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Author(s):
Bankova, Andriyana K.; Pasin, Chloé; Huang, Alice; Cicin-Sain, Caroline; Epp, Selina; Audige, Annette; Mueller, Nicolas J.; Nilsson, Jakob; Vilinovszki, Oliver; Nair, Gayathri; Wolfensberger, Nathan; Hockl, Philipp; Schanz, Urs; Trkola, Alexandra; Kouyos, Roger; Hasse, Barbara; Zinkernagel, Annelies S.; Manz, Markus G.; Abela, Irene A.; Müller, Antonia M. S.

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SHORT REPORT

Antibody response to a third SARS-CoV-2 vaccine dose in recipients of an allogeneic haematopoietic cell transplantation

Andriyana K. Bankova[1] | Chloé Pasin[2,3] | Alice Huang[1] | Caroline Cicin-Sain[1] | Selina Epp[2] | Annette Audige[2] | Nicolas J. Mueller[3] | Jakob Nilsson[4] | Oliver Vilinovszki[1,5] | Gayathri Nair[1] | Nathan Wolfensberger[1] | Philipp Hockl[1] | Urs Schanz[1] | Alexandra Trkola[2] | Roger Kouyos[2,3] | Barbara Hasse[3] | Annelies S. Zinkernagel[3] | Markus G. Manz[1] | Irene A. Abela[2,3] | Antonia M. S. Müller[1,6]

[1]Department of Medical Oncology and Hematology, University Hospital Zürich, Zürich, Switzerland
[2]Institute of Medical Virology, University of Zürich, Zürich, Switzerland
[3]Department of Infectious Diseases and Hospital Epidemiology, University Hospital Zurich, University of Zürich, Zürich, Switzerland
[4]Department of Immunology, University Hospital Zürich, Zürich, Switzerland
[5]Department of Internal Medicine, University Hospital Zürich, Zürich, Switzerland
[6]Department of Blood Group Serology and Transfusion Medicine, Medical University of Vienna, Vienna, Austria

Correspondence
Antonia M. S. Müller, Department of Blood Group Serology and Transfusion Medicine, Währinger Gürtel 18-20, 1090 Vienna, Austria.
Email: antonia.mueller@meduniwien.ac.at

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Summary
Allogeneic haematopoietic cell transplantation (allo-HCT) recipients show impaired antibody (Ab) response to a standard two-dose vaccination against severe acute respiratory syndrome coronavirus-2 and currently a third dose is recommended as part of the primary vaccination regimen. By assessing Ab titres 1 month after a third mRNA vaccine dose in 74 allo-HCT recipients we show sufficient neutralisation activity in 77% of the patients. Discontinuation of immunosuppression before the third vaccine led to serological responses in 50% of low responders to two vaccinations. Identifying factors that might contribute to better vaccine responses in allo-HCT recipients is critical to optimise current vaccination strategies.

KEYWORDS
allogeneic haematopoietic cell transplantation, severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), vaccine response

INDRODUCTION

Allogeneic haematopoietic cell transplantation (allo-HCT) recipients are at increased risk of developing severe coronavirus disease 2019 (COVID-19) with poor overall survival as compared to the general population.[1,2] In a prospective single-centre observational study, including 110 allo-HCT recipients and 86 healthy controls, we recently demonstrated impaired antibody (Ab) responses in this vulnerable patient cohort (62% vs. 100% in the healthy controls) after priming vaccination against severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2).[3] Factors contributing to low humoral response were age >65 years, allo-HCT within the past 12 months, systemic immunosuppressive therapy (IST) and presence of relapsed disease. Our findings are consistent with data from several other single-centre studies that

Andriyana K. Bankova and Chloé Pasin contributed equally as co-first authors.

