Serological response following BNT162b2 anti-SARS-CoV-2 mRNA vaccination in haematopoietic stem cell transplantation patients

Adult patients with haematological malignancies (HM) and coronavirus disease 2019 (COVID-19) have a higher mortality than healthy subjects.[1–3] In particular, haematopoietic stem-cell transplantation (HSCT) recipients have a poor prognosis,[4,5] strongly supporting the role of vaccination. Patients with HM also show an attenuated immune response to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)infection,[6] predicting a low rate of seroconversion after vaccination, as confirmed in several recent studies, particularly in B cell malignancies.[7–13] However, autologous or allogeneic HSCT recipients were reported to have the highest numerical responses.[7]

In the absence of dedicated trials and considering the importance of real-life data on anti-SARS-CoV-2 vaccination in HSCT recipients, we conducted a single-institution, prospective, cohort study. Eligibility criteria included autologous or allogeneic HSCT received ≥3 months before the first dose and completion of the programme. Patients with previous SARS-COV2 infection were excluded. Age and sex matched healthcare workers were employed as healthy controls (HC). Study population and control group received two doses of COVID-19 mRNA vaccine (Pfizer BioNTech) on days 1 and 21 between 1 April and 15 May 2021. Quantitative determination of anti-spike immunoglobulin G (IgG) antibodies was performed with the Abbott immunoassay. Results were reported as arbitrary units (AU), with a positivity cut-off of ≥50 AU/ml.

Primary objectives of the study were the rate of response to the vaccine and the titre of anti-spike antibodies, 4 weeks after vaccination completion. Secondary outcomes included comparisons of IgG titres between HSCT recipients and HC, as well as the identification of factors influencing the response.

Comparisons between groups were performed using Mann–Whitney test. Statistical analyses were carried out using GraphPad Prism version 8.3.0 (GraphPad Software Inc., San Diego, CA, USA).

Table I. Patients' characteristics.

	Allo-HSCT (N = 62)	Auto-HSCT (N = 52)
Sex: M/F, *n*	33/29	32/20
Age, years, median (range)	56 (28–70)	57 (20–71)
Haematological disease (*n*)	AML (38), ALL (5), SAA (4), CML (3), MDS (3), NHL (3), MM (2), CMML (1), MF (1), CLL (1), HL (1)	MM (26), NHL (19), HL (7)
Disease status at vaccination: active disease/complete remission, *n*	1/61	9/43
G1/G2/G3, *n*	14/23/25	5/29/18
Conditioning regimen, *n*	47 MAC/15 RIC	26 MEL200 23 FEAM 2 BEAM 1 TEAM
HSCT type, *n*	Sibling/MUD/HAPLO	Single/double (MM)
	28/31/3	34/18
Donor sex: M/F, *n*	39/23	N/A
Donor age, years, median (range)	34 (16-62)	N/A
a-GVHD/c-GVHD	22/17	N/A

M: male; F: female.

a-GVHD, acute graft-*versus*-host disease; c-GVHD, chronic graft-*versus*-host disease; allo-HSCT, allogeneic haematopoietic stem cell transplantation; auto-HSCT, autologous haematopoietic stem cell transplantation; ALL, acute lymphoblastic leukaemia; AML, acute myeloid leukaemia; BEAM, carmustine, etoposide, cytarabine, melphalan; CLL, chronic lymphocytic leukaemia; CML, chronic myeloid leukaemia; CMML, chronic myelomonocytic leukaemia; FEAM, fotemustine, etoposide, cytarabine, melphalan; G1, Group 1 (vaccination within 1 year after transplantation); G2, Group 2 (vaccination between 1 and 5 years after transplantation); G3, Group 3 (vaccination >5 years after transplantation); HAPLO, haploidentical donor; HL, Hodgkin lymphoma; MAC, myeloablative conditioning; MDS, myelodysplastic syndrome; MEL200, melphalan, 200 mg/m^2; MF, myelofibrosis; MM, multiple myeloma; MUD, matched unrelated donor; N/A, not applicable; NHL, non-Hodgkin lymphoma; RIC, reduced-intensity conditioning; SAA, severe aplastic anaemia; TEAM, thiotepa, etoposide, cytarabine, melphalan.

A total of 107 HC [60 males, 47 females; median (range) age 53 (16–69) years] and 114 HSCT patients [65 males, 49 females; median (range) age 56 (20–71) years], were enrolled. Patients' characteristics are reported in Table I. Patients were stratified in three groups, according to the time elapsed from transplant to vaccination: G1 ≤ 1 year (19 patients); G2 1–5 years (52 patients); G3 ≥ 5 years (43 patients).

All HC responded to vaccine, but only 96/114 patients (84%) achieved a response: 47/62 (76%) allogeneic recipients and 49/52 (94%) autologous recipients (Fig 1A,B).

