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Letter

Antibody response against SARS-CoV-2 Delta and Omicron variants after third-dose BNT162b2 vaccination in allo-HCT recipients

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Allogeneic hematopoietic stem cell transplant (allo-HCT) recipients are particularly at risk of severe COVID-19. In addition, they have lower serological response to two doses of mRNA vaccines as compared to healthy individuals (Redjoul et al., 2021a; Canti et al., 2021; Maillard et al., 2022). Whether they are protected following vaccination against the Delta and Omicron variants remains to be established.

We previously reported a study of 40 allo-HCT recipients immunized with the BNT162b2 mRNA vaccine at 3 weeks apart (days 0 and 21) (Canti et al., 2021). Among the 37 SARS-CoV-2 naive patients, 32 (86%) had detectable RBD binding antibodies (Ab) and 18 (49%) neutralizing Ab (NAb) against wild-type (WT) SARS-CoV-2 following primary immunization (two doses of vaccination). Anti-RBD and NAb titers were significantly lower in allo-HCT recipients than in healthy adults. Furthermore, among allo-HCT recipients, serological responses were less frequent in patients with moderate/severe chronic graft-versus-host disease (GVHD) as well as in patients who had received the anti-CD20 monoclonal Ab rituximab in the year before vaccination. Based on these observations, the protocol was amended to provide a booster dose 14–26 weeks after primary immunization (EudractCT # 2021-000673-83).

Here, we report the waning of Ab after primary BNT162b2 immunization and the Ab response to booster immunization (a third dose of vaccination) in 38 of the 40 allo-HCT patients enrolled in our initial study (Canti et al., 2021). Thirty-seven patients were SARS-CoV-2 seronegative at first vaccination, and one patient (#25) was weakly seropositive at first vaccination and diagnosed with COVID-19 6 days after the first vaccine dose and did not receive the second dose (Table S1). RBD binding Ab and immune cell subsets at baseline were quantified as previously reported (Canti et al., 2021). Nab titers that reduced the number of infected wells by 50% (NT50) were used as a proxy for the NAb concentration in serum, as previously reported (Canti et al., 2021; Ariën et al., 2021).

While prior publications have reported the waning of Ab following two doses of mRNA vaccine in healthy subjects (Levin et al., 2021), Ab waning in allo-HCT recipients has not yet been well documented. The booster dose was administered a median of 153 (range, 146–174) days after the first vaccine dose. RBD binding Ab levels decreased from a median of 497 BAU/mL (geometric mean [geomean] 325.7 BAU/mL; 95% CI: 140.0–757.6 BAU/mL) 28 days after the second vaccine dose (49 days after first vaccine) to a median of 152 BAU/mL (geomean 106.8 BAU/mL; 95% CI: 53.1–214.7 BAU/mL) on the day of booster immunization ($p < 0.0001$; among patients with detectable Ab on day 28 after second vaccine, pre-booster values were a median of 24% of those from day 28 after second vaccine) (Figure S1). Nineteen patients had detectable NAb against WT SARS-CoV-2 at day 28 post-dose two (50%). Before booster, 15 patients had detectable NT50 titers (40%), including 1 patient without detectable NAb at day 28 post-dose two. Among them, only 5 patients had detectable NT50 against the Delta variant.

One possibly vaccine-related suspected unexpected serious adverse reaction was observed after the booster vaccination: patient 7 was diagnosed with transverse myelitis on day 72 after booster immunization. Other adverse events are described in the supplemental information.

Binding RBD Ab levels increased from a median of 152 BAU/mL (geomean 106.8 BAU/mL; 95% CI: 53.1–214.7 BAU/mL) on the day of the booster dose to a median of 2,955 BAU/mL (geomean 1,958 BAU/mL, 95% CI: 1,002–3,827 BAU/mL) 28 days later ($p < 0.0001$) (Figure S1A). Of note, 4 of the 5 patients who failed to seroconvert after the two first doses of the vaccine responded to the booster dose. These data are in line with prior reports assessing binding Ab responses to a third dose of mRNA vaccine in

allo-HCT patients (Redjoul et al., 2021a; Maillard et al., 2022).