Irene A. Abela and Antonia M. S. Müller contributed equally as co-senior authors.

showed Ab responses to priming vaccination in HCT recipients ranging from 61% to 78%.[4–9]

In Switzerland a third dose of messenger RNA (mRNA) vaccines (Comirnaty® [BNT162b] or Moderna Covid-19 Vaccine® [mRNA-1273]) was approved in July 2021 for immunocompromised and in September 2021 for healthy individuals. To assess its efficacy we prospectively collected data on humoral responses in our previously described cohort of allo-HCT recipients and healthy controls at the University Hospital Zurich.[3] SARS-CoV-2 Ab titres (immunoglobulin [Ig]G, IgA, and IgM against receptor binding domain [RBD], S1 [subunit 1 of the spike protein], S2 [subunit 2 of the spike protein] and N [nucleoprotein] were assessed by multiplex AntiBody COronavirus Assay [ABCORA]). A neutralising threshold of 17 for the sum of S1 signal over cut-off (SOC) values for IgG, IgA and IgM (sum S1) was previously established.[3,10] The study was approved by the Cantonal Ethics Committee (BASEC No 2021-00261) and was conducted in accordance with the Declaration of Helsinki.

A total of 74 allo-HCT recipients and 62 healthy controls received a third mRNA vaccine dose from July 2021 to April 2022 (Figure S1). We included 52 allo-HCT recipients and 56 healthy controls with available Ab measurements 2–10 weeks after the third vaccination in the analysis (Figure S1; Table S1). Allo-HCT recipients were divided as previously established[3] into those receiving the first vaccine dose between 3 and 12 months (n = 26) or >12 months (n = 26) after allo-HCT. The median age of the allo-HCT recipients was 58 years as compared to 36.5 years in the healthy controls. Male sex was predominant in allo-HCT recipients (37/52 [71.2%]), whereas most healthy controls (43/56 [76.8%]) were females. The median time from second to third dose was comparable in allo-HCT recipients and healthy controls (221 vs. 233 days). The median time from third vaccine dose to Ab titre measurement was 36 days in allo-HCT recipients versus 32 days in healthy controls.

Overall, the AB levels were significantly higher after the third as compared to the second vaccine dose in all groups (p < 0.001; Figure 1A). Notably, the fold change in sum S1 (third/second dose) was greater in the 3–12 months (6.74, 95% confidence interval [CI] 3.69–12.0) than in the >12 months (2.57, 95% CI 1.66–4.00) and healthy control groups (1.52, 95% CI 1.38–1.68). Still, the Ab levels after the third vaccine dose were substantially higher in the >12 months and healthy control groups as compared to the 3–12 months group (p = 0.013). Accordingly, neutralisation titres were also higher in the >12 months versus 3–12 months group (Figure 1B). Moreover, we confirmed that sum S1 > 17 was a good predictor of neutralisation activity (Figure 1C).[10] In total, 40/52 allo-HCT recipients (77%) and all 56 healthy controls demonstrated sufficient neutralisation activity with sum S1 > 17 after the third vaccine dose, whereas in 12/52 allo-HCT recipients (23%) sum S1 did not reach the neutralisation threshold.

Next, we directly compared Ab responses after the second and the third vaccine dose in allo-HCT recipients, focusing on patients who had Ab measurements available 2–8 weeks after the second and after the third vaccination (data available for 43 patients; Figure S2). After the second vaccination, 22/43 allo-HCT recipients had a sum S1 < 17 and were considered low responders (18 in the 3–12 months and four in the >12 months subgroups). Among these, 11 patients (50%; nine in the 3–12 months and two in the >12 months subgroups) achieved a sum S1 > 17 after the third vaccination. In the other 11/22 patients sum S1 remained below the neutralisation threshold.

To identify factors contributing to successful vaccine response after a third vaccine dose in low responders to two vaccine doses we looked at different patient and HCT characteristics at the time of the third vaccination (Table 1). Among the responders after the third vaccination, only 18% had ongoing IST versus 55% in low responders (p = 0.047). In a linear regression model adjusted on responder status after two vaccine doses and IST at third vaccination, we found that IST at third vaccine dose was associated with lower sum S1 value (fold-change of sum S1 value in patients with IST at third dose vs. no IST = 0.30, 95% CI 0.10–0.95, p = 0.048). In addition, more low responders after the third vaccination had a history of moderate/severe graft-versus-host disease (GVHD) at priming vaccination (36.4% vs. 9.1% in responders) and an HLA-matched unrelated donor (72.7% vs. 36.4% in responders). Importantly, underlying lymphoid disease was more prevalent in low responders as compared to responders (36.4% vs. 9.1%). Given the small sample size further studies will be needed to identify additional factors that have an impact on the efficacy of a third vaccine dose in low responders to two vaccine doses.

