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TO THE EDITOR:

Booster effect after SARS-CoV-2 vaccination in immunocompromised hematology patients with prior COVID-19

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Patients with hematological malignancies have been excluded from the new zoonotic coronavirus (severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2]) vaccine trials,[1,2] despite being at higher risk for SARS-CoV-2 disease (COVID-19)–related mortality.[3-5] However, most health authorities worldwide have designated these patients as a priority for COVID-19 vaccination,[6-12] even in the absence of efficacy data in these highly immunosuppressed patients. In addition, on 12 August 2021, the US Food and Drug Administration amended the emergency use authorizations for the Pfizer-BioNTech and Moderna COVID-19 vaccines to allow for the use of an additional dose in immunocompromised individuals, such as solid organ transplant recipients or equivalently immunosuppressed patients. This emergency use authorization prompted the American Society of Hematology to consider a third dose in immunocompromised patients with hematological malignancies who were being actively treated or were receiving high-dose corticosteroids at vaccination and/or agents causing prolonged B-cell lymphopenia within 12 months before vaccination, those with chronic lymphocytic leukemia, and recipients of chimeric antigen receptor T cells or a hematopoietic stem cell transplant (within 2 years).[13] Again, the lack of prospective randomized clinical trials in immunosuppressed patients with hematological malignancies exploring the safety and efficacy of SARS-CoV-2 vaccines urge studies aimed at identifying which patients may or may not require a third vaccine dose before studying the potential benefit of this third booster dose.

To provide some rationale for these 2 pressing questions, we report a case-control analysis of the probabilities of exhibiting detectable SARS-CoV-2–reactive immunoglobulin G antibodies (SCoV2-R-A) at 3 weeks after a full vaccination schedule in a large series of patients with hematological malignancies and a history of SARS-CoV-2 infection (as defined by molecular or serological tests for SARS-CoV-2) before the first vaccine dose. The SCoV2-R-A detection rate in this cohort was compared with that observed in a control cohort of patients without evidence of prior SARS-CoV-2 infection at the time of vaccination. The latter included patients with hematological malignancies without prior polymerase chain reaction (PCR)-confirmed SARS-CoV-2 infection and a negative SCoV2-R-A serology test within 2 weeks of the first vaccine dose. The next step was to exclude patients with hematological malignancies and/or procedures not represented in the study group.

Both cohorts came from the Spanish Hematopoietic Stem Cell Transplantation and Cell Therapy Group multicenter prospective registry, which included 1568 consecutive patients with hematological malignancies who received a full vaccination schedule with any of the available compounds between 30 December 2020 and 30 June 2021 and who had available serological results performed 3 weeks after full vaccination. The algorithm selection of both cohorts is shown in supplemental Figure 1. All patients included in this registry

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Requests for data sharing may be submitted to José Luis Piñana (jlpinana@gmail.com)

The full-text version of this article contains a data supplement.