Rate of responders in the different groups and antibody titres are reported in Table II. The median antibody titres did not differ between HC and: (i) all transplanted patients; (ii) allogeneic recipients; (iii) all responders to the vaccine; and (iv) responders in the autologous subgroup (Fig 1C). In contrast, all the autologous recipients had lower antibody titres than HC, whereas allogeneic recipients responding to the vaccine had significantly higher titres than HC. Responders in the allogeneic subgroup showed significantly higher antibody titres than responders in the autologous subgroup (Fig 1C). In G1, all patients, allogeneic recipients and autologous recipients had significantly lower antibody levels than HC, whereas no differences were found in G2. In G3, no differences emerged between HC and either all patients or allogeneic recipients, but autologous recipients had significantly lower titres than HC (Fig 1D–F).

No differences were found when comparing autologous *versus* allogeneic HSCT, age of all patients, age of allogeneic recipients, sex, donor matching, conditioning, age and sex of donors, graft-*versus*-host disease, disease type and number of autologous HSCT (Figure S1A–M). Patients with myeloma in remission phase showed significantly higher antibody titres than patients with active disease (Figure S1N); autologous HSCT recipients younger than 57 years (median age) had significantly higher titres than older patients (Figure S1O).

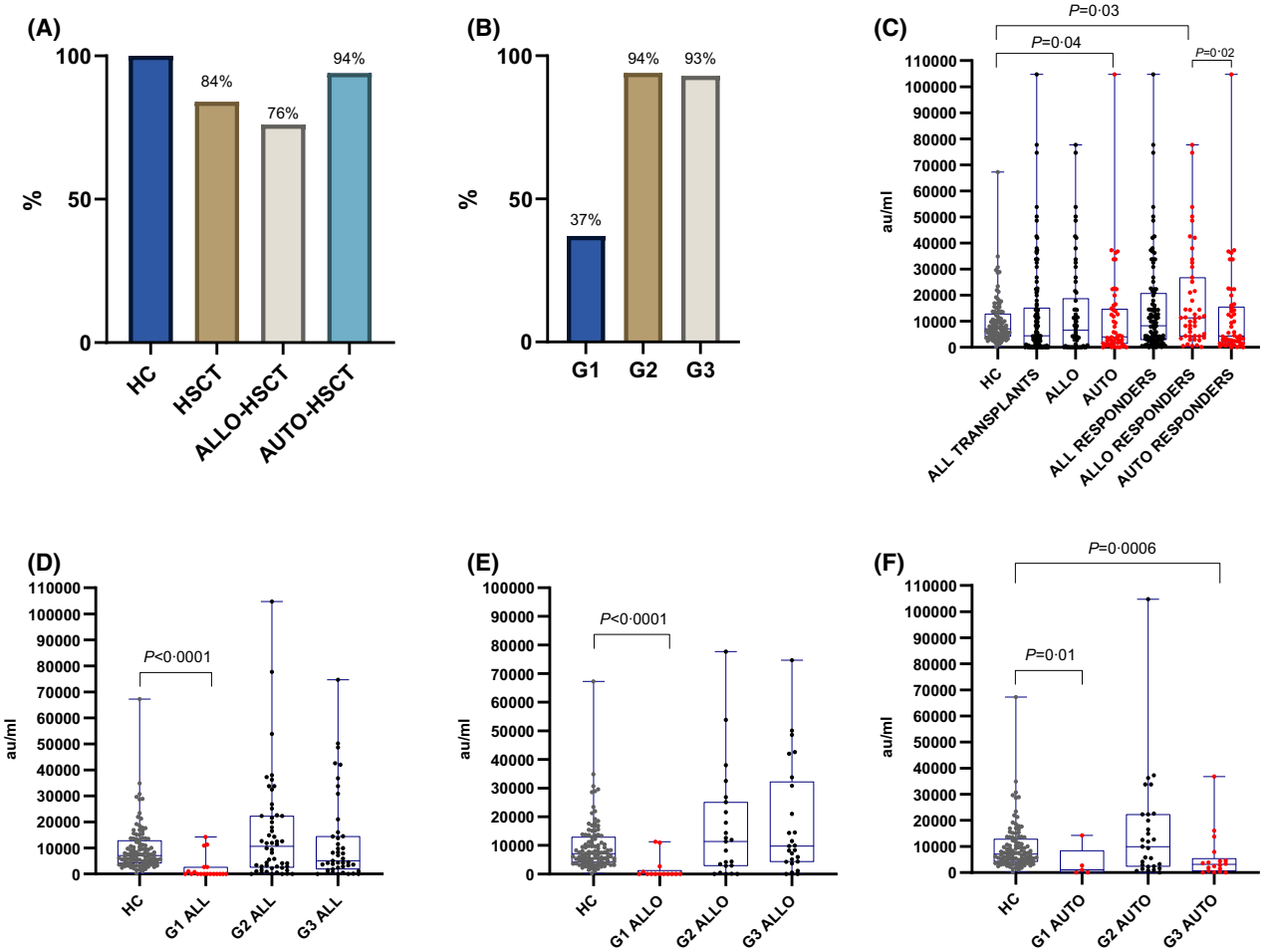

Fig 1. Characteristics of serological response to anti SARS-CoV-2 vaccination in HSCT patients. (A, B) Percentage of patients responding to vaccination. (C–F) Comparisons of anti-SARS-CoV-2 spike IgG titre (AU/ml) among different groups (Mann–Whitney test). Where not indicated, comparisons are not statistically significant. HC, healthy controls; HSCT, haematopoietic stem cell transplant; ALL, all patients; ALLO, allogeneic recipients; AUTO, autologous recipients; RESPONDERS, responders to vaccination (≥50 AU/ml); G1, Group 1 (vaccination within 1 year after transplantation); G2, Group 2 (vaccination between 1 and 5 years after transplantation); G3, Group 3 (vaccination >5 years after transplantation). [Colour figure can be viewed at wileyonlinelibrary.com]

Table II. Rates of response to vaccination and serum anti-SARS-COV2 antibody levels after vaccination.

	Responders/non responders, *n* (%)	Antibody titre, AU/ml, median (mean; range)
Healthy controls	107/0 (100/0)	7132 (9701; 217–67 282)
All patients	96/18 (84·2/15·8)	4481 (12 497; 0–104 689)
Allo-HSCT	47/15 (75·8/24·2)	6·576 (13 701; 0–77 673)
Auto-HSCT	49/3 (94·2/5·8)	4·023 (11 062; 1·3–104 689)
G1	7/19 (36·8/63·2)	13 (2308; 1·3–14 211)
G2	49/52 (94·2/5·8)	10 673 (15 834; 0–104 689)
G3	40/43 (93/7)	5090 (12 694; 1·3–74 676)

Allo-HSCT, allogeneic haematopoietic stem cell transplantation; Auto-HSCT, autologous haematopoietic stem cell transplantation; G1, Group 1 (vaccination within 1 year after transplantation); G2, Group 2 (vaccination between 1 and 5 years after transplantation); G3, Group 3 (vaccination >5 years after transplantation).

No relevant side-effects were recorded. With a median follow-up of 12 weeks, no cases of COVID-19 occurred.

