8$) and ibrutinib-treated patients ($n = 10$). (D) Diagram show the secretion of TNFα by CD3+ CD8+ T cells stimulated with S peptides before and after vaccination in treatment-naïve ($n = 7$) and ibrutinib-treated patients ($n = 11$). (E) Diagram show the secretion of IL-4 by CD3+ CD4+ T cells stimulated with S peptides before and after vaccination in treatment-naïve ($n = 9$) and ibrutinib-treated patients ($n = 10$). All data are presented as mean ± SEM (*$p < 0.05$, **$p < 0.01$). CLL, chronic lymphocytic leukemia

cells manipulate and modify the functions of the surrounding milieu influencing the possibility to mount cellular immune response. To our knowledge our study is the first in the context of CLL that unravels the T cell population comparing the cellular response between paired samples collected before and after 1 month from COVID-19 vaccination. T cells isolated by both treatment naïve and ibrutinib-treated CLL patients are able to mount a cellular response upon stimulation with SARS-CoV-2 peptides, but this immune response to spike peptides resulted independent by SARS-CoV-2 vaccination. These data need to be interpreted in the context of the limitations of the study design and patient population related to the small sample size of included patients. In this scenario, patients with CLL need to keep safety precautions and social distance. There are still several unanswered questions related to the achievement of an adequate immune response, our evidence suggest to elaborate new strategies to prevent COVID-19 in these frail patients considering approaches related to booster doses of vaccine, heterogeneous vaccinations and passive immunization via monoclonal antibodies.

AUTHOR CONTRIBUTIONS

Stefania Fiorcari and Roberto Marasca conceived the research. Stefania Fiorcari, Rossana Maffei and Roberto Marasca coordinated the research and interpreted the results. Stefania Fiorcari wrote the manuscript. Stefania Fiorcari, Claudio Giacinto Atene and Nicolò Mesini performed experiments. Stefania Fiorcari acquired and analyzed flow cytometric data. Stefania Fiorcari and Claudio Giacinto Atene performed the statistical analyses. Corrado Colasante, Stefano Pozzi, Emiliano Barbieri, Monica Maccaferri, Giovanna Leonardi and Giulia Debbia collected samples and performed clinical evaluation. Roberto Marasca revised critically and approved the final version of the manuscript. Monica Maccaferri, Giovanna Leonardi, Leonardo Potenza, Mario Luppi, revised and approved the final version of the paper.

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CONFLICT OF INTEREST

Roberto Marasca Abbvie, Janssen, Astrazenica: Honoraria and Janssen, Beigene: travel grant (unrelated COIs). **Mario Luppi** Advisory Board Abbvie, Novartis, MSD, Sanofi, Grifols, Gilead sci, Daiichi-Sankyo, Jazz Pharma Travel Grant Gilead sci (unrelated COIs).

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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TRANSPARENT PEER REVIEW

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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