Table 1. Patient characteristics according to prevaccination COVID-19

Characteristics	Prior COVID-19 (n = 99)	Control cohort (n = 362)	*P*
Prior COVID-19			
Diagnosed by PCR	82 (82)		
Positive serostatus prior to vaccination	33 (41)		
Negative serostatus prior to vaccination	18 (22)		
Detected by prevaccine serological test	17 (30)		
Asymptomatic infection	16 (16)		
URTD symptoms	19 (19)		
LRTD symptoms	76 (76)		
Oxygen requirement	18 (18)		
ICU admission	5 (5)		
Time from COVID-19 to vaccination, median (range), d	185 (33-422)		
Serological status prior to vaccination			NT
Positive	50 (50)	0	
Negative	18 (18)	362 (100)	
NT	31 (31)	0	
Time from serology to vaccination, median (range), d	0 (0-330)	0 (0-14)	.6
Type of vaccine			.001
Moderna mRNA-1273	76 (76)	328 (90)	
Pfizer-BioNTech BNT162b2	22 (22)	30 (8)	
Adenoviral vector based	1 (1)	4 (1)	
Age, y			.84
Median (range)	59 (20-88)	59 (18-88)	
18-40	6 (6)	66 (18)	
41-50	19 (19)	45 (12)	
51-60	26 (26)	73 (20)	
61-70	26 (26)	110 (31)	
>71	22 (22)	68 (19)	
Males	56 (56)	203 (56)	.99
Baseline disease			.06
AL/MDS	25 (25)	141 (39)	
B-cell NHL	21 (21)	69 (19)	
MM	15 (15)	45 (12)	
CLL	17 (17)	31 (9)	
HD	6 (6)	36 (10)	
MPN	11 (11)	29 (8)	
Others	4 (4)	11 (3)	
Type of stem cell transplant			.01
Allo-HSCT	29 (29)	186 (51)	
ASCT	6 (6)	24 (7)	
Disease status at vaccination			.001
Complete remission	59 (59)	264 (73)	
Partial remission	16 (16)	19 (5)	
Not in response	20 (20)	51 (14)	
First-line therapy	4 (4)	28 (8)	
Treatment given during vaccination	39 (39)	119 (43)	.5

Unless noted otherwise, data are n (%).

AL/MDS, acute leukemia/myelodysplastic syndrome; allo-HSCT, allogeneic hematopoietic stem cell transplantation; ASCT, autologous stem cell transplantation; BTKI, Bruton's tyrosine kinase inhibitor; CLL, chronic lymphocytic leukemia; HD, Hodgkin disease; ICU, intensive care unit; LRTD, lower respiratory tract disease; mAb, monoclonal antibody; MM, multiple myeloma; MPN, chronic myeloproliferative neoplasm; NT, not tested; TKI, tyrosine kinase inhibitor; URTD, upper respiratory tract disease.

Table 1. (continued)

Characteristics	Prior COVID-19 (n = 99)	Control cohort (n = 362)	*P*
Treatment planned after vaccination	38 (38)	98 (27)	.05
Time from last treatment to COVID-19 vaccine			.03
Untreated	16 (16)	30 (8)	
Active treatment	39 (39)	119 (33)	
≥6 mo to 1 y	6 (6)	25 (7)	
≥1 y	37 (37)	187 (52)	
Immunosuppressant drugs at vaccination	22 (22)	81 (22)	.3
Corticosteroids at vaccination	16 (16)	52 (14)	.6
Daratumumab	5 (5)	13 (4)	.6
Venetoclax	3 (3)	6 (2)	.4
Anti-CD20 mAb	19 (19)	56 (15)	.9
BTKI therapy	10 (10)	17 (5)	.05
Other TKI therapy	2 (2)	12 (3)	.7
Lenalidomide maintenance	6 (6)	23 (6)	.99
Ruxolitinib therapy	4 (4)	6 (2)	.3
Blood count before vaccination ($\times 10^9$/mL)			
Absolute neutrophil count, median (range)	3.08 (0.72-31.0)	3.03 (.06-22.1)	.9
Absolute lymphocyte count, median (range)	1.91 (0.5-41.3)	1.82 (0.28-194.2)	.6
Absolute lymphocyte count $< 1 \times 10^9$/mL	9 (9)	54 (15)	.2
Time from second dose to serology, median (range), d	21 (14-51)	21 (14-57)	.8
Time between vaccine doses, median (range), d	28 (18-91)	28 (19-91)	.78
SCoV2-R-A detection at 3 wk after full vaccination	92 (93)	281 (78)	<.0001
Follow-up after complete vaccination, median (range), d	28 (15-109)	27 (16-89)	.9
COVID-19 after vaccination	0	2 (0.6)	.99

Unless noted otherwise, data are n (%).

