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ORIGINAL PAPER

Clinical outcomes and immune responses to SARS-CoV-2 vaccination in severe aplastic anaemia

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Summary

Patients with severe aplastic anaemia (SAA) are often not vaccinated against viruses due to concerns of ineffective protective antibody response and potential for pathogenic global immune system activation, leading to relapse. We evaluated the impact of COVID-19 vaccination on haematological indices and disease status and characterized the humoural and cellular responses to vaccination in 50 SAA patients, who were previously treated with immunosuppressive therapy (IST). There was no significant difference in haemoglobin ($p = 0.52$), platelet count ($p = 0.67$), absolute lymphocyte ($p = 0.42$) and neutrophil ($p = 0.98$) counts prior to and after completion of vaccination series. Relapse after vaccination, defined as a progressive decline in counts requiring treatment, occurred in three patients (6%). Humoural response was detectable in 90% (28/31) of cases by reduction in an *in-vitro* Angiotensin II Converting Enzyme (ACE2) binding and neutralization assay, even in patients receiving ciclosporin (10/11, 90.1%). Comparison of spike-specific T-cell responses in 27 SAA patients and 10 control subjects revealed qualitatively similar CD4+ Th1-dominant responses to vaccination. There was no difference in CD4+ ($p = 0.77$) or CD8+ ($p = 0.74$) T-cell responses between patients on or off ciclosporin therapy at the time of vaccination. Our data highlight appropriate humoural and cellular responses in SAA previously treated with IST and true relapse after vaccination is rare.

KEYWORDS
bone marrow failure, SARS-CoV-2 vaccination, severe aplastic anaemia

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INTRODUCTION

Coronavirus Disease 2019 (COVID-19) caused by SARS-CoV-2 has led to significant morbidity and mortality in patients with haematological diseases.[1] Severe aplastic anaemia (SAA) is a rare, life-threatening bone marrow failure disorder that presents with pancytopenia and a hypocellular marrow due to immune-mediated destruction of haematopoietic stem cells (HSC). SAA patients are at high risk for infection due to disease-related neutropenia and immunosuppressive therapy (IST). Evidence of an immune-mediated pathophysiology includes improvement in blood counts after IST and dependence on maintenance calcineurin inhibitors like ciclosporin (CSA) to maintain adequate counts, *in-vitro* studies demonstrating dysregulation of $CD8^+$ cytotoxic T cells and abnormal production of type 1 cytokines including interferon gamma (IFN-γ) inducing apoptosis of HSC.[2–5]

SAA patients have had variable clinical outcomes with acute COVID-19 infection. In a review of 23 unvaccinated AA patients, outcomes of acute infection ranged from full recovery to hospitalization in intensive-care units and included one death.[6] In a case series of five patients with acute COVID-19 infection, none required interruption of IST or met criteria for relapse, but post-infection complications included reactivation of herpes zoster and recurrent ileitis with bowel perforation requiring surgical resection.[7]

SAA patients are often not vaccinated to protect against routine viruses due to concerns of an ineffective protective specific antibody response to viral antigens and potential global immune system activation that might exacerbate in relapse. In 2016, the British Society for Standards of Haematology recommended against vaccinating AA patients treated with IST because of the potential risk for relapse based on several clinical observations of AA onset or relapse following immunization.[8] Although limited to case reports without any definite causal relationship, this recommendation has been widely accepted. Acute viral infections are a suspected trigger for AA and emerging case reports have described individuals who developed COVID-19-associated acquired AA.[9,10] Therefore, evaluation of the risk–benefit profile of COVID-19 vaccination in this population is warranted.

Globally, vaccination against SARS-CoV-2 has been an effective strategy to prevent severe disease, and its efficacy through the study of antibody response in at risk populations is ongoing. Retrospective reviews of patients undergoing haematopoietic cell transplantation (HSCT) and chimaeric antigen receptor T-cell therapy, respectively, have demonstrated suboptimal humoural responses to vaccination particularly in the former group who received systemic IST within three months of vaccination[11,12]. Two studies evaluating the antibody response in 11 and 16 AA patients respectively, revealed appropriate rise in antibody levels against SARS-CoV-2 spike protein after vaccination.[13,14] Similar findings were also observed in a larger cohort of 175 patients with AA and paroxysmal nocturnal haemoglobinuria.[15] Humoural assessments of SAA patients who received standard IST in the context of clinically relevant variants using neutralization assays has not been performed.