To our knowledge, the NAb response against SARS-CoV-2 variants to a third-dose vaccine of mRNA vaccine in allo-HCT recipients has not yet been reported. SARS-CoV-2 WT NT50 titers increased from a geomean 52.5 (95% CI: 37.3–73.8) on the day of the booster dose to 566.8 (95% CI: 351.8–913.4) 28 days later ($p < 0.0001$) (Figure S1B). Geometric mean of Delta variant NT50 titers increased from 28.8 (95% CI: 25.4–32.6) on the day of the booster dose to 200.4 (95% CI: 129.3–310.7) 28 days later ($p < 0.0001$). After booster immunization, 33 (87%), 31 (82%), and 23 (60.5%) patients had detectable NAb against the WT, Delta, and Omicron variants, respectively. As previously observed in healthy individuals (Zeng et al., 2021; Gruell et al., 2022), patients had higher NT50 titers against the WT virus (median 1,078, geomean 566.8, $p < 0.0001$) than against the Delta (median 202, geomean 200.4) and the Omicron (median 80.5, geomean 74.4, $p < 0.0001$) variants following booster immunization. Furthermore, there were strong correlations between binding RBD Ab and NAb levels ($p < 0.001$; Figure S1C).

Moderate/severe chronic GVHD ($n = 10$) was significantly ($p < 0.05$) associated with lower levels of RBD binding Ab and of NAb to SARS-CoV-2 WT and Delta variant before and after booster immunization (Figures S1D–S1F). GVHD was also associated with lower NAb titers against the Omicron variant after booster immunization ($p = 0.0002$; only 1 of the 10 patients with chronic GVHD had detectable NAb against Omicron) (Figure S1G). Among patients without moderate/severe chronic GVHD, rituximab administration within the year before first vaccination was associated with lower RBD binding Ab levels before but not after booster immunization.

There was a correlation beween absolute counts of unswitched memory B cells ($r = 0.51$, $p = 0.001$), class-switched memory B cells ($r = 0.40$, $p = 0.01$), naive B cells ($r = 0.35$, $p = 0.03$), and follicular helper T cells ($r = 0.37$, $p = 0.027$) assessed at baseline of the first immunization and anti-RBD-Ab levels assessed after booster immunization.

Finally, we observed six cases of (mild) COVID-19 infection after third vaccination (see supplemental information).

Three prior studies have assessed the impact of a third dose vaccine in allo-HCT recipients (Redjoul et al., 2021b; Le Bourgeois et al., 2021; Maillard et al., 2022). Redjoul et al. assessed the efficacy of a third dose of vaccine in 42 patients with anti-spike RBD IgG < 4,160 AU/mL (as a surrogate for protection) following two doses of the BNT162b2 vaccine. The third dose was given 51 ± 22 days after the second vaccine. Following the third dose, binding Ab increased significantly from 737 ± 1,009 to 11,099 ± 18,607 AU/mL, with 20 patients reaching the 4,160 AU/mL threshold (Redjoul et al., 2021b). Similarly, Le Bourgeois et al. assessed the efficacy of a third dose of vaccine in 80 allo-HCT patients and observed that 9 patients failed to seroconvert after the third-dose regimen, while two patients seronegative after the second vaccine dose seroconverted with the third dose (Le Bourgeois et al., 2021). More recently, Maillard et al. investigated the impact of a third dose vaccine in 181 allo-HCT recipients (Maillard et al., 2022). The third vaccine was given a median of 54 days after dose 2. Twenty-nine of 70 patients (41%) with no Ab response after the first two doses seroconverted, while booster vaccine increased Ab titers in remaining patients. Unfortunately, none of these studies assessed the impact of the third dose vaccine on NAb. Our study observed that all but one patient seroconverted with the three-dose vaccine but that 18% of the patients failed to develop NAb against the Delta and 39.5% against the Omicron variant. Another difference between prior studies and ours is that the delay between second and third vaccine was significantly longer in our cohort. This might explain the high efficacy of the booster dose in our cohort. Further studies are needed to determine whether a forth vaccine dose is useful in patients who failed to achieve NAb after the first three doses.