AL/MDS, acute leukemia/myelodysplastic syndrome; allo-HSCT, allogeneic hematopoietic stem cell transplantation; ASCT, autologous stem cell transplantation; BTKI, Bruton's tyrosine kinase inhibitor; CLL, chronic lymphocytic leukemia; HD, Hodgkin disease; ICU, intensive care unit; LRTD, lower respiratory tract disease; mAb, monoclonal antibody; MM, multiple myeloma; MPN, chronic myeloproliferative neoplasm; NT, not tested; TKI, tyrosine kinase inhibitor; URTD, upper respiratory tract disease.

gave their signed informed consent according to the Declaration of Helsinki. The local ethics committee of the Hospital Clinic Universitario of Valencia approved the registry and study protocol (reference code 35.21).

The presence of SCoV2-R-A was determined at each center using serological enzyme-linked immunosorbent assays or chemiluminescence immunoassays, following the manufacturers' instructions, and based on their availability at the microbiology services of each participating center. The techniques used are shown in supplemental Table 1. For this study, we defined antibody detection or seropositivity when SCoV2-R-A were detected at any level above the lower limit level of detection for each of the tests used. The primary end points were to compare the rate of postvaccination seropositivity for SCoV2-R-A between cohorts, to identify the main factors associated with seropositivity, and to describe the characteristics of SCoV2-R-A detection in patients with prior SARS-CoV-2 infection as a model of a somewhat more natural immunological booster.

Overall, this series included 461 patients with hematological malignancies. The first cohort included 99 patients with prior SARS-CoV-2 infection, whereas the control cohort included 362 patients without prior COVID-19 history and a negative SCoV2-R-A serological test before the first vaccine dose. The clinical characteristics of both cohorts are detailed in Table 1. Eighty-two of 99 patients (82%) had prior PCR-confirmed COVID-19, whereas 17 (17%) were diagnosed at the time of SCoV2-R-A serological testing within 2 weeks of the first vaccine dose. Fifty-one of 82 patients with PCR-confirmed COVID-19 (62%) had pre-vaccination serological test results available. Of them, 33 (65%) were SCoV2-R-A positive and 18 (35%) were SCoV2-R-A negative. Differences between these cohorts included a higher rate of messenger RNA (mRNA)-1273 (or Moderna) vaccine administration and a higher frequency of recipients of allogeneic stem cells, whereas patients with prior SARS-CoV-2 infection had lower rates of baseline disease in complete remission, lower rates of patients treated >1 year before vaccination, and higher rates of tyrosine kinase inhibitor therapy. In terms of safety, self-reported adverse events were more common in patients with prior SARS-CoV-2 infection (14%) than in patients without (5%; $P = .003$) (supplemental Table 2). The SCoV2-R-A detection rate in patients with prior SARS-CoV-2 infection was 93% compared with 78% in those without ($P < .0001$). Of note, 15 of 18 patients (83%) with prior COVID-19 and negative SCoV2-R-A serostatus before vaccination mounted a SCoV2-R-A serological response at 3 weeks after full vaccination. Univariate and multivariate logistic regression analyses of factors associated with the detection of SCoV2-R-A at

Table 2. Logistic regression univariate and multivariate analyses of factors predicting SARS-CoV-2–reactive antibody detection after full vaccination