While vaccine efficacy to SARS-CoV-2 has largely been determined by the production of high-affinity neutralizing antibodies, a growing focus is the cell-mediated T-cell response to vaccination. Long-term studies on patients who recovered from the closely related SARS infection in the early 2000s demonstrated that SARS-specific T cells were present over one decade after infection,[16] while memory B cells and antibodies were below the limit of detection within 2–3 years.[17] A cell-mediated response to SARS-CoV-2 may boost the humoural response and create higher-affinity protective antibodies. Such data are lacking in SAA.

We aimed to assess the impact of COVID-19 vaccination on clinical outcomes in SAA patients previously treated with IST (with or without ongoing CSA) as well as characterize the humoural response through neutralization assays of relevant variants and cellular responses to vaccination.

METHODS

Retrospective data were collected from 50 patients enrolled on National Institutes of Health (NIH) protocols #NCT01623167, #NCT02979873 and #NCT04304820. Protocols were approved by the Institutional Review Board of the National Heart, Lung, and Blood Institute and monitored by an independent Data Safety and Monitoring Board. Informed consent was obtained in accordance with the Declaration of Helsinki.

Diagnostic criteria for SAA were standardized among all trials and included a bone marrow cellularity of 30% or less and at least two of the following three criteria were met: an absolute neutrophil count (ANC) of 0.5×10^9/l or less, an absolute reticulocyte count of 60×10^9/l or less, and a platelet count (PLT) of 20×10^9/l or less. All patients enrolled on the above protocols either did not have suitable donors, meet clinical eligibility for HSCT, or had personal preference to not pursue HSCT and received standard IST with horse anti-thymocyte globulin (h-ATG), CSA, and eltrombopag (EPAG) for SAA. Inclusion criteria for this study included all patients with confirmation of SARS-CoV-2 vaccination between January and November 2021 with available clinical data. Current SAA disease status at the time of vaccination was recorded as complete response (CR), partial response (PR) and non-response (NR). CR required an ANC of 1.0×10^9/l or better, a PLT of 100×10^9/l or better, and a haemoglobin (HGB) level of 100 g/l or higher. PR status was assigned to patients who did not meet criteria for SAA or CR. PR was further divided into weak (PLT ≤50 K/μl) or strong response (PLT >50 K/μl). Those who still met criteria for SAA after receiving standard IST were categorized in a NR group. Relapse definition per clinical protocol was a progressive and substantial decline in blood counts requiring reinitiation of high-dose CSA.

Clinical data collected included available peripheral blood counts one year prior to vaccination to last available

laboratory evaluation, history of acute COVID-19 infection, SAA status at time of vaccination, CSA therapy at time of vaccination, CSA dose, vaccine type, number of vaccine doses, SAA status after vaccination from last available laboratory evaluation, time from initial IST to first vaccine dose, time from initial IST to relapse if applicable, and time from initial IST and completion of vaccination series to humoural and cellular response evaluation, respectively.

At time of analysis, within the United States, the Pfizer vaccine had been approved for children and adults of age five years or older. Moderna and Janssen vaccines had been approved for adults aged 18 years and older. Both Pfizer and Moderna vaccines were administered as two-dose series given 21 days and 28 days apart respectively. Only one dose was administered for Janssen for completion of the vaccination series. Outside of the United States, AstraZeneca and Sinovac were approved for adults of age 18 years or older as a two-dose series with a dose interval of 8–12 weeks and 2–4 weeks respectively.

Vaccine-elicited humoural response was assessed in available sera from SAA patients obtained after completion of vaccination series using two methodologies — an Angiotensin II Converting Enzyme (ACE2) inhibition assay and a SARS-CoV-2 pseudovirus neutralization assay. The ACE2 inhibition assay measures the ability of the SARS-CoV-2 antibodies present in the sera to compete and inhibit binding of human ACE2 (hACE2) to the receptor-binding domain (RBD) fragment in the SARS-CoV-2 spike (S) protein. The qualified fold reduction range of ACE2 binding to SARS-CoV-2 RBD is between fourfold and 1000-fold. The SARS-CoV-2 pseudovirus neutralization assay expresses the titre at which the sample neutralizes by 50% (ID50) and 80% (ID80) against wild-type (WT), omicron, beta, and delta pseudoviruses. For pseudovirus neutralization, samples were considered detectable at ID50 above 20%.

