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SHORT REPORT

Humoral response to mRNA-based COVID-19 vaccine in patients with immune thrombocytopenia

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Summary
Data for COVID-19 vaccine response in patients with immune thrombocytopenia (ITP) are very limited. In a study of 28 patients with ITP, anti-severe acute respiratory syndrome coronavirus 2 spike antibody titres were measured after vaccination. The seroconversion rate for ITP patients was 91.3%, comparable to that in healthy controls (HCs). However, the antibody titre in ITP patients was significantly lower than that in HCs and declined with ageing. Furthermore, the antibody titre in ITP patients who received a minimum prednisolone dose of at least 5 mg/day at any time-point at or after initial vaccination was lower than that in other patients.

KEYWORDS
corticosteroids, COVID-19, humoral response, immune thrombocytopenia (ITP), SARS-CoV-2, vaccine

INTRODUCTION

Since the worldwide spread of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), vaccination using one of two subtypes of mRNA-based vaccines, BNT162b2 or mRNA-1273, has been an effective public health measure for reducing the risk of infection and severe complications from the virus responsible for coronavirus disease-2019 (COVID-19).[1,2] However, there has been a lack of data on the efficacy of vaccines in immunocompromised patients including patients with immune thrombocytopenia (ITP). ITP is mainly managed with corticosteroids, which may hamper the response to a vaccine.[3–6] Therefore, we investigated the antibody titres of SARS-CoV-2 after COVID-19 vaccination in patients with ITP.

PATIENTS AND METHODS

Both patients who had been diagnosed with ITP prior to vaccination and those who were diagnosed with ITP after vaccination were included in this study. All of the patients were vaccinated with two doses of an mRNA-based COVID-19 vaccine, either BNT162b2 or mRNA-1273, and all of the patients visited the Blood Disorders Center at Aiiku Hospital during the period from 1 June 2021 to 31 March 2022. Anti-SARS-CoV-2S immunoassays were performed at three months ± two weeks and six months ± four weeks after the second vaccination as previously reported.[7,8] All but one of the patients did not receive a third dose of the vaccine prior to the six-month blood sampling, and this one patient was excluded from the six-month analysis. The diagnosis and response criteria of ITP were defined according to International Consensus Guidelines.[9]

Abbreviations: AIIRD, autoimmune inflammatory rheumatic disease; HC, healthy controls; IQR, interquartile range; ITP, immune thrombocytopenia; PSL, prednisolone; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; TPO-RA, thrombopoietin receptor agonist.

We recruited healthcare workers aged 55 years and older at Aiiku Hospital who had received two doses of BNT162b2 vaccine as healthy controls (HCs). Individuals with a known history of COVID-19 were excluded from both cohorts of patients and HCs.

RESULTS

Twenty-eight patients with ITP and 28 HCs were included. There were no significant differences between the two groups in gender ratio (ITP vs. HCs: 57.1% females vs. 64.3% females, $p = 0.5984$) and mean age [ITP vs. HCs: 65.1 (±15.0) years vs. 60.2 (±4.4) years, $p = 0.1060$] (Table 1). Patient details are shown in Table S1. Two patients were diagnosed with ITP after vaccination. Of the remaining 26 patients, 20 patients were on active treatment, five patients were under treatment-free observation after the treatment, and one patient was treatment-naive at the time of initial vaccination. All of the patients who were receiving treatment were in response, including 17 patients in complete response. The median dose for the 11 patients receiving prednisolone (PSL) at the time of initial vaccination was 5 (range: 1–7.5) mg, and all were in remission.

Seroconversion rates at three months after the second vaccination for patients with ITP and HCs were 91.3% and 100%, respectively ($p = 0.1984$). However, patients with ITP showed significantly lower antibody titres than those in HCs at both three months [313.0 (interquartile range, IQR: 146.0–731.0) U/ml vs. 945.0 (IQR: 402.5–1358.0) U/ml, $p < 0.01$] and six months [159.0 (71.7–644.0) U/ml vs. 582.5 (240.5–1007.3) U/ml, $p < 0.05$] after vaccination (Figure 1A; Figure S1A). The median antibody titres in ITP patients with a median age of 68 years or older were significantly lower than those in patients younger than 68 years at both three months [179.0 (95.9–363.5) U/ml vs. 605.5 (286.8–1065.8) U/ml, $p < 0.05$] and six months [103.4 (49.6–192.0) U/ml vs. 680.0 (171.5–1107.0) U/ml, $p < 0.01$] after vaccination (Figure 1B; Figure S1B). Age and antibody titres were negatively correlated (Figure 1C).