Characteristics	Univariate analysis*	*P*	Multivariate analysis*	*P*
Prior COVID-19	3.79 (1.69-8.49)	.001	4.04 (1.71-9.5)	.001
Type of vaccine				
Moderna mRNA-1273	1			
Pfizer-BioNTech BNT162b2	0.94 (0.45-1.9)	.87		
Adenoviral vector based	0.05 (0.006-0.5)	.01	NT	
Age, y				
18-40	1			
41-50	1.16 (0.48-2.7)	.7		
51-60	1.75 (0.75-4.05)	.19		
61-70	0.93 (0.45-1.9)	.84		
>71	0.7 (0.32-1.49)	.35		
Male sex	1.6 (1.01-2.57)	.045		
Baseline disease				
AL/MDS	1			
B-cell NHL	0.47 (0.25-0.87)	.016	0.42 (0.2-0.8)	.01
MM	1.01 (0.46-2.23)	.9		
CLL†	0.77 (0.34-1.7)	.5		
HD	0.64 (0.28-1.4)	.3		
MPN	3.85 (0.87-16.9)	.079		
Others	2.8 (0.35-22.4)	.3		
Disease status at vaccination				
Complete remission	1			
Partial remission	1.39 (0.5-3.7)	.5		
Not in response	1.2 (0.6-2.55)	.5		
First-line therapy	0.44 (0.2-0.97)	.04		
Time from last treatment to COVID-19 vaccine				
Untreated	1			
Under treatment	0.42 (0.15-1.16)	.09		
>6 mo-1 y	0.29 (0.08-0.99)	.05		
≥1 y	0.6 (0.21-1.55)	.27		
Stem cell transplant				
Yes	1.1 (0.69-1.7)	.67		
Allo-HSCT	1.19 (0.73-1.9)	.42		
ASCT	0.69 (0.28-1.6)	.39		
Corticosteroids at vaccination	0.39 (0.19-0.82)	.008	0.39 (0.18-0.84)	.016
Daratumomab	0.8 (0.26-2.5)	.73		
Venetoclax	1.9 (0.23-15.4)	.54		

AL/MDS, acute leukemia/myelodysplastic syndrome; allo-HSCT, allogeneic hematopoietic stem cell transplantation; ASCT, autologous stem cell transplantation; BTKI, Bruton's tyrosine kinase inhibitor; CLL, chronic lymphocytic leukemia; HD, Hodgkin disease; mAb, monoclonal antibody; MM, multiple myeloma; MPN, chronic myeloproliferative neoplasm; NT, not tested; TKI, tyrosine kinase inhibitor.

*Data are odds ratio (95% confidence interval).

†We included 48 patients with CLL. Seventeen (35%) were assigned to the watch-and-wait approach, whereas 5 (10%) were >1 year after allo-HSCT, and 9 (19%) were in complete remission for >1 y before vaccination without active therapy. The remaining 17 patients with CLL were on treatment at the time of vaccination. Four of them received BTKI (n = 2) or venetoclax (n = 2), both in combination with anti-CD20 therapy, whereas 13 patients were on BTKI only. Thus, only 13 of 48 patients with CLL (27%) received rituxan prior to vaccination, and 9 of them received it >1 year before vaccination. This highly heterogenous population of patients with CLL may have precluded our ability to identify poor responders.

‡We included 90 patients with B-cell NHL, of whom 69 (77%) received anti-CD20 therapy prior to vaccination (including 11 vaccinated after ASCT) and 21 (23%) were vaccinated after allogeneic stem cell transplantation. Thus, a high collinearity (100%) was observed between B-cell NHL not allografted and prior anti-CD20 therapy. In multivariate analyses, if we include rituxan along with the baseline disease, the only significant variable associated with a lower response rate was B-cell NHL. In contrast, after removing baseline disease and including prior anti-CD20 therapy, we observed a significant association with lower response rate. The rest of the significant variables remained unchanged.

Table 2. (continued)

Characteristics	Univariate analysis*	P	Multivariate analysis*	P
Anti-CD20 mAb‡	0.458 (0.26-0.8)	.006	0.41 (0.23-0.75)	.003
No	1			
<3 mo	0.2 (0.08-0.48)	.0001		
3-6 mo	0.2 (0.02-1.4)	.11		
>6 mo-1 y	0.6 (0.06-5.9)	.68		
≥1 y	0.81 (0.37-1.7)	.59		
BTKI therapy	0.5 (0.22-1.2)	.15		
TKI therapy	3.1 (0.4-24.3)	.27		
Lenalidomide maintenance	2.12 (0.6-7.1)	.22		
Ruxolitinib therapy	0.9 (0.19-4.5)	.9		
Lymphocyte count $< 1.0 \times 10^9$/mL	0.32 (0.18-0.58)	.0001	0.35 (0.19-0.67)	.004

AL/MDS, acute leukemia/myelodysplastic syndrome; allo-HSCT, allogeneic hematopoietic stem cell transplantation; ASCT, autologous stem cell transplantation; BTKI, Bruton's tyrosine kinase inhibitor; CLL, chronic lymphocytic leukemia; HD, Hodgkin disease; mAb, monoclonal antibody; MM, multiple myeloma; MPN, chronic myeloproliferative neoplasm; NT, not tested; TKI, tyrosine kinase inhibitor.