T-cell immune responses to vaccination were assessed using available peripheral blood mononuclear cells (PBMC) samples from SAA patients obtained after completion of the vaccination series. PBMC were stimulated with SARS-CoV-2 protein (S) peptide and nucleocapsid (N) peptide pools as a negative control and stained with antibodies to T-cell markers. Intracellular cytokine staining (ICS) was performed to identify the type of cytokine produced by each cell upon stimulation. Flow cytometry was performed to assess the frequency of spike-specific CD4$^+$ and CD8$^+$ T cells and their cytokine production. Polyfunctional analysis was performed to measure T cells that produce multiple cytokines. Samples were compared to 10 healthy controls. Control samples for the T cell analysis were collected under the Vaccine Research Center's (VRC), National Institute of Allergy and Infectious Diseases (NIAID), NIH protocol VRC 200 (NCT00067054) in compliance with the NIH Institutional Review Board (IRB)-approved protocol and procedures. All subjects met protocol eligibility criteria and agreed to participate in the study by signing the NIH IRB-approved informed consent. Research studies with these samples were conducted while protecting the rights and privacy of the study participants.

Peripheral blood counts including haemoglobin (HGB), platelet count (PLT), ANC and absolute lymphocyte count (ALC) prior to and after vaccination were compared using the Student's paired t-test. Statistical significance was determined at alpha below 0.05. Univariate and regression analyses were performed using R statistical software version 4.0.2. Humoural response analysis was performed using Microsoft Excel and Graph Pad Prism 8.0.0 for Windows. Cellular response analysis was performed using FlowJo software version 10.7.1. Polyfunctional analysis was performed after Boolean gates were applied using Pestle version 2 and SPICE version 6.1.[18] Additional details about the statistical methods are provided in the Supporting Information (Tables S1 and S2).

RESULTS

Clinical outcomes

A total of 50 patients with SAA from January 2021 to November 2021 were studied, with a median age of 41 years (range 9–78 years). 29 females (58%) and 21 males (42%) were included in the analysis. All patients received standard IST with EPAG. At vaccination, 28 patients (56%) were classified as CR, 19 patients (38%) were classified as PR, and three (6.0%) patients were classified as NR. 15 patients (30%) were on CSA therapy at time of vaccination. Detailed patient baseline demographics and disease characteristics are reported in Table 1. 47 (94%) patients did not have any changes in disease status after vaccination. Among 40 patients with available blood counts three months prior to and after completion of vaccination series, there were no significant differences in HGB ($p = 0.52$) PLT ($p = 0.67$), ANC ($p = 0.98$), and ALC ($p = 0.42$) (Figure 1; Figures S2–S5). There was no significant difference in counts based on disease status at time of vaccination (Figure S1; Tables S3, S4).

Relapse after vaccination was identified in three (6.0%) cases and were seven months, three years, and four years from initial IST treatment, respectively. All three relapsed patients had a weak PR (PLT $< 50 \times 10^9$/l) to IST. Relapse rate among patients with weak PR was 60% (3/5) and among PR it was 16% (3/19; Figure S3).

Relapse #1 and Relapse #2 received an initial Pfizer inoculation and did not receive the second dose because of declining blood counts. In Relapse #3, relapse occurred four weeks after completion of a full Moderna series. Relapse #1, a 36-year-old male with history of seronegative hepatitis and chronic perirectal abscess on daily antibiotic therapy was seven months from standard IST therapy and on daily CSA at time of vaccination. EPAG had been discontinued one month prior to vaccination. One month after receiving his first Pfizer inoculation, relapse occurred with trilineage count decline, and he was restarted on high-dose CSA and EPAG. He ultimately went off study and successfully underwent haploidentical HSCT. Relapse #2, a 59-year-old female, who had received standard IST three years prior to vaccination, discontinued sirolimus on an active protocol evaluating the use of sirolimus to prevent relapse two