Finally, in 15/52 (28.8%) allo-HCT recipients SARS-CoV-2 infection was recorded. There was a trend toward higher infection rate in low responders as compared to responders after the third vaccine dose (50% vs. 22.5%, p = 0.08). The majority of patients (n = 14) were infected after January 2022 when Omicron became the dominant variant worldwide and in Switzerland. These 14 patients showed either asymptomatic/mild (13) or moderate (one) disease and did not require hospitalisation. Two of these patients qualified for monoclonal Ab treatment with sotrovimab according to local criteria at that time. Only one patient with the Delta variant, as identified per SARS-CoV-2 sequencing, had a severe disease course and was hospitalised. This patient was a low responder after three vaccine doses and received monoclonal Ab treatment with casirivimab/imdevimab in combination with dexamethasone and remdesivir.

In two recent prospective studies a third vaccine dose led to augmentation of both cellular and humoral responses in immunocomprimised patients with haematological malignancies (e.g., multiple myeloma and B-cell lymphoma).[11,12] For HCT recipients, several single centre retrospective studies demonstrated encouraging results of third vaccination, even in those who did not respond to priming vaccination.[6,13,14] Abid et al.[13] reported a seroconversion rate of 59% in 75 previous non-responders. The study by Maillard et al.[6] investigated humoral responses after a third vaccine dose in 181 allo-HCT recipients and demonstrated seroconversion in 29/70 non-responders and a significant increase in Ab titres in 39/46 low responders. Similarly, the study by Redjoul et al.[14] found a significant increase in the spike