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3 weeks after full vaccination are shown in Table 2. Multivariate analysis confirmed that prior COVID-19 was the main factor associated with detectable SCoV2-R-A after vaccination (odds ratio, $P = .001$), whereas diagnosis of B-cell non-Hodgkin lymphoma (NHL), corticosteroid use, and lymphopenia ($<1 \times 10^9$ lymphocytes per milliliter) at vaccination were associated with lower rates of SCoV2-R-A detection. Prior exposure to anti-CD20 therapy was also significantly associated with a lower response rate when we removed B-cell NHL from the multivariate analysis model (see footnote "‡" in Table 2).

Our findings indicate that patients with hematological malignancies with prior history of SARS-CoV-2 infection before vaccination achieve a high SCoV2-R-A detection rate (93%), similar to that reported in clinical trials of healthy subjects with mRNA vaccines.[1,2] The most important limitation of this study is the use of several serological tests that may differ with regard to their detection range, sensitivity, and specificity. Thus, further confirmation of our findings using World Health Organization standardized tests is a priority for future research. Our finding indicates that these patients may not require an immediate SARS-CoV-2 vaccine booster dose, irrespective of current or past treatments, type and status of disease, or the absolute lymphocyte count at the time of vaccination. Furthermore, SARS-CoV-2 full-dose vaccination was able to reach seroconversion in 83% of patients with prior negative SCoV2-R-A, despite prior COVID-19. These data suggest that a booster dose in these highly immunosuppressed patients could likely elicit a humoral response similar to that observed in the healthy population and likely higher than prior experiences with mRNA SARS-CoV-2 vaccine booster doses in recipients of solid organ transplants, where the additional dose increased the seroconversion rate from 40% to 68%.[14,15] Although the SARS-CoV-2 antibody detection rate in patients with hematological malignancies and prior SARS-CoV-2 infection is similar to that in the general population, and an up-front third dose could be questionable, it remains to be determined whether the duration of such a response is similar to the general population's because immunocompromised patients may have more rapidly decreasing antibody titers, especially those who have undergone allogeneic stem cell transplantation or those in active treatment. If such a serological behavior is confirmed, a third dose could be advisable in this scenario. In line with early studies, we report that B-cell NHL[6,11] (or treatment with anti-CD20 monoclonal antibodies), lymphopenia ($<1 \times 10^9$ lymphocytes per milliliter),[8] and corticosteroid therapy[16] were associated with a lower probability of mounting SCoV2-R-A. After removing patients with B-cell NHL from the multivariate analysis, the significant effect of anti-CD20 monoclonal antibody therapy could be linked to chronic lymphocytic leukemia. However, we were not able to properly analyze the effect of anti-CD20 monoclonal antibody therapy in patients with chronic lymphocytic leukemia because of the limited number of such patients. Until more disease-specific data are available, these factors could be used to guide physicians in patient counseling with respect to a third vaccine dose. However, we believe that a third dose should be given in the context of prospective randomized clinical trials to overcome the lack of such evidence in these highly immunosuppressed patients. Finally, limitations of this study include the use of different serological tests in each center (results were not harmonized), the lack of neutralizing antibody testing, and the lack of SCoV2-R-A quantification in a significant number of cases. In contrast, the multicenter design, along with the large number of patients included, should be regarded as strengths.

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Contribution: J.L.P., A.C., and A.S. conceived and designed the study; R.G.-S., M.G.-R., G.A.M.-M., I.R.-G., M.T., P.M.-B., S.M.-C., M.C., V.C., A.T., S.R.-P., and C.S. recruited patients for the study; and J.L.P., D.N., and R.M. analyzed data and generated the tables and figures.

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