There are limitations in our study, including the small sample size, the absence of data on T cell response to the vaccine, and the absence of Ab assessment at the time of COVID-19 onset in 5 of the 6 patients diagnosed with COVID-19 after third vaccination.

In conclusion, in contrast to what has been observed after solid organ transplantation (Jurdi et al., 2022), but as observed in solid cancer patients (Zeng et al., 2021), our data indicate that a majority of allo-HCT patients without active moderate/severe chronic GVHD are able to produce NAb against Delta and Omicron variants in response to a third dose of the BNT162b2 vaccine. Whether this response is sufficient to prevent severe COVID-19 remains to be established in larger studies.

SUPPLEMENTAL INFORMATION

Supplemental information can be found online at https://doi.org/10.1016/j.ccell.2022.02.005.

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DECLARATION OF INTERESTS

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Supplemental information

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SUPPLEMENTAL INFORMATION

SUPPLEMENTAL METHODS

SARS-CoV-2-specific binding antibodies were quantified using the FDA-approved WANTAI (Beijing Wantai Biological Pharmacy Enterprise, Beijing, China) SARS-CoV-2 Ab ELISA as previously reported (Canti et al., 2021). The limit of quantification (LOQ) of the assay is 5 BAU/mL. Values below LOQ were attributed an arbitrary value of 2.5 BAU/mL in the graphs and statistical analyses (Pannus et al., 2021).

SARS-CoV-2 neutralizing antibodies against wild type (WT), Delta and Omicron variant strains were quantified as previously reported (Mariën et al., 2021) (Ariën et al., 2021). The Reed-Muench method was used to calculate the neutralizing Ab titer that reduced the number of infected wells by 50% (NT50), which was used as a proxy for the neutralizing Ab concentration in the sample. Values below LOQ were arbitrarily attributed a value of 25 in the graphs and statistical analyses while values above 1600 were arbitrarily attributed a value of 1700.

Absolute counts of unswitched memory B cells, class-switched memory B cells, naive B cells, naive T cells, and follicular helper T cells were quantified as previously reported (Canti et al., 2021).

Comparisons of Ab titers between two time points were assessed using Wilcoxon matched-pairs signed rank tests while comparisons of Ab titers between groups were assessed with the Mann-Whitney test. Correlations were calculated using Spearman r correlation tests. Statistical analyses were carried out with Graphpad Prism 9.0 (Graphpad Software, San Diego, CA, USA).

Ab waning after day 49

Of note 3 of the 38 patients were given i.v. Ig (Privigen^{R}) between the second and third dose of the vaccine. Their anti-RBC Ab on days 49 and at booster dose were 179 and 181 BAU/mL, 44 and 11 BAU/ML, and 2652 and 154 BAU/mL, respectively.

Geometric mean of NT50 titers decreased from 70.3 (95% CI: 46.9-105.4) on day 49 to 52.5 (95% CI: 37.3-73.8) on the day of the booster dose (P = 0.0008).

Safety of the booster dose

Four serious adverse events (SAEs) were reported during the 28-day period after the booster dose. Patient #4 experienced catheter infection 28 days after booster dose. Patient #19 was diagnosed with FLT3-ITD AML relapse on day 7 after booster dose. It was her second relapse after transplantation and she has started on gilteritinib. She unfortunately succumbed from AML 116 days after booster dose. Patient #21 was diagnosed with gastric cancer one week before the booster dose and was hospitalized on day 25 after booster vaccination for surgery. Finally, patient #22 was diagnosed with AML relapse on day 28 after booster dose. He was rescued with a second allo-HCT following a sequential conditioning regimen. These four SAEs were considered as not related to the vaccine. In addition to these serious adverse events, one patient (patient #28) reported persistent exertional dyspnea starting after booster vaccine. She had no evidence of myocarditis with normal cardiac echography and normal cardiac enzymes. She also had normal hemoglobin level, normal CT angiography of the chest and normal pulmonary function tests. Finally, one Suspected Unexpected Serious Adverse Reaction (SUSAR) was observed. Patient #7 was diagnosed with transverse myelitis on day 72 after booster dose. She was treated by high-dose steroids with improvement of her neurological condition. This complication was considered possibly related with the vaccine.