TABLE 1 Demographic and disease characteristics of SAA patients

	All patients	Humoural and cellular response cohort	Cellular response control cohort
Number of patients (*n*, %)	50 (100.0%)	31 (62.0%)	10
Male	21 (42.0%)	14 (45.2%)	4 (40.0%)
Female	29 (58.0%)	17 (54.8%)	6 (60.0%)
Age, years (median, range)	42 (9–78)	44 (15–73)	46 (31–73)
<18	8 (16.0%)	3 (9.7%)	0 (0.0%)
18–39	17 (34.0%)	11 (35.5%)	3 (30.0%)
40–59	16 (32.0%)	12 (38.7%)	6 (60.0%)
>60	9 (18.0%)	5 (16.1%)	1 (10.0%)
Race			
White	32 (64.0%)	21 (67.7%)	3 (30.0%)
Black or African American	8 (16.0%)	5 (16.1%)	1 (10.0%)
Asian	4 (8.0%)	2 (6.5%)	1 (10.0%)
Multiple race/unknown	6 (12.0%)	3 (9.7%)	5 (50.0%)
Time from initial IST to first vaccine dose			
Less than 6 months	3 (6.0%)	2 (6.5%)	N/A
6 months–2 years	8 (16.0%)	5 (16.1%)	
Greater than 2 years	39 (78.0%)	24 (77.4%)	
Disease status at vaccination			
CR on CSA	6 (12.0%)	3 (9.7%)	
CR off CSA	22 (44.0%)	15 (48.4%)	
PR on CSA	9 (18.0%)	8 (25.8%)	N/A
PR off CSA	10 (20.0%)	5 (16.1%)	
NR[a]	3 (6.0%)	0 (0.0%)	
Vaccine type			
Pfizer	30 (60.0%)	20 (64.5%)	3 (30.0%)
Moderna	14 (28.0%)	9 (29.0%)	7 (70.0%)
Sinovac	3 (6.0%)	1 (3.2%)	0 (0.0%)
AstraZeneca	2 (4.0%)	1 (3.2%)	0 (0.0%)
Janssen (J&J)	1 (2.0%)	0 (0.0%)	0 (0.0%)
Completion of vaccination series			
Yes	48 (96.0%)	29 (93.5%)	10 (100.0%)
No	2 (4.0%)	2 (6.5%)	0 (0.0%)
History of acute infection			
Yes	1 (4.0%)[b]	0 (0.0%)	2 (20.0%)[c]
No	49 (96.0%)	31 (100.0%)	8 (80.0%)

Abbreviations: CR, complete response; CSA, ciclosporin; NR, non-response; PR, partial response.

[a]*N* = 1 on danazol therapy.

[b]Preceding first vaccine dose.

[c]Between completion of vaccination series and response evaluation.

days before her first Pfizer inoculation. She also developed trilineage decline requiring initiation of high-dose CSA and mycophenolate mofetil. Relapse #3, a 78-year-old female, demonstrated steady decline in platelet count six months prior to vaccination. Substantial bilineage (HGB and PLT) decline was noted two weeks after completion of the Moderna series, prompting reinitiation of high-dose CSA. Relapse #2 and Relapse #3 were both able to achieve a strong second PR with reinitiation of IST as of their last visits in March 2022.

Humoural immune responses

Available sera from 31 SAA patients after completion of COVID-19 vaccination were assessed for humoural immune
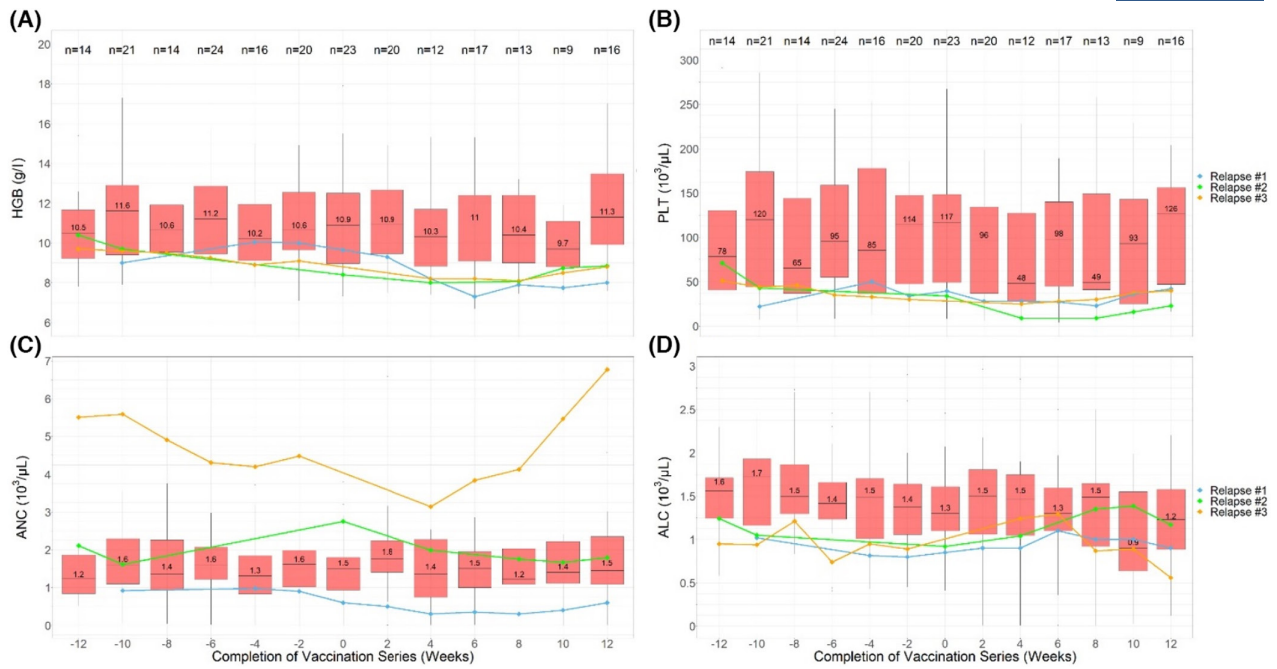
FIGURE 1 Peripheral blood counts in severe aplastic anaemia (SAA) prior to, at time of, and after completion of SARS-CoV-2 vaccination series. Three relapsed individuals are identified by overlying line graphs. *n*, number of SAA patients with available counts at each time point (day −7 + day +6 of reported week). Completion of series set at 0 weeks. (A) Haemoglobin (HGB), (B) platelet count (PLT), (C) absolute neutrophil count (ANC) and (D) absolute lymphocyte count (ALC). [Colour figure can be viewed at wileyonlinelibrary.com]

