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TRANSPLANT INFECTIOUS DISEASE

BRIEF COMMUNICATION

Antibody response to mRNA SARS-CoV-2 vaccination in 182 patients after allogeneic hematopoietic cell transplantation

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Abstract

Introduction: Patients after allogeneic stem cell transplantation are at high risk for infection-related complications, and vaccination efficacy might be impaired depending on the immune reconstitution. In this study, we evaluate their response to mRNA vaccines against SARS-CoV-2.

Methods: During routine follow-up visits, patients were asked about their vaccination status and if they had a previous infection with SARS-CoV-2. In fully vaccinated patients, the antibody titer was measured using the Roche Elecsys Anti-SARS-CoV-2 S test. A titer of <1 U/L was considered as negative, titers of ≥250 U/ml as a high antibody titer, and a titer of 50–249 U/ml as a low antibody titer. Patient characteristics were evaluated by chart review to identify risk factors for poor vaccination response.

Results: The majority of patients developed a high antibody titer (138 out 182 patients, 75.8%). Risk factors for a low antibody titer were immunosuppressive therapy, a lymphocyte count <0.9 G/L, ongoing treatment for the underlying malignancy, and active graft-versus-host disease (GvHD). Donor type, underlying disease, a previous SARS-CoV-2 infection, and sex did not significantly influence the response to the vaccination.

Discussion: While patients undergoing allogeneic stem cell transplantation have been excluded from the initial registration trials, our real-world experience with a large patient cohort confirms the data of previous studies, showing that most patients do have a good response to mRNA vaccines against SARS-CoV-2. Nevertheless, a significant proportion of patients shows an inadequate vaccination, which can be improved after a third vaccination in most cases despite immunosuppressive therapy.

KEYWORDS
allogeneic hematopoietic cell transplantation, mRNA vaccination, post-transplant care, SARS-COV-2 vaccination

Abbreviations: GvHD, graft-versus-host disease; HCT, hematopoietic cell transplantation

1 | INTRODUCTION

The unprecedented fast development of several vaccines against SARS-CoV-2 has brought back hope in the battle against the pandemic. Patients after allogeneic hematopoietic cell transplantation (HCT) present a unique group with high risks of infection-related complications.[1] Revaccination post transplant prevents loss of protective immunity for vaccine-preventable diseases, but vaccination efficacy depends on immune reconstitution. mRNA vaccines represent a new generation of vaccines. Randomized trials have shown high safety and efficacy for prevention of severe SARS-CoV-2 infection, but recipients of allogeneic HCT were not included into these trials.[2,3]

2 | METHODS

Patients after allogeneic transplant were systematically asked about their vaccination status at their routine follow-up visits. If they had received two SARS-CoV-2 vaccinations or one dose of vaccination after a COVID-19 infection (as in these patients only one vaccination had been suggested at that time by the Federal Office of Public Health Switzerland), SARS-CoV-2 Spike antibody titers were measured.

Only patients who consented to the general research were assessed and data were anonymized after finishing the data collection process. One hundred eighty-two patients with antibody measurements between March 23 and September 1, 2021 were included.

Immunosuppressive therapy as well as maintenance or preemptive therapy for underlying malignancy were recorded and graft-versus-host disease (GvHD) was documented. Patients were considered to have an immunosuppressive therapy if they had one or more of the following medications: calcineurin inhibitor (ciclosporin or tacrolimus), prednisone, mycophenolate mofetil, ruxolitinib, ibrutinib, and/or rituximab within the last 6 months or ongoing extracorporeal photopheresis. Patients' characteristics, the underlying disease, and transplant characteristics were collected from the patients' charts.

SARS-CoV-2 vaccinations were organized by the authorities, hence patients were vaccinated in vaccination centers in their local communities. Only the two mRNA vaccines, BNT162b2 by BioNTech Pfizer and mRNA-1273 by Moderna, both approved by the Swiss Agency for Therapeutic Products (Swissmedic) were available. Vaccines were allocated by the authorities on an area-by-area basis. Therefore, patients' allocation to a vaccine was based on the availability of the vaccine as provided by the authorities. All patients who underwent two vaccinations got the same type of vaccine twice with 1-month interval in between.