We evaluated the relationship between immunosuppressive treatment and antibody titres in patients with exclusion of two patients before the development of ITP and one patient who was treatment-naive at the time of initial vaccination. The median antibody titres at three months [169.0 (51.4–258.5) U/ml vs. 584.5 (339.5–871.8) U/ml, $p < 0.05$] and six months [71.2 (32.2–75.8) U/ml vs. 447.0 (136.5–755.0) U/ml, $p < 0.01$] were significantly lower in patients who were receiving PSL at a dose of at least 5 mg/day at the time of initial vaccination than those of patients who were PSL-free or were administered less than 5 mg (Figure 1D; Figure S1C). Even among the patients on active treatment, the median antibody titres at three months [169.0 (51.4–258.5) U/ml vs. 584.5 (425.0–871.8) U/ml, $p < 0.01$] and six months [71.2 (32.2–75.8) U/ml vs. 447.0 (103.5–719.0) U/ml, $p < 0.05$] were significantly lower in patients who were receiving at least 5 mg/day PSL than those in patients receiving less than 5 mg PSL or other treatment.

TABLE 1 Patients' characteristics

	ITP ($n = 28$)
Mean age (±standard deviation) (years)	65.1 (±15.0)
Sex: male/female	12/16
Patients with seroconversion, *n* (%)	
Three months after the second dose	21/23 (91.3)
Six months after the second dose	23/24 (95.8)
Onset of ITP	
Prior to initial vaccination	26
After initial vaccination	2
On active therapy at the time of vaccination	
Yes	20
Corticosteroids only	6
TPO-RA only	7
Corticosteroids and TPO-RA	5
Other single-agent therapy	2
No	8
Treatment off in complete response	5
Treatment-naive	1
Before the onset	2
Rituximab administration prior to vaccination	5
Median duration from last rituximab administration to vaccination (range) (months)	19 (2–49)
Treatment line(s) at the time of initial vaccination	
Median (range)	2 (0–6)
0 (Treatment-naive 1, Before the onset 2)	3
1	9
2	9
3	2
4	3
5	1
6	1
Status at the time of vaccination	
Response	25
Complete response	17
Treatment-naive or before the onset	3
Vaccine subtype	
BNT162b2	24
mRNA-1273	4
Median duration from diagnosis to vaccination (range) (months)	37.5 (2–497)

Abbreviations: ITP, immune thrombocytopenia; TPO-RA, thrombopoietin receptor agonist.

Furthermore, patients who received a minimum PSL dose of at least 5 mg/day at any time-point from the initial vaccination to six-month blood sampling had a significantly lower antibody titre at six months than that in all other patients [71.2 (43.6–122.5) U/ml vs. 608.0 (150.0–1005.0) U/ml, $p < 0.001$] (Figure 1E). A similar result of six-month antibody