Serological response to the booster dose

The only patients who failed to seroconvert with the 3-dose schedule was a patient with extensive chronic GVHD who was on ruxolitinib and photopheresis at the time of the booster dose.

Neutralizing Ab response following the booster dose

Seven patients (18%) failed to have NAb against the Delta variant after the booster. This included 4 of 9 patients with moderate/severe chronic GVHD at first dose administration (resolved at the time of the booster dose in one of them), one patient diagnosed with moderate/severe chronic GVHD before the second and the third dose and two patients without moderate/severe chronic GVHD but given rituximab in the year before the first vaccination.

Breakthrough COVID-19 cases

We observed six cases of COVID-19 infection after third vaccination. **Patient #3** was diagnosed with COVID-19 on day 27 (Ay.34 Delta variant) after third dose. She had only mild symptoms and was treated with an injection of casirivimab / imdevimab monoclonal antibodies. She had no detectable anti-RBD Ab at the time of the booster dose administration and 29 IU/ml anti-RBD Ab (and no neutralizing Ab) the day of monoclonal antibody administration. **Patient #4** was diagnosed with COVID-19 on day 160 after third dose. She had mild symptoms and was treated with an injection of sotrovimab monoclonal antibodies. She had high anti-RBD levels (2382 BAU/mL) and NAb against Delta (119) and but not NAb against Omicron variants after the booster dose. **Patient #6** was diagnosed with COVID-19 on day 77 (Ay.43 Delta variant) after third dose and was also treated with casirivimab / imdevimab monoclonal antibodies. She also had mild symptoms. This infection occurred despite high anti-RBD levels (3444 BAU/mL) and detectable NT50 Ab against the Delta variant (133) 28 days after the booster dose. **Patient #12** was diagnosed with COVID-19 on day 146 after third dose. She had mild

symptoms and was treated with an injection of sotrovimab monoclonal antibodies. She had high anti-RBD levels (2468 BAU/mL) and NAb against Delta (269) and Omicron (63) variants after the booster dose. **Patient #20** was diagnosed with COVID-19 on day 154 after third dose. He had mild symptoms and did not receive monoclonal antibodies. He had high anti-RBD levels (10095 BAU/mL) and NAb against Delta (594) and Omicron (126) variants after the booster dose. **Patient #32** was diagnosed with COVID-19 on day 133 after third dose. He had no symptoms and was treated with an injection of sotrovimab monoclonal antibodies. He had high anti-RBD levels (7810 BAU/mL) and NAb against Delta (317) and Omicron (87) variants after the booster dose.

Ethics approval and consent to participate

The study was approved by the Comité d'Ethique Hospitalo-Facultaire Universitaire de Liège (EC2021/73, 11 March 2021) and the Federal Agency for Medicines and Health Products of Belgium (EudractCT # 2021-000673-83). Each patient signed a written informed consent to participate in the study.