Antibody titers were measured using the Elecsys Anti-SARS-CoV-2 Spike assay on the cobas e801 platform (Roche, Rotkreuz, Switzerland) as part of the routine laboratory tests performed on site in the laboratory of the University Hospital Basel.[4] Titers of <1.0 U/ml were considered as negative, a titer of 1–249 U/ml as a low antibody, and titers of ≥250 U/ml as a high antibody titer. By dilution, a maximum titer of 2500 U/ml could be measured, values above were given as >2500 U/ml and were assumed to be 2500 U/ml for the statistical analyses. For those patients with a third vaccination because of an insufficient antibody titer (negative or low), a further antibody titer measurement was recommended to assess response and data were collected by chart review.

Statistical analyses were performed using SPSS. Statistical significance was evaluated with chi-square test and a p-value <.05 was considered as statistically significant.

3 | RESULTS

Antibody titers were measured in 182 patients with a median age of 56 years (range 21–80 years) (Table 1). The median interval between transplantation and the first vaccination was 3.25 years (range 3 months to 34 years). Median time between second vaccination and antibody measurement was 51 days (range 6–187 days). In all patients with no measurable or a low antibody titer, this interval was at least 2 weeks. No significant difference in antibody levels could be detected among patients with an interval between last vaccination and antibody measurement less than 60 days ($n = 115$) and individuals with a longer interval. Both BNT162b2 by BioNTech Pfizer and mRNA-1273 by Moderna were almost equally administered (47.3% and 52.7%).

At the time of the first vaccination, 93 (51%) patients had either acute or chronic GvHD, with 77 (42%) under immunosuppressive therapy. More than a quarter of patients (51, 28%) had lymphopenia in the last full blood count before vaccination. GvHD treatment included calcineurin inhibitors in 58 (31.9%) patients and steroids in 22 (12.1%) patients, 15 (8.2%) patients received a combination of both. Overall, 18 (9.9%) patients received second-line immunosuppressive therapy with mycophenolate mofetil, ruxolitinib, or ibrutinib. Two patients (1.1%) were treated with an anti-CD20 antibody and four (2.2%) patients with an anti-CD38 antibody within 6 months prior to the first vaccination. Five patients (2.7%) underwent photopheresis treatment. Intravenous immunoglobulins were given to 17 (9.3%) patients within the last 3 months before vaccination. An ongoing antitumor treatment with either hypomethylating agents or targeted therapies, such as tyrosine kinase inhibitors, was given to 27 patients (14.8%).

Ongoing immunosuppressive therapy was associated with a higher risk for impaired response to vaccination. Only 62.3% (48/77) patients with at least one immunosuppressive therapy had a high antibody titer compared to 84.8% (89/105 patients) in patients without immunosuppressive therapy. Out of 24 patients with more than one immunosuppressive therapy, eight had no detectable and five a low antibody titer. Accordingly, an adequate vaccination response could be demonstrated in only 45% (11 patients). Both patients after CD20 antibody therapy did not have a measurable antibody titer. The three patients with CD38 antibody treatment but no concomitant immunosuppressive therapy, all showed a low antibody titer.

