

Antibody titers after SARS-CoV-2 mRNA vaccination in patients with aplastic anemia—A single-center study

Letter to the editor,

In 2020, the SARS-CoV-2 virus spread all over the world also affecting patients with hematologic diseases.¹ Patients with aplastic anemia (AA) were thought to be at particular risk for severe or fatal courses of COVID-19 due to cytopenias caused by the underlying disease as well as through their immunosuppressive treatment regimens.^{1,2} Consequently, the European Society for Blood and Marrow Transplantation (EBMT) and the Severe Aplastic Anemia Working Party (SAAWP) recommended to carefully consider the timing of initiation of immunosuppressive treatment (IST) and/or allogeneic stem cell transplantation (ASCT) to prevent AA patients from avoidable cytopenias and hospitalization.³ One milestone in the control of the pandemic was the development of SARS-CoV-2-specific vaccinations. For mRNA or vector-based types of vaccines, it has been shown that levels of neutralizing antibodies against the spike protein of SARS-CoV-2 correlate with the risk of infection and hospitalization in healthy individuals.⁴ As anti-thymocyte globuline (ATG) and cyclosporine A (CSA) are known to impair T- and B-cell-mediated immune responses, it is presumed that immune responses to SARS-CoV-2 vaccination of AA patients under IST may be inappropriate, especially in the first months after ATG/CSA initiation.^{3,5} Up to now, no data have been published about antibody titers following vaccination of patients with AA.

We initiated a retrospective analysis of post-vaccination antibody levels and blood counts in patients with AA or AA/PNH overlap syndrome.

Sixteen patients (8 female/8 male, median age 57.5 years, range 24–69 years) were identified with sufficient data within the Aachen Registry for Telomeropathies and Aplastic Syndromes.⁶ Written informed consent for the registry was obtained according to the approval by the local ethic committee EK (332/20). All patients are currently undergoing immunosuppressive treatment including ATG and CSA and/or additional treatments with Eltrombopag or C5-complement inhibitors at the University Hospital of RWTH Aachen. All patients treated with ATG received horse ATG (ATGAM[®]). Details about treatments including time intervals between diagnosis, ATG application, and first vaccination are shown in [Table 1](#). All 16 patients received at least two vaccinations and all antibody titers against the SARS-CoV-2 spike protein were measured within the first 7 months after the second vaccination. Measurement of antibody titers against the nucleoprotein (N)

of SARS-CoV-2 was not carried out. Eighty-eight percent (14/16) of the patients received BTN162B2 (Pfizer/BioNTech), 6% (1/16) mRNA-1273 (Moderna), and 6% (1/16) ChAdOx1 (AstraZeneca), respectively. One quarter (4/16) received a third vaccination with BTN162B2 (Pfizer/Biontech). In our cohort, no symptomatic COVID-19 infection after vaccination was observed. Concerning asymptomatic SARS-CoV-2 infections, the patients did not report positive results for SARS-CoV-2-specific PCR or rapid antigen test during follow-up.

Analysis of the vaccination-induced antibody levels against the SARS-CoV-2 spike protein showed that all patients developed detectable antibody titers with a median of 553 BAU/ml (range 168–1040 BAU/ml) within the first 6 months after the second vaccination. In spite of the small number of patients, we observed a tendency to lower antibody levels in our two patients who received two vaccinations within the first 2 months after ATG treatment (#9: 168 BAU/ml; #1: 406 BAU/ml 2 months after second vaccination). We did not observe further correlations of treatment modalities and antibody levels.

Since antibody levels against the SARS-CoV-2 spike protein are known to rapidly decrease within the first weeks after second vaccinations in healthy individuals,⁷ we stratified our patients antibody titers in a cross-sectional approach according to the time after second vaccination. Here, we found a continuous decline in antibody levels from a median of 848 BAU/ml (range 176–1040 BAU/ml) after the 1st month to 410 BAU/ml (range 168–1040 BAU/ml) in the 2nd month and to 367 BAU/ml (range 223–936 BAU/ml) after 3 to 6 months after the second vaccination ([Figure 1A](#)). Antibody levels were comparable to those recently published in a large cohort of health care workers with mean antibody levels of 760, 688, and 501 BAU/ml after 1, 2, and 3 months, respectively.⁷ Our observation of declining antibody levels was further confirmed in six patients where individual follow-up measurements of the vaccination levels were available. Here, all patients except for one (patient #10, [Table 1](#)) showed declining antibody levels over time ([Figure 1B](#)). Of note, third vaccinations resulted in adequate and rapid increase in the antibody levels >1040 BAU/ml in four of our patients with available follow-up data ([Figure 1C](#)).

Recent reports showed a possible relationship between vaccination and relapse or de novo AA.^{8,9} All patients within this cohort, showed stable blood counts in all three lineages after any of



the vaccinations given during follow-up, except for patient #10 who developed two episodes of isolated, self-limiting mild neutropenia after the first and second vaccination (Figure 1D, compare patient #10, Table 1). The respective episodes lasted approximately 6 weeks after the first vaccination and 24 weeks after the second vaccination with a minimum of 0.96 neutrophilic granulocytes/nl. Of note, this patient did not show any decline in antibody levels during individual follow-up.