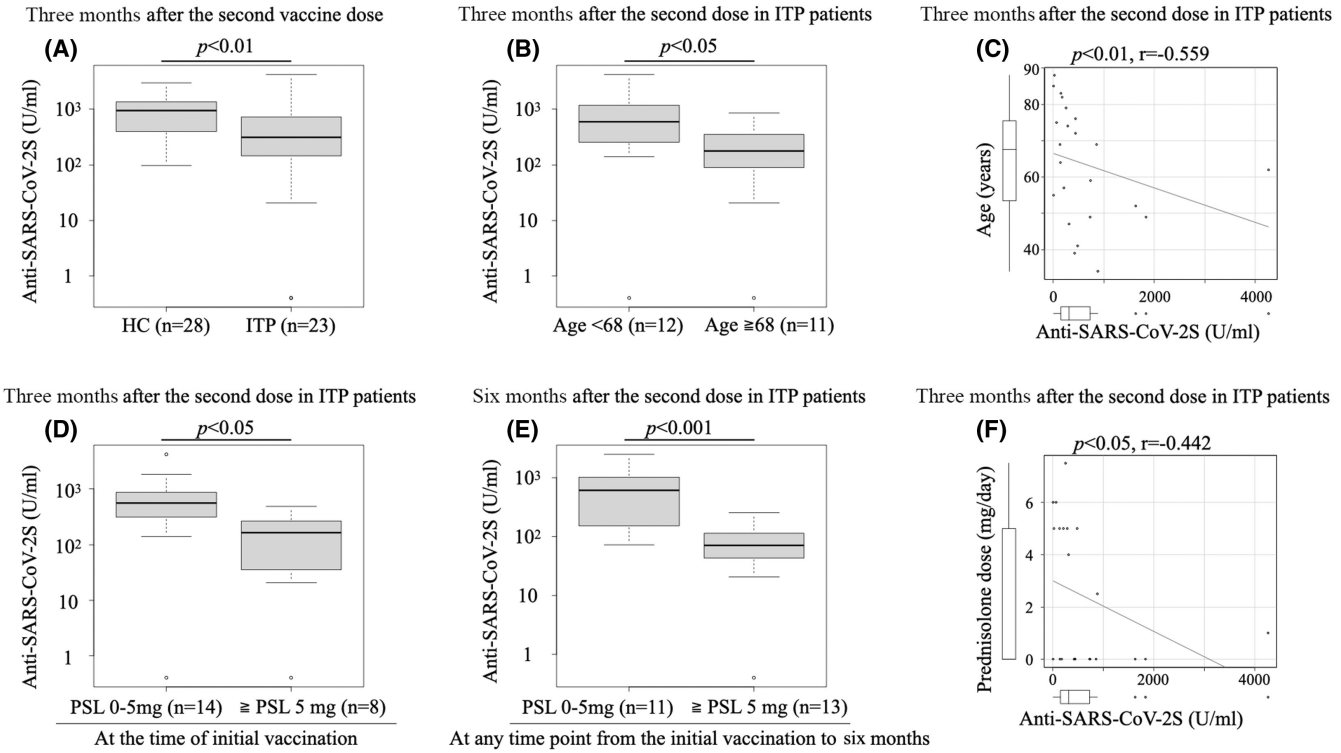

FIGURE 1 The Mann–Whitney *U* test was used to compare medians of antibody titres. The boxes show interquartile range and the centre line shows the median. (A) Anti-SARS-CoV-2S antibody titres in healthy controls and in patients with ITP at three months after the second dose of vaccination. (B) Anti-SARS-CoV-2S antibody titres in ITP patients with a median age of 68 years or older and in ITP patients younger than 68 years of age at three months after the second dose of vaccination. (C) Spearman's correlation coefficient (*R*) and *p* values between age and anti-SARS-CoV-2S antibody titres at three months in ITP patients ($n = 23$). (D) Anti-SARS-CoV-2S antibody titres at three months after vaccination in patients who were receiving PSL at a dose of at least 5 mg/day at the time of initial vaccination and in patients who were PSL-free or were administered less than 5 mg. One patient who was treatment-naive at the time of initial vaccination was excluded from this analysis. (E) Anti-SARS-CoV-2S antibody titres at six months after vaccination in patients who received a minimum PSL dose of at least 5 mg/day at any time-point from the initial vaccination to six-month blood sampling and in all other patients including patients receiving PSL less than 5 mg. (F) Spearman's correlation coefficient (*R*) and *p* values between PSL dose at the time of initial vaccination and antibody titres at three months after the second dose of vaccination ($n = 22$). HC, healthy controls; ITP, immune thrombocytopenia; PSL, prednisolone; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

titre was obtained for the patients on active treatment, including patients who started treatment after vaccination [71.2 (43.6–122.5) U/ml vs. 472.0 (150.0–756.0) U/ml, $p < 0.01$]. PSL dose at the time of initial vaccination and antibody titres at three months were negatively correlated (Figure 1F). Five patients had received rituximab prior (2–48 months, median 19 month) to the first vaccine dose (Table 1; Table S1). Three of the five patients also received a minimum PSL dose of at least 5 mg/day at any time-point from the initial vaccination to six months. Although patients who had received rituximab had lower antibody titres at three months [104.2 (0.4–266.8) U/ml vs. 431.0 (159.5–823.8) U/ml, $p = 0.0885$] and six months [60.1 (32.5–95.2) U/ml vs. 253.0 (71.8–752.0) U/ml, $p = 0.0648$] than the other patients, there were no statistically significant differences. One patient with hypogammaglobulinaemia who received rituximab 19 months prior to vaccination and another patient who received rituximab two months prior to vaccination, who also received 6 mg/day of PSL at the time of vaccination, were seronegative. There were no significant differences in antibody titres depending on receiving active treatment or not, on treatment lines, disease status, or vaccine subtypes. During the follow-up period, none of the ITP patients or healthy individuals developed documented COVID-19 infection.