Furthermore, patients with a lymphocyte count below normal ($<0.9 \times 10^9$/L) prior to the first vaccination, an interval of less than a year since the allogeneic transplantation, and an ongoing antitumor treatment had significantly more often low antibody titers. There was a nonsignificant trend to a poorer response in case of active acute or

TABLE 1 Patient characteristics

	Overall	Negative antibody titer	Low antibody titer	High antibody titer	*p*-Value
Number of patients, *n* (%)	182 (100)	15 (8.2)	30 (16.5)	137 (75.3)	
Median age at vaccination, years (range)	56 (21–80)	60 (35–74)	59 (24–75)	56 (21–80)	
Sex, *n* (%)					.654
Female	62 (34.1)	4 (26.7)	12 (40.0)	46 (33.6)	
Male	120 (65.9)	11 (73.3)	18 (60.0)	91 (66.4)	
Interval transplant to first vaccination					
Interval in months, median (range)	39 (3–410)	19 (3–139)	22 (3–223)	45 (3–410)	
Transplantation <1 year before vaccination, *n* (%)	32 (17.6)	5 (33.3)	10 (33.3)	17 (12.4)	.006
Transplantation ≥1 year before vaccination, *n* (%)	150 (82.4)	10 (66.7)	20 (66.7)	120 (87.6)	
Median interval second vaccination to antibody measurement, days (range)	51 (6–187)	38 (15–120)	44 (13–131)	54 (6–187)	
Indication for transplant, *n* (%)					.700
ALL	25 (13.7)	1 (6.7)	2 (6.7)	22 (16.1)	
MDS/AML	93 (51.1)	9 (60.0)	15 (50.0)	69 (50.4)	
Lymphoma	20 (11.0)	3 (20.0)	3 (10.0)	14 (10.2)	
MPN	25 (13.7)	1 (6.7)	6 (20.0)	18 (13.1)	
Other	19 (10.4)	1 (6.7)	4 (13.3)	14 (10.2)	
Vaccine, *n* (%)					.117
mRNA-1273	96 (52.7)	5 (33.3)	13 (43.3)	78 (56.9)	
BNT162b2	86 (47.3)	10 (66.7)	17 (56.7)	59 (43.1)	
Donor, *n* (%)					.616
Matched related donor	65 (35.7)	3 (20.0)	11 (36.7)	51 (37.2)	
Matched unrelated donor	81 (44.5)	10 (66.7)	14 (46.7)	57 (41.6)	
Mismatched related donor	16 (8.7)	2 (13.3)	1 (3.3)	13 (9.5)	
Mismatched unrelated donor	18 (9.9)	0 (0)	3 (10.0)	15 (10.9)	
Unrelated donor	2 (1.1)	0 (0)	1 (3.3)	1 (0.7)	
Immunosuppressive therapy at first vaccination, *n* (%)					.000
Yes	77 (42.3)	14 (93.3)	15 (50.0)	48 (35.0)	
No	105 (57.7)	1 (6.7)	15 (50.0)	89 (65.0)	
Lymphocyte count before first vaccination, *n* (%)					.000
$<0.9 \times 10^9$/L	51 (28.0)	9 (60.0)	15 (50.0)	27 (20.0)	
$>0.9 \times 10^9$/L	129 (70.9)	6 (40.0)	15 (50.0)	108 (80.0)	
No previous FBC available	2 (1.1)				
Acute or chronic GvHD, *n* (%)					.055
Yes	93 (51.1)	12 (80.0)	16 (53.3)	65 (47.4)	
No	89 (48.9)	3 (20.0)	14 (46.7)	72 (52.6)	

(Continues)

TABLE 1 (Continued)

	Overall	Negative antibody titer	Low antibody titer	High antibody titer	*p*-Value
Ongoing tumor treatment at first vaccination, *n* (%)					.001
Yes	27 (14.8)	2 (13.3)	11 (36.7)	14 (10.2)	
No	155 (85.2)	13 (86.7)	19 (63.3)	123 (89.8)	
SARS-CoV-2 infection before second vaccination, *n* (%)					.226
Yes	12 (6.6)	1 (6.7)	0 (0)	11 (8.0))	
No	170 (93.4)	14 (93.3)	30 (100)	126 (92.0)	

Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; GvHD, graft-versus-host disease; MDS, myelodysplastic syndrome; MPN, myeloproliferative neoplasm.

chronic GvHD. Patients' sex, age, underlying disease, and donor characteristics were not associated with the antibody titer after vaccination.