responses. The median time from completion of a vaccination series to sample collection was 124 days (IQR 67–157). Neutralizing antibodies were detectable across all variants in evaluations across patients and collection windows except for four patients who did not demonstrate specific antibodies to omicron and beta variants (Table S6). 28 (90.3%) patients had detectable fold reductions in ACE2 binding. 10 out of 11 (90%) patients on CSA at time of vaccination had detectable reduction in ACE2 binding, three of whom were on therapeutic twice-daily dosing. Three (9.7%) patients did not have detectable fold reduction in ACE2 binding (Figure 2A); all three patients with undetectable reduction in ACE2 binding were 138, 152, and 234 days from vaccination (Table S5). Two of them had received only one vaccine dose and did not complete the intended two-dose series, due to declining blood counts consistent with a relapse (Relapse #1 and Relapse #2) after first inoculation. In our cohort, reduction in ACE2-binding of RBD positively correlated with the pseudotyped neutralization assay across all variants (Figure 2B).

Cellular responses

Available PBMC from 31 SAA patients and 10 healthy control subjects after completion of COVID-19 vaccination series were analysed to assess cellular responses. The median time from completion of vaccination series to sample collection was 124 days (IQR 77–157) in the AA cohort and 115 days (IQR 31–228) in the healthy control group. Four samples were excluded for comparison of the SAA cohort to healthy controls: two sample evaluations were performed after receiving

a third booster dose and two patients only received one inoculation due to subsequent declines in blood counts and eventual relapse. Nine out of 27 (33%) patients were receiving CSA at the time of vaccination. Similar to healthy controls, SAA patients exhibited a CD4+ Th1-dominant response to vaccination (Figures S7 and S8A). There was an inverse relationship in both SAA and healthy controls between CD4+ Th1-type responses and time from completion of vaccination series to response evaluation (Figure 3A). CD8+ responses were observed in response to vaccination in both SAA and healthy controls, but qualitatively appears blunted in SAA (Figure S8B). Comparison of SAA patients receiving or not receiving CSA therapy at time of vaccination did not reveal any significant difference in CD4+ ($p = 0.77$) and CD8+ ($p = 0.74$) T-cell responses (Figure 3C). In response evaluation in two patients after receiving a third booster dose, there were robust CD4+ Th1-type responses (Figure 3D). Polyfunctional analysis revealed a predominant Th1-type response in CD4+ T cells with little Th2-type cytokines or IL-21 detected, and similar cytokine profiles for both the SAA cohort on and off CSA, and the control cohort (Figure 3B).