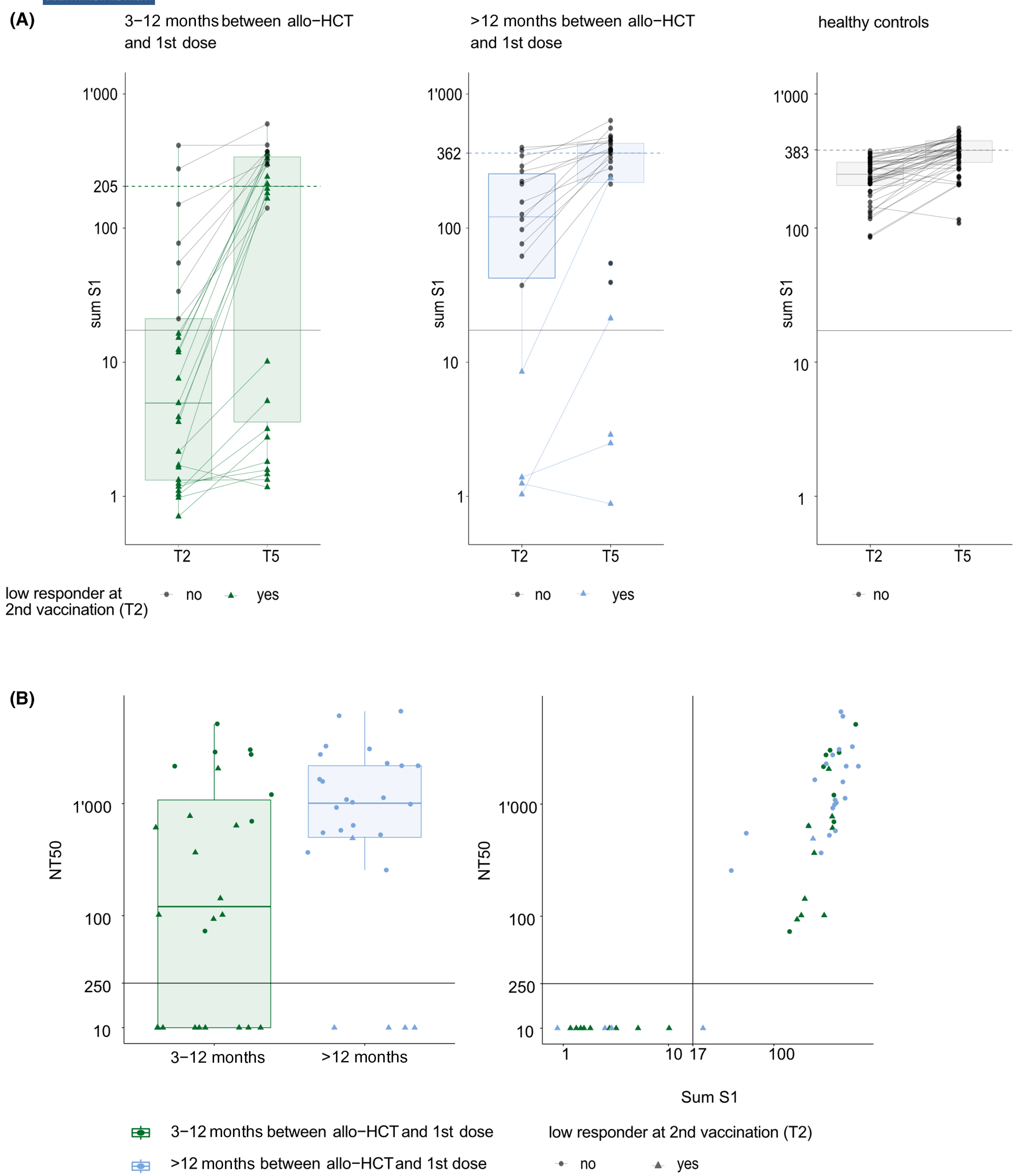

FIGURE 1 Antibody responses in allogeneic haematopoietic cell transplantation (allo-HCT) recipients and healthy controls after third vaccine dose. (A) Boxplots showing antibody responses (sum S1 = sum of S1 signal over cut-off (SOC) values for immunoglobulin [Ig]G, IgA and IgM) 1 month after the second and the third vaccine dose in allo-HCT recipients stratified by time between transplantation and first vaccination (green, 3–12 months; blue, >12 months) and healthy controls (grey). Antibody responses after the second and third vaccine dose from the same individual are connected with a line. Low responders at second vaccination are represented by triangles. Horizontal solid line corresponds to the neutralising threshold of 17: low responders have antibody values below that threshold. Horizontal dashed lines correspond to median antibody responses among each group (green, 3–12 months; blue, >12 months; and grey, healthy controls). (B) Boxplots showing neutralisation titres against wild-type Wuhan-HU-1 in allo-HCT recipients stratified by time between transplant and first vaccination (green, 3–12 months; blue >12 months). Horizontal line corresponds to 50% neutralisation titre (NT50) = 250. (C) Scatterplot of NT50 versus sum S1 values in allo-HCT recipients. Each dot corresponds to a patient, coloured by its group (green, 3–12 months; blue >12 months; low responders at second vaccination are represented by triangles). Horizontal line corresponds to NT50 = 250 and vertical line to sum S1 = 17.

TABLE 1 Baseline characteristics of low responders after second vaccine dose

Characteristics	Overall (*n* = 22)	Responder after third dose (*n* = 11)	Low responder after third dose (*n* = 11)
Patient age (years), *n* (%)			
17–45	3 (13.6)	2 (18.2)	1 (9.1)
45–65	13 (59.1)	5 (45.5)	8 (72.7)
65–75	6 (27.3)	4 (36.4)	2 (18.2)
Gender, *n* (%)			
Male	16 (72.7)	7 (63.6)	9 (81.8)
Female	6 (27.3)	4 (36.4)	2 (18.2)
Conditioning intensity, *n* (%)			
MAC	2 (9.1)	2 (18.2)	0 (0)
RIC	20 (90.9)	9 (81.8)	11 (100)
IST at third dose, *n* (%)			
No	14 (63.6)	9 (81.8)	5 (45.5)
Yes	8 (36.4)	2 (18.2)	6 (54.5)
History of acute GVHD at priming vaccination, *n* (%)			
No/mild	17 (77.3)	10 (90.9)	7 (63.6)
Moderate/severe	5 (22.7)	1 (9.1)	4 (36.4)
Chronic GVHD at third dose, *n* (%)			
No/mild	17 (77.3)	8 (72.7)	9 (81.8)
Moderate/severe	5 (22.7)	3 (27.3)	2 (18.2)
History of relapse at priming vaccination, *n* (%)			
No	17 (77.3)	8 (72.7)	9 (81.8)
Yes	5 (22.7)	3 (27.3)	2 (18.2)
Relapse at third dose, *n* (%)			
No	21 (95.5)	10 (90.9)	11 (100)
Yes	1 (4.5)	1 (9.1)	0 (0)
Disease type, *n* (%)			
Myeloid	17 (77.3)	10 (90.9)	7 (63.6)
Lymphatic	5 (22.7)	1 (9.1)	4 (36.4)
Other	0 (0)	0 (0)	0 (0)
Donor type, *n* (%)			
HLA-identical sibling	8 (36.4)	6 (54.5)	2 (18.2)
HLA-matched unrelated	12 (54.5)	4 (36.4)	8 (72.7)
HLA-haploidentical	2 (9.1)	1 (9.1)	1 (9.1)
HLA-mismatched unrelated	0 (0)	0 (0)	0 (0)
Graft type, *n* (%)			
PBSC	22 (100)	11 (100)	11 (100)