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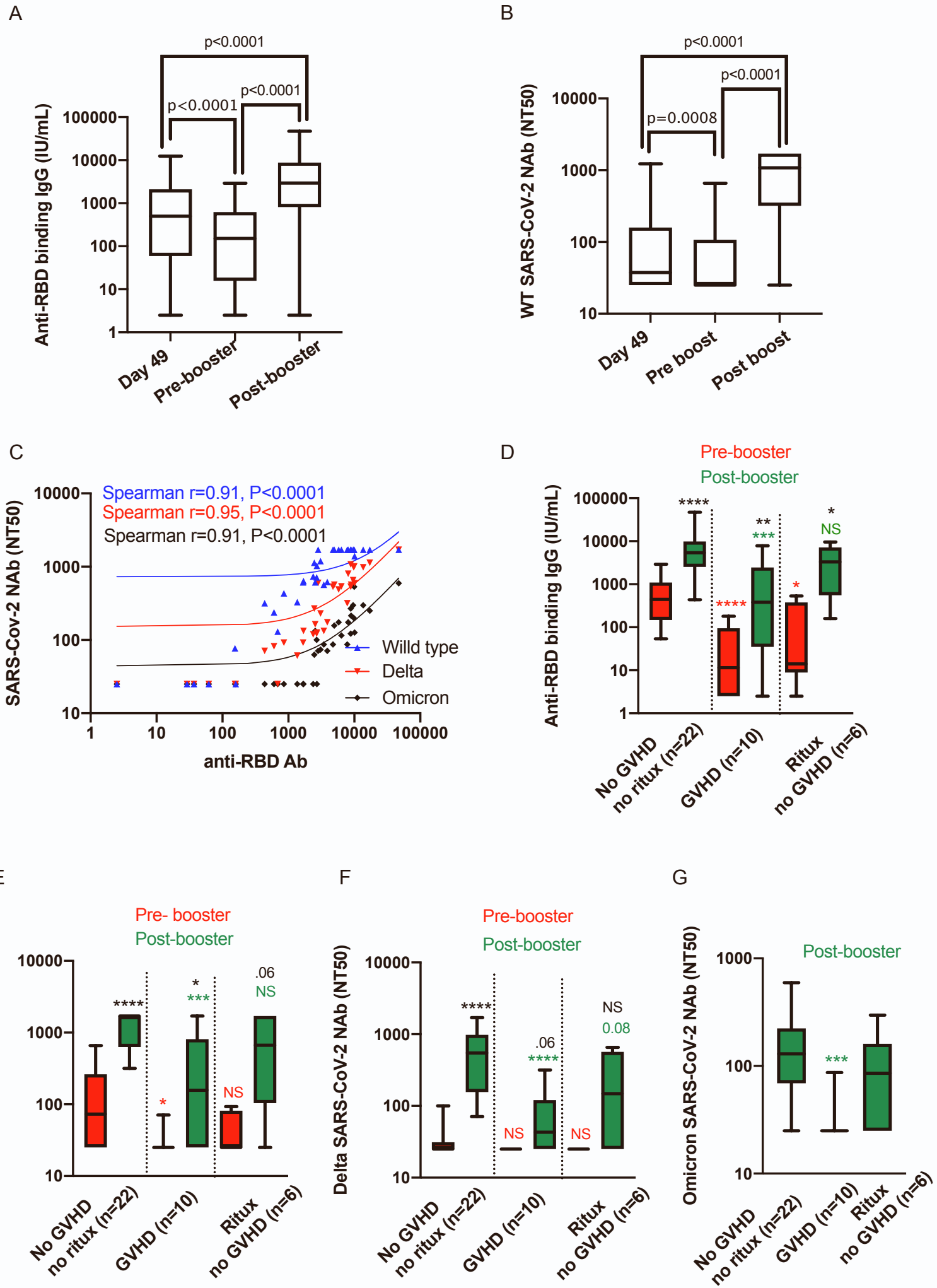
SUPPLEMENTAL TABLE S1. CHARACTERISTICS OF THE PATIENTS (n=38).

Age at vaccination (years); median (min, p25, p75, max)	60 (26, 54, 70, 76)
Sex (# males / # females)	19 / 19
Delay between vaccination and transplantation (months); median (min, p25, p75, max)	31 (6, 14, 42, 58)
Donor type (# MSD / MUD/ MMUD / Haplo)	8 / 24 / 1 / 5
Conditioning regimen (# patients)	
Fludarabine + 2 Gy TBI	5
Fludarabine + Melphalan	16
Fludarabine + busulfan	4
Cyclophosphamide + 12 Gy TBI	6
Thiotepa + busulfan + fludarabine	2
Sequential	3
Fludarabine + Cyclophosphamide + 2 or 4 Gy TBI	2
ATG (# yes / no)	27 / 11
PTCY (# yes / no)	6 /32
Chronic GVHD	
Never / only mild	27
Prior moderate/severe solved[(1)]	1
Ongoing moderate / severe[(2)]	10
Rituximab (none or ≥2yrs, ≥ 1 but < 2 yrs, > 6 months but < 1 yr at first vaccine), # of patients	26, 5, 7[(3),(4)]
Systemic immunosuppression at inclusion	
None	24
Tacrolimus	5
Photopheresis	1

Photopheresis + mPDN < 32 mg/day	1
MMF	1
MMF + mPDN < 32 mg/day	1
Sirolimus	1
Sirolimus + mPDN < 32 mg/day	2
Photopheresis + ruxolitinib	2

