REGULAR ARTICLE

blood advances

COVID-19 vaccination in patients with immune thrombocytopenia

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Key Points

- A decrease in platelet count after SARS-CoV-2 vaccination is similar in patients with ITP and healthy controls.
- Risk factors for exacerbation of ITP after SARS-CoV-2 vaccination include low platelet count, younger age, and current therapy.

Immune thrombocytopenia (ITP) is an acquired autoimmune disorder that is characterized by low platelet count and increased bleeding risk. COVID-19 vaccination has been described as a risk factor for de novo ITP, but the effects of COVID-19 vaccination in patients with ITP are unknown. We aimed to investigate the effects of COVID-19 vaccination in patients with ITP on platelet count, bleeding complications, and ITP exacerbation (≥50% decline in platelet count, or nadir platelet count $< 30 \times 10^9$/L with a >20% decrease from baseline, or use of rescue therapy). Platelet counts in patients with ITP and healthy controls were collected immediately before and 1 and 4 weeks after the first and second vaccinations. Linear mixed-effects modeling was applied to analyze platelet counts over time. We included 218 patients with ITP (50.9% female; mean age, 55 years; and median platelet count, 106×10^9/L) and 200 healthy controls (60.0% female; mean age, 58 years; median platelet count, 256×10^9/L). Platelet counts decreased by 6.3% after vaccination. We did not observe any difference in decrease between the groups. Thirty patients with ITP (13.8%; 95% confidence interval [CI], 9.5-19.1) had an exacerbation and 5 (2.2%; 95% CI, 0.7-5.3) suffered from a bleeding event. Risk factors for ITP exacerbation were platelet count $< 50 \times 10^9$/L (odds ratio [OR], 5.3; 95% CI, 2.1-13.7), ITP treatment at time of vaccination (OR, 3.4; 95% CI, 1.5-8.0), and age (OR, 0.96 per year; 95% CI, 0.94-0.99). Our study highlights the safety of COVID-19 vaccination in patients with ITP and the importance of the close monitoring of platelet counts in a subgroup of patients with ITP. Patients with ITP with exacerbation responded well on therapy.

Introduction

Vaccination against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is critical to control the COVID-19 pandemic. The European Medicines Agency has authorized 4 vaccines for use in the European Union: the BNT162b2 (Comirnaty) vaccine, the messenger RNA (mRNA)-1273 (Spikevax) vaccine, the ChAdOx1-S (Vaxzevria) vaccine, and the Ad26.COV2.S (Johnson & Johnson) vaccine.[1-4] Reports of

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The full-text version of this article contains a data supplement.

serious adverse events, including vaccine-associated immune thrombocytopenia (ITP), thrombosis, and the rare occurrence of vaccine-induced immune thrombotic thrombocytopenia, has led to the restrictive use of the ChAdOx1-S and Ad26.COV2.S vaccines.[5,6]

ITP is an acquired autoimmune disorder that is characterized by low platelet count ($<100 \times 10^9$/L), resulting from platelet destruction and impaired platelet production, that leads to increased bleeding risk.[7] ITP is likely to arise from defective immune tolerance in addition to a possible triggering event.[7] COVID-19 infection has recently been identified as a risk factor for ITP development,[8] and a large population study showed a small increased risk for de novo ITP after the ChAdOx1-S vaccine but not after the BNT162b2 vaccine.[9] These findings illustrate that immunological events like infection and vaccination in the COVID-19 pandemic could be an important risk factor in the development and exacerbation of ITP.

Exacerbation of thrombocytopenia in patients with ITP after COVID-19 vaccination has been described in retrospective studies, but a systematic evaluation of platelet counts over time is missing.[10-13] Therefore, it is still unclear how COVID-19 vaccination affects patients with ITP over time, if and when thrombocytopenia develops, and when they are at risk for bleeding.

To gain a better understanding of the effect of COVID-19 vaccination in patients with ITP, we systematically monitored platelet counts, bleeding events, and ITP exacerbations in routine clinical practice.

Methods

Trial design and oversight

We conducted a multicenter observational study across 9 participating hospitals in The Netherlands. The study was designed and conducted in accordance with the Declaration of Helsinki. The medical ethical committee of Erasmus MC and the local research committees approved the study protocol and amendments (MEC-2021-0238). Erasmus MC was the sponsor, served as the coordinating center, and was responsible for maintenance of the database, validation and analyses of data, and trial coordination.