Patients vaccinated with mRNA-1273 by Moderna showed a better response compared to patients vaccinated with BNT162b2 by BioNTech Pfizer with a titer ≥250 U/L in 81.3% (78 patients) and 68.6% (59 patients), respectively (*p*-value .048). Nevertheless, this was not significant when comparing the three groups with a negative, low, and high titer.

Within our cohort, 12 patients had a proven COVID-19 infection. One patient was tested positive after the first vaccination (confirmed by PCR test), the other 11 patients were tested positive before getting vaccinated. As vaccination guidelines in Switzerland issued by the authorities were continuously adapted, six patients received two vaccinations after their infection while the other six received only one vaccination in an earlier phase of the pandemic. All but one of these patients had a high antibody titer. The one patient with a negative titer did receive two vaccinations but was under an immunosuppressive therapy for chronic GvHD with mycophenolate mofetil.

Two patients reported severe complications after their vaccination. One of them had persistent fever and a systemic inflammatory reaction having had a COVID-19 infection 6 months earlier. The other patient developed a perimyocarditis after the first vaccination and had to be hospitalized. Despite this inflammatory response, he only developed a low antibody titer (110 U/ml) and underwent therefore uneventful second vaccination 5 months apart with colchicine prophylaxis. Mild side effects were not systematically assessed.

Out of the 45 patients with an insufficient antibody titer after two vaccinations, data about a third vaccination were available in 10 out of 15 patients (66.6%) with a previously negative titer and 21 out of 30 patients (70%) with a low titer. Out of these 31 patients, 20 patients (64.5%) had a titer of >250 U/ml after their third vaccination, with 16 (48.5%) having a titer above the quantifiable range (>2500 U/ml). Eleven patients showed no adequate response (titer ≤250 U/ml) after the third vaccination. All but one had ongoing immunosuppressive therapy, with the remaining having severe hypogammaglobulinemia with recurrent substitution therapy. Two of the 45 patients had a SARS-CoV-2 infection before their third vaccination. One patient with a previous titer of 202 U/ml had a mild SARS-CoV-2 infection with an increase of his antibody titer to 1936 U/ml after symptomatic treatment, the other patient had a more severe infection with COVID pneumonia and received antibody treatment with Casirivimab und Imdevimab as well as Remdesivir. Expectedly, the antibody titer was >2500 U/L thereafter.

4 | DISCUSSION

Rebuilding protective immunity is of paramount importance for patients after allogeneic HCT. Several reports showed that SARS-CoV-2 vaccination is significantly less effective in patients after allogeneic HCT compared to the general population,[5–13] reporting seroconversion in 68%–83%. As the vaccination is safe and feasible, it remains a pivotal part in preventing COVID-19 in this vulnerable patient population. Some reports[6–8] include only patients vaccinated with BNT162b2 (BioNTech Pfizer), including two prospective trials,[12,13] while others[5,9–11] include results after vaccination with BNT162b2 or mRNA-1273 (Moderna).

In our patients, we found a response to vaccination with either BNT162b2 or mRNA-1273 in 92% of patients, with high titers in 75% (Figure 1). The rate of any antibody response is slightly higher than previously reported and might be partially explained by the higher median interval between HCT and vaccination of 39 months compared with roughly 2 years in other studies.[6,8,10,11] We can confirm the findings of other reports[6,7,10,11] that time interval less than 1 year between HCT and vaccination is a risk factor for an insufficient antibody response, while others have not.[9] Ongoing antitumor therapy (high antibody titers in 14/27, 52%), any type of systemic pharmacological immunosuppression at the time of vaccination (48/77, 62%), and lymphopenia (27/51, 53%) were other factors significantly associated with sufficient antibody response, going in line with larger study cohorts with mainly BNT162b2 vaccination.[8,11] Age had no impact on response rate.