(1) > 3 months out of systemic immunosuppression; (2) including one patient diagnosed with moderate/severe chronic GVHD between the second and the third dose (and treated by MMF) and one patient whose moderate/severe chronic GVHD resolved between the second and the third dose; (3) including one patient with moderate/severe chronic GVHD and 6 patients without moderate/severe chronic GVHD; (4) including 2 patients who had received the rituximab < 1 year before the third dose vaccine . MSD, HLA-identical sibling donor; MUD, 10/10 HLA-matched unrelated donor; MMUD, 1/10 HLA-mismatched unrelated donor; Haplo, HLA-haploidentical donor; TBI, total body irradiation; ATG, anti-thymocyte globulin; PTCY, post-transplant cyclophosphamide; MMF, mycophenolate mofetil; mPDN, methyl-prednisolone.


A
p<0.0001
p<0.0001
p<0.0001
Anti-RBD binding IgG (IU/mL)
100000
10000
1000
100
10
1
Day 49
Pre-booster
Post-booster
B
p<0.0001
p<0.0001
p=0.0008
WT SARS-CoV-2 NAb (NT50)
10000
1000
100
10
Day 49
Pre boost
Post boost
C
Spearman r=0.91, P<0.0001
Spearman r=0.95, P<0.0001
Spearman r=0.91, P<0.0001
SARS-Cov-2 NAb (NT50)
10000
1000
100
10
1
10
100
1000
10000
100000
anti-RBD Ab
Willd type
Delta
Omicron
D
Pre-booster
Post-booster
Anti-RBD binding IgG (IU/mL)
100000
10000
1000
100
10
1
****
**
***
*
NS
****
*
No GVHD
no ritux (n=22)
GVHD (n=10)
Ritux
no GVHD (n=6)
E
Pre- booster
Post-booster
WT SARS-CoV-2 NAb (NT50)
10000
1000
100
10
****
*
***
.06
NS
*
NS
No GVHD
no ritux (n=22)
GVHD (n=10)
Ritux
no GVHD (n=6)
F
Pre-booster
Post-booster
Delta SARS-CoV-2 NAb (NT50)
10000
1000
100
10
****
NS
.06
****
NS
0.08
NS
NS
No GVHD
no ritux (n=22)
GVHD (n=10)
Ritux
no GVHD (n=6)
G
Post-booster
Omicron SARS-CoV-2 NAb (NT50)
1000
100
10
***
No GVHD
no ritux (n=22)
GVHD (n=10)
Ritux
no GVHD (n=6)

SUPPLEMENTAL FIGURE S1. (A-B). Ab waning and Ab response to the third vaccine dose. Dynamics of (A) RBD binding Ab (n=38) and (B) NAb (NT50) (n=38) against WT SARS-CoV-2 from day 49 after first dose of mRNA vaccine to pre-booster immunization and 28 days after booster immunization. Ab levels were compared using the Wilcoxon matched-pairs signed rank tests. **(C) Spearman correlations between RBD binding Ab and NAb against WT, Delta and Omicron SARS-CoV-2 variant titers** post-booster immunization. **(D-G): Ab responses to mRNA vaccination according to the presence of moderate/severe chronic GVHD at first and/or third vaccine dose or rituximab administration within the first year before the first vaccine dose**. (D) RBD binding Ab (n=38). (E) NAb (NT50) against WT SARS-CoV-2 (n=38). (F) NAb (NT50) against SARS-CoV-2 Delta variant (n=38). (G) NAb against the Omicron variant (only assessed after booster dose) (n=38) *: $p<0.05$; **: $p<0.01$; ***: $p<0.001$; ****: $p<0.0001$. Red stars refer to Mann-Whitney tests comparing pre-booster titers between subgroups. Green stars refer to Mann-Whitney tests comparing post-booster titers between subgroups. Black stars refer to Wilcoxon matched-pairs signed rank tests comparing pre- and post-boost values within subgroups. In panels A-B and D-G, box extends from the 25^{th} to 75^{th} percentiles, horizontal line shows the median, and whiskers go down to the smallest value and up to the largest.