DISCUSSION

Our study documents the clinical impact of SARS-CoV-2 vaccination in a cohort of patients with SAA post IST treatment by systematically assessing its effect on haematological indices and disease status. We found that most SAA patients, irrespective of disease duration and time from initial IST, do not show any decline in blood counts after completion of a vaccination series.
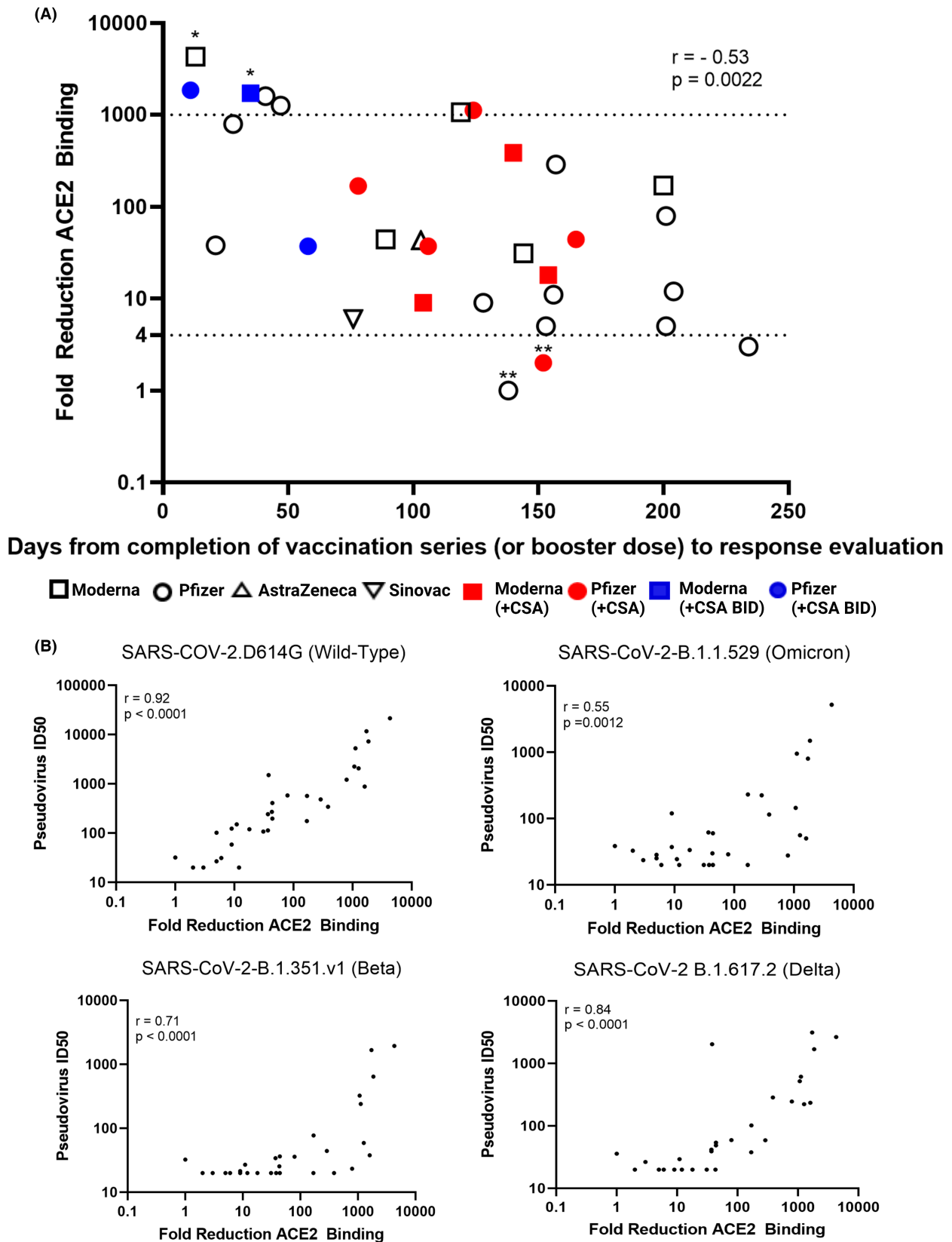
FIGURE 2 Humoural responses to SARS-CoV-2 vaccination in severe aplastic anaemia (SAA) cohort (*n* = 31). (A) *R* values: Spearman's rho. Fold reduction in Angiotensin II Converting Enzyme (ACE2) binding to wild-type receptor-binding domain (RBD) from time of vaccination to response evaluation. *, evaluation after booster dose; **, only one vaccine dose received. (B) Graphs show pseudovirus