The most relevant available data on the response to a complete vaccination cycle after HSCT refer to 192 autologous and 122 allogeneic recipients.[7] In both groups, median antibody titres, 7–21 days after the second dose, were comparable to HC, with no patients failing to respond. Notably, the large majority of patients had been transplanted >1 year before vaccination. Another recent study found that only 38% of 55 allogeneic recipients, after a single dose of Pfizer-BioNTech or Astra-Zeneca vaccines, had a response. Older age and concurrent immunosuppression were significantly associated with lack of response.[14]

Overall, our present study confirms that most of the transplanted patients respond to a complete vaccination cycle. Responders in the allogeneic group had even higher antibody levels than HC. Conversely, all autologous recipients had significantly lower antibody titres than HC. Around 16% of patients failed to respond at all, mostly among those transplanted within 1 year before vaccination. Allogeneic and autologous recipients had instead antibody levels comparable to HC if vaccination was performed between 1 and 5 years after transplant. Among the patients vaccinated >5 years after HSCT, allogeneic recipients had antibody titres comparable to HC; in contrast, autologous recipients had significantly lower titres than HC.

After allogeneic and autologous HSCT, both the quantitative and functional recovery of B and T cells are delayed up to 1 year or more. This might explain the lower antibody titres and the larger number of non-responders in G1. The reduced serological response of autologous recipients in G3, compared to HC, might reflect the possible role of an underlying, still active disease and of ongoing salvage treatments, in the absence of a 'healthy' and consolidated immune system provided by the donors in the allogeneic setting. As numbers are too low, we cannot draw any definitive inference on other possible predictors of response that would warrant further investigation.

In conclusion, in our present experience, HSCT recipients tolerated the BNT162b2 vaccine well and mounted an antibody response in the majority of cases 1 month after the second dose. However, lack of response was not rare, especially within allogeneic recipients. The main factor influencing the response was the time elapsed from HSCT, with lower responses occurring within the first year from transplant and differences between autologous and allogeneic groups in patients transplanted >5 years before vaccination. Here, a consolidated, complete immune reconstitution in allogeneic HSCT recipients, as well as age and a still-active disease in the autologous setting, could have played opposite pivotal roles and might be considered, if confirmed in larger studies, to plan 'tailored' vaccination programmes.

Conflicts of interest

Immacolata Attolico declares that she has no conflict of interest.

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Supporting Information

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

Fig S1. Comparison of anti-SARS-CoV-2 spike IgG titre (AU/ml) among different groups [Mann–Whitney test; statistically significant differences (<0·05) were observed only in the last two comparisons].

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