Participants and procedures

Adult patients with a history of ITP, according to Rodeghiero et al,[14] and who received ≥1 COVID-19 vaccination were enrolled. Patients were scheduled to receive 2 vaccinations, ~4 weeks apart. Without existing guidelines about how to monitor patients with ITP after COVID-19 vaccination, we decided to measure platelet counts at baseline, followed by measurements 1 and 4 weeks after the first and second vaccinations as part of routine clinical practice. Data on platelet counts of healthy controls were obtained at baseline, as well as at 4 weeks after the first and the second mRNA-1273 vaccinations, from the Renal patients COVID-19 VACcination Immune Response (RECOVAC IR) study (Central Committee on Research Involving Human Subjects, NL76215.012.21).[15] Healthy controls included the partner, sibling, or household member of the patient included in the RECOVAC IR study.[15]

Objectives and outcomes

The primary objective was to study platelet dynamics in patients with ITP after COVID-19 vaccination. Secondary outcomes were symptomatic bleeding (defined as World Health Organization [WHO] bleeding ≥ grade 2) and exacerbation of ITP (defined as the development of any of the following: ≥50% decline in platelet count compared with baseline, >20% decline in platelet count compared with baseline and a platelet nadir $< 30 \times 10^9$/L, or need for rescue medication). Rescue medication was defined as treatment change at the discretion of the treating physician (ie, switch to other ITP medication, start new ITP medication, addition of concomitant ITP medication, or intensification of current ITP treatment), all independently of change in platelet count and vaccine-specific and nonspecific adverse events. Finally, risk factors for ITP exacerbation were studied.

Statistical analyses

Descriptive statistics are expressed as median and interquartile range (IQR), mean and standard deviation, or counts with percentages. Characteristics of patients with ITP and healthy controls were compared using Fisher's test or Wilcoxon's rank-sum test with continuity correction. To identify the effect of COVID-19 vaccination over time while taking into account intrasubject variability, a linear mixed-effects model was applied to the log-transformed platelet count. After log transformation, platelet count had closer to a normal distribution, allowing for a better model fit. The exponentiated model coefficients can be interpreted as ratios of the geometric means and percentage differences. A random intercept per patient was included. In this model, time was considered a grouped variable, and no interaction between time and ITP status was included because of the to lack of interaction ($P = .78$ of the interaction term). We corrected the model using fixed effects for age, sex, duration of ITP, presence of any treatment at the start of vaccination, receiving any previous ITP treatment, splenectomy, rescue medication, and treatment in an academic center. Rescue medication was treated as a time-varying covariate. It was set to 0 at the start and at 1 after the first date of rescue medication. A Friedman test was performed in the subgroups of patients with ITP grouped by baseline platelet count with steps of 50×10^9/L platelets. The 95% confidence intervals (CIs) of the crude percentages of patients with exacerbation and bleeding were calculated using the Clopper-Pearson method. A logistic regression model was created to identify risk factors for exacerbation. All other statistical analyses were performed with IBM SPSS Statistics 25 and R version 4.1.1. with package lme4.

Results

Patient characteristics

We included 218 patients with ITP (50.9% female) aged 55 (17) years and 200 healthy controls (60.0% female) aged 58 (13) years between 1 February 2021 and 16 July 2021 (Table 1). All healthy controls received the same vaccine (mRNA-1273 vaccines),[15] but patients with ITP received 3 different types of vaccines: 201 (92.2%) received the mRNA-1273 vaccine, 16 (7.3%) received the BNT162b2 vaccine, and 1 (0.5%) received the ChAdOx1-S vaccine (supplemental Figure 1). Of the patients with ITP, 213 (97.7%) received both vaccinations. Reasons for not receiving the second vaccination were death from esophageal varices bleeding (n = 1), deemed unsafe by treating physician (n = 2), or prior infection with SARS-CoV-2 virus (n = 2).

Healthy controls and patients with ITP had similar baseline characteristics, with the exception of a small difference in mean age (58.2 and 55.2 years, respectively; $P = .047$) and median baseline platelet count (256×10^9/L and 106×10^9/L respectively; $P < .001$) (Table 1). One hundred and ninety-six (89.9%) patients with ITP had primary ITP for a median duration (IQR) of 5.8 (10.6) years.