neutralization compared to fold reduction in ACE2 binding for each variant. [Colour figure can be viewed at wileyonlinelibrary.com]
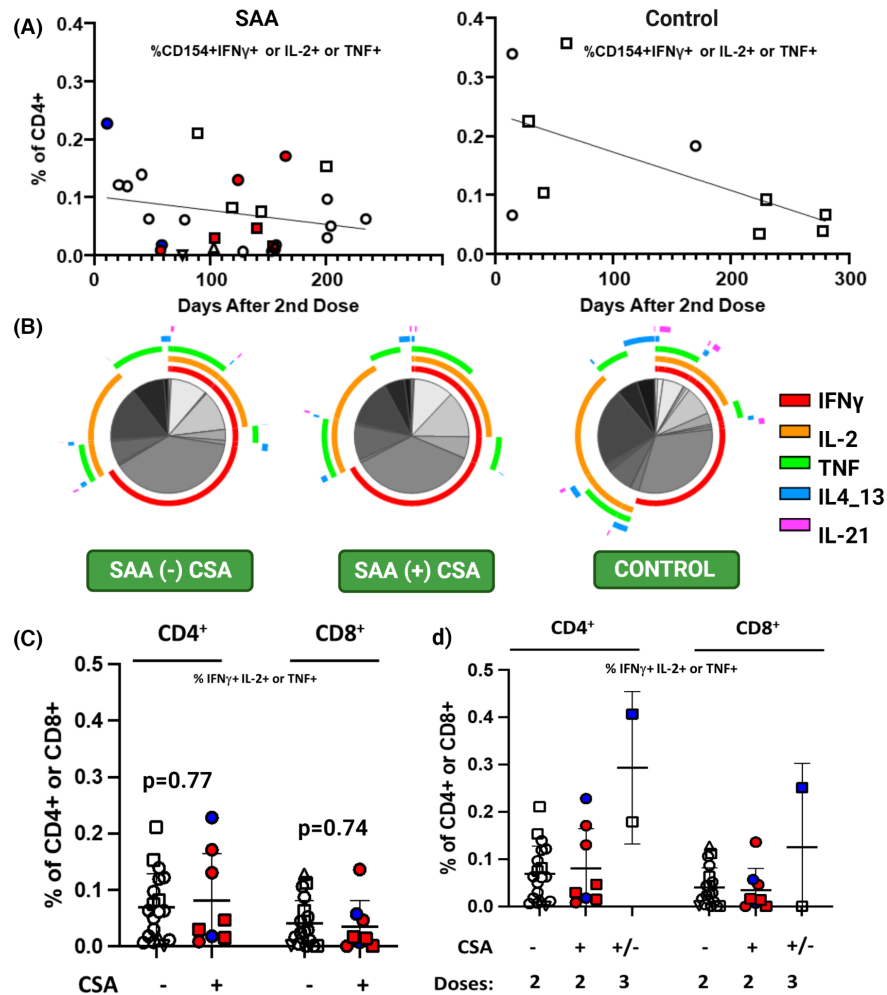
FIGURE 3 Cellular responses to SARS-CoV-2 vaccination in severe aplastic anaemia (SAA) cohort (*n* = 27) and healthy controls (*n* = 10) after completion of vaccination series. (A) CD4 Th1 responses. (B) Comparison of polyfunctional evaluation of SARS-CoV-2-specific T cells in SAA patients based on ciclosporin (CSA) treatment at time of vaccination and healthy controls. (C) Comparison of CD4 and CD8 responses in SAA cohort based on receiving CSA at time of vaccination. (D) CD4 and CD8 responses in SAA cohort including two patients (*n* = 29) who received a booster dose prior to evaluation. [Colour figure can be viewed at wileyonlinelibrary.com]