Abbreviations: IST, immunosuppressive therapy; MAC, myeloablative conditioning; RIC, reduced-intensity conditioning; GVHD, graft-versus-host disease; PBSC, peripheral blood stem cells.

glycoprotein-specific IgG RBD (IgG[S-RBD]) levels in 22/42 allo-HCT recipients (52%) with low Ab titre levels. However, none of these studies identified factors, associated with improved or impaired serological responses in low responders after two vaccine doses.

Our results are in line with these reports and highlight the importance of a third mRNA vaccine dose in both responders and low responders to priming vaccination.[6,9,13,14] Importantly, a three-dose vaccination schedule against COVID-19 has been recommended by both the American Society of Transplantation and Cellular Therapy (ASTCT) and the European Society for Blood and Marrow Transplantation (EBMT) in patients after HCT and chimeric antigen receptor T-cell therapy.[15,16]

Our data point toward the positive effect of IST discontinuation on serological responses in low responders to two vaccine doses. In addition, we were able to show that in both allo-HCT recipients and healthy controls, a third vaccine dose led to a significant improvement of the humoral immune response. Achieving higher neutralising Ab titres is crucial,[17] as variants with mutations in epitopes on the spike protein can result in increased viral resistance to neutralising Ab and have been shown to reduce vaccine effectiveness.[18,19]

Given the variable efficacy of the third vaccine dose in allo-HCT recipients two questions remain to be answered: (i) What might be its optimal timing in responders versus low responders?, and (ii) What might be the factors positively affecting response rates in low responders? In our patient cohort, the median time between allo-HCT and the third dose was 644 days with a median time between the second and third dose of 221 days. As expected, we observed a trend to better humoral responses in patients being vaccinated >12 months after allo-HCT. However, given that a third vaccine dose can now be administered as early as 1 month after the second dose, we believe that the implementation of longitudinal Ab measurements can guide us toward the identification of vaccine low responders and optimal timing of a third vaccination in this highly variable and vulnerable patient population.

Finally, for allo-HCT recipients who are at increased risk of developing an inadequate humoral response after vaccination, systematic implementation of preventive monoclonal Ab treatment to decrease the incidence and severity of COVID-19[20] as well as the addition of a subsequent fourth vaccine dose should be considered.

AUTHOR CONTRIBUTIONS

Andriyana K. Bankova, Chloé Pasin, Irene A. Abela, and Antonia M. S. Müller conceived and designed the study and analysed data. Selina Epp, Annette Audige, and Irene A. Abela designed and performed binding antibody experiments. Selina Epp conducted neutralisation experiments, and Irene A. Abela analysed data. Chloé Pasin performed data analyses. Andriyana K. Bankova, Caroline Cicin-Sain, Alice Huang, Chloé Pasin, Irene A. Abela, and Antonia M. S. Müller were involved in patient recruitment, provided samples from study and diagnostic repositories, and analysed patient data. Andriyana K. Bankova, Chloé Pasin, Antonia M. S. Müller and Irene A. Abela wrote the manuscript, which all authors commented on. Irene A. Abela and Antonia M. S. Müller supervised the study.

CONFLICT OF INTEREST

No conflicts of interest in relation to this project declared.

DATA AVAILABILITY STATEMENT

All data can be requested by e-mail to Irene A. Abela at irene.abela@usz.ch.

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ORCID

Andriyana K. Bankova https://orcid.org/0000-0002-5072-9591
Chloé Pasin https://orcid.org/0000-0001-8730-790X
Irene A. Abela https://orcid.org/0000-0002-5566-8628
Antonia M. S. Müller https://orcid.org/0000-0003-4420-9466

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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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