Hence, our analysis suggests that patients with AA and AA/PNH overlap syndrome under IST including C5 inhibitors can develop sufficient levels of spike protein-directed antibodies similar to levels observed in healthy individuals. Of note, even patients who were vaccinated within the first month after ATG administration showed at least modest immune response despite the known immunosuppressive effect of ATG on the T- and B-cell response. This observation suggests that SARS-CoV-2 vaccinations can be at least partially effective and therefore argues in favor of vaccination closely after ATG administration. Further studies on the efficacy of the vaccination on T-cell stimulation will be needed to elucidate the impact of ATG on SARS-CoV-2 vaccination immune response. Furthermore, we observed that antibody levels in AA patients declined after second vaccination as previously reported for healthy individuals.⁷ For all patients who received a third vaccination, we found a substantial increase in

What is the new aspect of your work?

We provide first data on the vaccination titers against SARS-CoV-2 in patients with aplastic anemia.

What is the central finding of your work?

Vaccination titers in AA patients undergoing immunosuppression show dynamics comparable to healthy individuals and third vaccination results in adequate and sufficient antibody response. No relapse or relevant changes in blood counts were observed after vaccination. Patients vaccinated after ATG show a modest antibody response.

What is (or could be) the specific clinical relevance of your work?

Our data indicate that immunosuppression in AA patients does not affect development of antibody levels comparable to healthy individuals without evidence for relapse or changes in blood counts. AA patients can be vaccinated within the first weeks after ATG treatment.

TABLE 1 Characteristics of reported patients including patient number, sex, age, diagnosis, treatment, and time between initial diagnosis (or application of ATG) and first SARS-CoV-2 vaccination in months

Pat. #	Sex	Age	Diagnosis	Treatment	Time point of first vaccination		
					Months after diagnosis	Months after ATG	Vaccine
1	F	58	sAA/PNH Overlap	ATG/CSA/Epag/c5 inhibitor	5	1	BTN162B2
2	M	63	sAA/PNH Overlap	ATG/CSA/c5 inhibitor	136	134	BTN162B2
3	M	69	sAA	ATG/CSA/Epag	46	46	ChAdOx1
4	F	50	vsAA	ATG/CSA	21	20	BTN162B2
5	F	57	nsAA	CSA	(-) 0.5	no ATG	BTN162B2
6	M	54	nsAA	ATG/CSA/Epag	13	5	BTN162B2
7	F	60	sAA	ATG/CSA	56	(-) 4	BTN162B2
8	M	59	nsAA	CSA/Epag	41	no ATG	BTN162B2
9	M	37	vsAA	ATG/CSA/Epag	2	1	BTN162B2
10	F	58	sAA	ATG/CSA	17	14	BTN162B2
11	F	51	nsAA/PNH Overlap	CSA/Epag/c5 inhibitor	(-) 4	no ATG	BTN162B2
12	F	57	sAA	ATG/CSA	25	24	mRNA-1273
13	F	58	vsAA	ATG/CSA/Epag	10	9	BTN162B2
14	M	24	nsAA	CSA	10	no ATG	BTN162B2
15	M	62	sAA	CSA	46	20	BTN162B2
16	M	28	vsAA	ATG/CSA/Epag	10	8	BTN162B2

Abbreviations: AA/PNH overlap syndrome, aplastic anemia/paroxysmal nocturnal hemoglobinuria overlap syndrome; ATG, anti-thymocyte globulin; c5 inhibitor, complement factor 5 inhibitor Eculizumab or Ravulizumab; CSA, cyclosporine A; Epag, Eltrombopag; nsAA, non-severe aplastic anemia; sAA, severe aplastic anemia; vsAA, very severe aplastic anemia.

Note: Two patients received vaccination before diagnosis of AA (patients #5 and #11) and are shown as negative values. One patient (patient #7) received ATG treatment between first and second vaccinations.