DISCUSSION

Patients with autoimmune diseases have shown high rates of hospitalization, severe disease and death in the case of SARS-CoV-2 infection.[3–6,10,11] Moreover, patients with autoimmune diseases showed lower antibody titres after COVID-19 vaccination than those in healthy individuals.[3–6,10,11] However, data for COVID-19 vaccine responses in patients with ITP are very limited. Furthermore, since ITP develops after COVID-19 vaccination in both healthy individuals and pre-existing ITP patients, the vaccine response in ITP patients is a great concern for both patients and their physicians.[8,12]

Here we revealed that the seroconversion rate after vaccination in ITP patients was comparable to that in HCs; however, the median antibody titre was significantly lower in ITP patients than in HCs. In contrast, it has been reported that patients with autoimmune inflammatory rheumatic disease (AIIRD) have significantly lower seroconversion rates as well

as antibody titres than healthy individuals.[4,5] Risk factors for reduced immunogenicity included older age and treatment with corticosteroids, rituximab, mycophenolate mofetil and abatacept.[5] In these studies, the fact that corticosteroids were commonly used in combination with other immunosuppressants in patients with AIIRD had precluded analysis of the dose-dependent effect of corticosteroids on vaccines. The immunological response to COVID-19 vaccines might be reduced by the immune dysfunction due to autoimmune disorders itself and more potent immunosuppressive therapies in patients with AIIRD. The efficacy of the COVID-19 vaccine also declined with advancing age in patients with ITP. The response to vaccination might be insufficient in patients with ITP, especially in elderly patients with ITP.

Corticosteroids used at doses greater than physiologic doses can reduce the immune response to vaccines.[13] To date, there have been only limited studies about the correlation between treatment with corticosteroids and COVID-19 vaccine response, and it has been shown that active treatment with corticosteroids reduced immunogenicity in patients with autoimmune disease.[3–5] At the moment, the dose-dependent effect of corticosteroids on vaccine response remains unknown. In our study, the antibody titre in patients who received a minimum PSL dose of at least 5 mg/day at any time-point at or after initial vaccination was significantly lower than that in other patients. Additional PSL was administered after vaccination in three patients with a dose of at least 20 mg/day as initial or re-induction treatment for ITP and in one heavily treated patient with high-dose dexamethasone as re-induction therapy. Corticosteroids induce immunosuppression in a dose-dependent manner.[14] Based on these findings and our results, antibody titres may be decreased by corticosteroids in a dose-dependent manner after COVID-19 vaccination.

Our study has several limitations. Healthy controls are health care workers. Although our hospital did not accept COVID-19 patients, it is undeniable that they had asymptomatic COVID-19 infections. The number of patients was small, which made it difficult for us to obtain definitive results in subanalysis including rituximab. This study evaluates only the humoral immunity, but not T-cell immunity, which is also important in preventing a severe course of COVID-19.[15]

In conclusion, the results of our study may help to select better treatment options for ITP patients although they should be confirmed by further large-scale studies.

AUTHOR CONTRIBUTIONS

Akio Mori designed the study, analysed the data, and wrote the manuscript. Masahiro Onozawa revised and approved the manuscript. Mirei Kobayashi, Shihori Tsukamoto, Hajime Senjo, Takashi Ishio, Emi Yokoyama, Koh Izumiyama, Makoto Saito and Masanobu Morioka performed recruitment and treatment of patients and provided critique to the manuscript. Haruna Muraki performed experiments and provided critique to the manuscript. Takanori Teshima revised the manuscript. Takeshi Kondo designed and supervised the study, and approved the manuscript. All authors read and approved the final manuscript.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

DATA AVAILABILITY STATEMENT

The datasets generated and/or analysed during the current study are available from the corresponding author upon reasonable request.

CLINICAL TRIAL REGISTRATION

This study was part of a prospective observation study (UMIN000045267) and it was conducted in compliance with ethical principles based on the Helsinki Declaration and was approved by the institutional review board of Aiiku Hospital on 27 August 2021 (No. 202108181).

PATIENT CONSENT STATEMENT

Written informed consent was obtained from all individuals included in the study.

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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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