Even with risk factors, a sufficient serologic response with high antibody titers can be observed in more than 50% of patients, with another 20%–30% of patients with an insufficient response can be improved by a third vaccination.[11,14] In our cohort, this proportion was even higher,

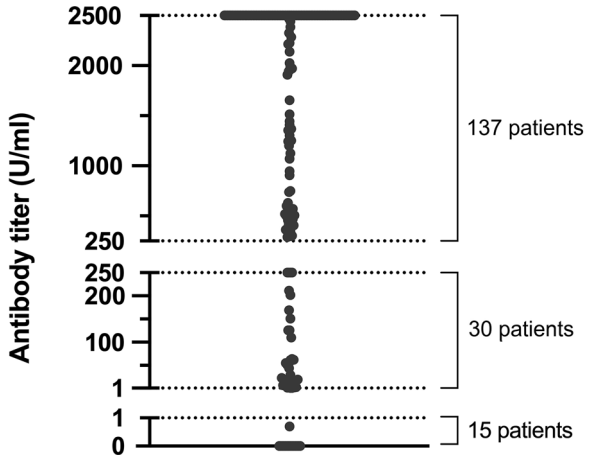

FIGURE 1 Antibody titer after second SARS-CoV-2 vaccination. Out of 182 patients, 15 patients had a negative antibody titer (antibody titer 0 to <1 U/ml) and 30 patients a low antibody titer (1–249 U/ml). Among the 137 patients with a highly positive antibody titers (≥250 U/ml), 82 patients had an antibody titer above the quantifiable range of the test (shown as 2500 U/ml)

supporting the approach of a full-dose third vaccination in patients with inadequate response after two vaccinations.

Among 73 patients with none of the described risk factors, all showed a serological response, but still two (3%) had only a low antibody titer. Both had BNT162b2 vaccine. In our series, patients vaccinated with mRNA-1273 showed a higher rate of sufficient antibody response (titer ≥250 U/L) compared to BNT162b2, suggesting that mRNA-1273 might be slightly more effective also in this patient population.

Our study has some limitation. Due to the retrospective study design, the time interval between last vaccination and antibody assessment was not standardized. Although there was no significant difference in antibody levels between patients assessed within less than 60 days versus longer time intervals, we cannot exclude the patients in the latter group might had different characteristics, allowing longer intervals between visits. Furthermore, it was not possible to collect data on mild side effects or mild transient manifestations of GvHD. However, both a careful interim history as well as a systematic assessment for signs and symptoms of GvHD are part of every follow-up visit so that both serious side effects and new or aggravating GvHD manifestations would have been noted. Finally, we cannot exclude asymptomatic infections as an additional reason for measurable antibody levels without baseline serology, but we believe that due to the high awareness of the symptoms and a low threshold for testing among patients and closely associated persons, the rate of oligo- or asymptomatic infections are likely low. Of note, this study was done before appearance of the SARS-CoV-2 Omicron variant

In conclusion, mRNA vaccination shows a favorable risk profile in recipients of allogeneic HCT.[12,13] In contrast to other post-transplant vaccinations that are usually performed at the transplant center, all patients were vaccinated by community-operated vaccination centers in the catchment area, making it more challenging for a transplant team to assess response to vaccination. Response rate is high in patients without pharmacological immunosuppression, lymphopenia, or active antitumor therapy, especially when the patient is more than 1 year after transplant. mRNA-1273 seems slightly more immunogenic than BNT162b2. However, measurement of antibody response is recommended in all patients to confirm successful seroconversion, which is successful in a significant proportion of patients.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

AUTHOR CONTRIBUTIONS

Astrid Beerlage, Luca Valore, Roby Mathew, Till Junker, Beatrice Drexler, and Jörg Halter collected the clinical data. Astrid Beerlage, Karoline Leuzinger, and Hans H. Hirsch collected the laboratory results. Astrid Beerlage, Jakob R Passweg, and Jörg Halter performed the statistical analysis. Astrid Beerlage and Jörg Halter prepared and edited the manuscript. All authors revised the manuscript.

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