Three patients (6%) had a substantial decline in blood counts requiring reinitiation of IST with CSA: two after receiving one dose and one shortly after completing the two-dose series. Comparable relapse rate and clinical outcomes were recently reported in four out of 135 AA individuals with outcomes ranging from transfusion independence after reinitiating IST to undergoing transplant[19]. Notably, in our study, all three subjects had blood counts categorized as weak PR with PLT below 50×10^9/l and demonstrated instability prior to vaccine inoculation irrespective of time from initial SAA diagnosis and treatment.

Although not evaluated directly, our study does not support the theoretical concern for global pathologic immune activation after vaccination in SAA, as evidenced by sustained blood counts and low rates of relapses. Based on these results, we believe that for SAA patients with stable blood counts after completion of IST treatment (past six months), COVID-19 vaccines are safe and do not lead to relapse. Our findings may not be generalizable to all SAA patients treated with IST and risk–benefit discussion should be undertaken

in cases with unstable or borderline blood counts. Though dedicated studies are needed, our data suggest that other vaccinations which are commonly avoided in SAA patients, and/or in other autoimmune diseases due to fear for disease flare after vaccination, may also be safely administered.

Vaccine-elicited humoral responses evaluated by fold reduction in ACE2 binding were observed in more than 90% of SAA patients, confirming published reports of antibody response in AA patients. Similar to data published in healthy subjects after vaccination with the Moderna series, responses were observed but waned six months after vaccination.[20] In our cohort, undetectable responses were observed as early as four months after completion of vaccination series (Figure 2B). Our study found that the ACE2 binding assay moderately correlated with the pseudovirus neutralization assay against all variants with stronger correlations seen with WT. The ACE2 binding assay was run on a WT RBD plate which may explain the strongest correlation seen between ACE2 binding and WT neutralization

compared to other variants. Two patients who received a third booster dose showed significant fold reduction in ACE2 binding (above the detection of 1000-fold). Our findings also confirm a recently published report that additional vaccine doses lead to improved responses[14] — SAA patients are likely to benefit from additional vaccine doses to maintain detectable humoural responses to COVID-19 vaccination.

Cell-mediated immune response to COVID-19 vaccination was characterized by a $CD4^+$ Th1-type dominant response similar to that in healthy control subjects. SAA patients on maintenance CSA, contrary to its known suppressive effect of T cells, were able to achieve similar responses to SAA patients not on CSA at time of vaccination. Our study revealed that, qualitatively, $CD8^+$ responses to vaccination may be blunted in SAA patients. This finding is contrary to a recent report suggesting $CD8^+$ T-cell-dependent activation as a possible explanation for increased relapse risk in AA.[19] Cellular responses waned as time elapsed from completion of vaccination series. A similar finding was reported by evaluating the antibody and cellular response to COVID-19 vaccination in patients receiving maintenance IST for immune-mediated inflammatory diseases,[21] stressing the importance of booster doses to maintain cellular immunity after vaccination. Polyfunctional analysis revealed that IFN-γ is a dominant cytokine produced in both SAA and healthy controls. While abnormal IFN-γ production is important in the pathogenesis of SAA, its production in response to SARS-CoV-2 vaccination is not deleterious. A higher frequency of IFN-γ-secreting SARS-CoV-2-specific T cells has been identified in patients with mild compared to severe acute COVID-19 infection.[22] Emerging data regarding the protective and prognostic role of T-cell immunity in acute SARS-CoV-2 infection could have implications in SAA patients who develop acute SARS-CoV-2 infection.

There are several limitations of our study. The number of studied individuals, albeit a modest-sized cohort given the rarity of SAA, is limited due to the retrospective nature of our study. We report on experiences from a single institution identified as a tertiary reference medical centre which may impact the generalizability of our results. Additionally, our cohort included only a small proportion of patients within their first six months of IST treatment (ATG, CSA, +/− EPAG). While we did observe humoural and cellular responses in some of these patients, our results cannot be applied to this group; indeed, our practice is to avoid vaccination and instead administer ixagevimab and cilgavimab at this time for these patients. A subgroup (25%) of included patients were on CSA at the time of vaccination; both humoural and cellular responses were observed but due to small numbers, definite conclusions cannot be drawn. Further studies with larger samples sized are needed to confirm the safety and efficacy of vaccines within these subgroups. Lastly, while our findings are encouraging and suggest that vaccination may provide protection for this vulnerable population, thresholds that define adequate protection remain unknown.

In conclusion, SARS-CoV-2 vaccination in SAA patients previously treated with IST does not significantly impact haematological indices and disease status. SAA patients who have unstable blood counts or are classified as PR require a more in-depth risk/benefit assessment prior to SARS-CoV-2 vaccination and a close follow-up post vaccination for relapse. Durable humoural and cellular responses are observed in SAA even in those on CSA. Additional vaccine doses are likely beneficial in SAA to maintain humoural and cellular immunity against COVID-19 as variants continue to emerge.

CONFLICT OF INTERESTS

Neal S. Young. has a cooperative research and development agreement (CRADA) with Novartis that provides research funding. The remaining authors declare no competing financial interests.

DATA AVAILABILITY STATEMENT

De-identified data will be shared with other researchers upon reasonable request to the corresponding author. The sharing will require a detailed proposal to the study investigators and a data transfer agreement must be signed.

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SUPPORTING INFORMATION

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