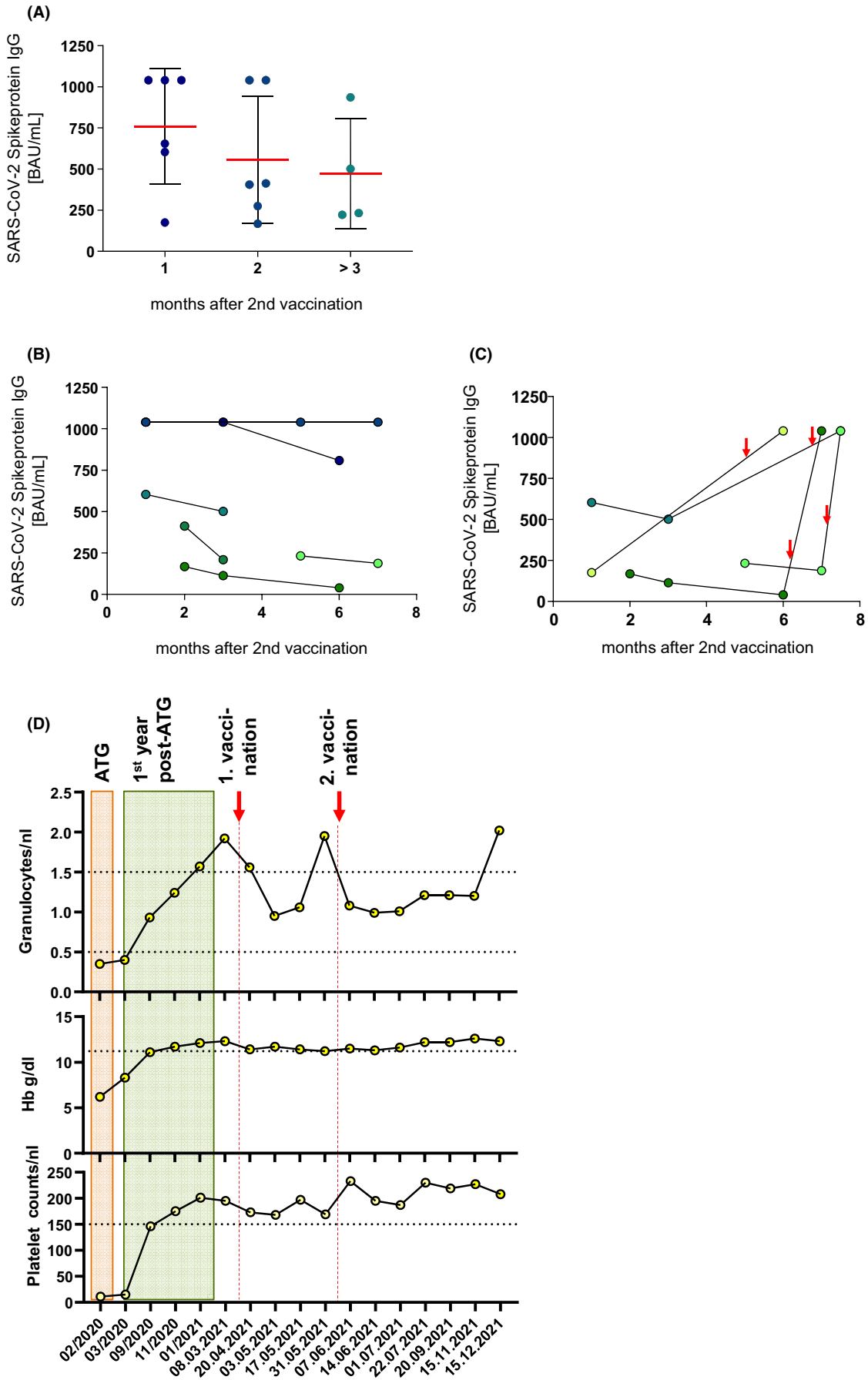


FIGURE 1 Vaccination response in AA and AA/PNH patients after second SARS-CoV-2 vaccination. (A) SARS-CoV-2 spike protein IgG titers in BAU/ml of 16 patients with AA or AA/PNH overlap syndrome measured 1, 2, or 3 to 6 months after second SARS-CoV-2 vaccination (red line = median, whiskers = 25% or 75% percentiles). Plot of individual patient follow-up of the SARS-CoV-2 spike protein IgG titers [BAU/ml] 1 to 7 months after second SARS-CoV-2 vaccination before (B) and after (C) third vaccination ("booster"). Time point of the third vaccination is indicated by the red arrows. (B: compare patient numbers #4, #5, #9, #10, #12, and #15. C: compare patient numbers #3, #4, #9, and #15, see Table 1) (D) Blood counts of neutrophils, hemoglobin values, and platelets after two vaccinations with BNT162b2 in patient #10

antibody levels to >1040 BAU/ml. Of note, no relapse of AA or clinically relevant changes in blood counts were observed after vaccination in our cohort. Until now, the antibody threshold for sufficient protection against symptomatic COVID-19 infection has not yet been identified.¹⁰ As patients with AA receive continuous immunosuppressive therapy, we propose to aim for higher antibody titers to increase the chance of preventing symptomatic COVID-19 infection in this vulnerable patient group. Therefore, two different strategies are conceivable: Booster vaccinations can be carried out after 6 months according to the actual recommendations of the World Health Organization¹⁰ or earlier based on the individual decline in the antibody levels during follow-up. To what extent the 6 months interval between vaccinations or individualized vaccination schemes is sufficient to protect against severe disease, particularly in the context of immunosuppression and new emerging variants needs to be evaluated in future studies.

In summary, we provide first data that patients with AA and AA/PNH overlap syndrome show similar antibody dynamics as observed in healthy individuals without evidence of relapse or relevant changes in blood counts. Further studies are warranted to determine the optimal vaccination scheme and protection against COVID-19 in patients with AA.

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CONFLICT OF INTERESTS


The other authors have nothing to disclose.

AUTHOR CONTRIBUTION

FB and JW conceived and planned the study design, interpreted the data, and wrote the manuscript. SI and KK supported the study and interpreted the data. SI, THB, and JP analyzed the data, planned the study design, and revised the manuscript.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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