Table 1. Characteristics of patients with ITP and healthy controls

	Patients with ITP (N = 218)			
	All patients with ITP (N = 218)	Patients with ITP without exacerbation* (n = 188)	Patients with ITP with exacerbation* (n = 30)	Healthy controls (N = 200)
Age, y†	55.2 ± 16.8	56.7 ± 16.4	46.3 ± 11.7	58.2 ± 13.4
Females	111 (50.9)	97 (51.6)	14 (46.7)	120 (60.0)
Baseline platelet count, median (IQR), $\times 10^9$/L	106 (110)	108 (108)	84 (143)	256 (83)
ITP classification‡				
Primary ITP	196 (89.9)	168 (89.4)	28 (93.3)	
Secondary ITP	21 (9.6)	20 (10.6)	2 (6.7)	
Duration of ITP, median (IQR), y	5.8 (10.6)	6.0 (10.4)	4.8 (14.9)	
ITP duration‡				
Newly diagnosed	1 (0.5)	1 (0.5)	0 (0.0)	
Persistent	11 (5.0)	9 (4.8)	2 (6.7)	
Chronic	136 (62.4)	115 (61.2)	21 (70.0)	
Remission	69 (31.7)	63 (33.5)	6 (20.0)	
Unknown	1 (0.5)	0 (0.0)	1 (3.3)	
Prior splenectomy	27 (12.4)	22 (11.7)	5 (16.7)	
Prior ITP treatment§	138 (63.6)	114 (60.6)	24 (80.0)	
Rescue medication in 6 mo prior to COVID-19 vaccination¶	16 (7.3)	5 (2.7)	11 (36.7)	
Current therapy	64 (29.5)	48 (25.5)	16 (53.3)	
Glucocorticoids	16 (7.4)	15 (8.0)	1 (3.3)	
Rituximab	1 (0.5)	0 (0)	1 (3.3)	
TPO-RAs				
Eltrombopag	25 (11.5)	20 (10.6)	5 (16.7)	
Romiplostim	16 (7.4)	7 (3.7)	9 (30.0)	
Other	6 (2.8)	6 (3.2)	0 (0.0)	

TPO-RAs, thrombopoietin receptor agonists.
Unless otherwise noted, data are n (%).
*Exacerbation is defined as the development of any of the following: ≥50% decline in platelet count compared with baseline, >20% decline in platelet count compared with baseline and a platelet nadir $< 30 \times 10^9$/L, or use of rescue medication. Rescue medication was defined as any treatment change by discretion of the treating physician (ie, switch to other ITP medication, start of new ITP medication, addition of concomitant ITP medication, or intensification of current ITP treatment).
†Data are mean ± standard deviation.
‡According to the definition of Rodeghiero and colleagues.[14]
§Defined as having ≥1 therapy before COVID-19 vaccination.
¶Defined as any treatment change by discretion of the treating physician (ie, switch to other ITP medication, start of new ITP medication, addition of concomitant ITP medication, or intensification of current ITP treatment).

One hundred and thirty-six (62.4%) patients had chronic ITP, and 69 (31.7%) were in remission. Sixty-four (29.5%) patients with ITP were receiving ITP treatment at the time of first vaccination. Sixteen (7.3%) patients with ITP had used rescue medication in the 6 months prior to COVID-19 vaccination.

COVID-19 vaccination and platelet count response

During our study, a decrease in platelet count was observed in 55% (n = 120) of patients with ITP and 63% (n = 126) of healthy controls (Figure 1A). In patients with ITP grouped by baseline platelet count, no significant difference in the decrease in platelet count over time was found, with the exception of patients with ITP with baseline platelet counts $> 150 \times 10^9$/L (Figure 1B). A large variability in platelet counts was observed across patients with ITP (intraclass correlation, 0.75; Figure 2).

In the mixed-effects analysis, a significant (6.3%) decrease in platelet count compared with baseline was found 4 weeks after the second vaccination (Figure 3; supplemental Table 1). We corrected for age, sex, duration of ITP, current treatment, receiving any prior ITP treatment, splenectomy, rescue medication, and treatment in an academic center. We did not observe any difference in the decrease between the groups.

Factors significantly associated with decreased platelet counts were longer duration of ITP (defined as years between ITP diagnosis and COVID-19 vaccination) and the presence of current treatment. In contrast, previous splenectomy was associated with increased platelet counts (Figure 3; supplemental Table 1).

ITP exacerbation and complications after COVID-19 vaccination

Thirty (13.8%; 95% CI, 9.5-19.1) patients with ITP experienced an exacerbation during the study period (Table 1). Eighteen (8.3%) patients had a ≥50% decline in platelet count compared with baseline, 18 (8.3%) patients had a >20% decline in platelet count

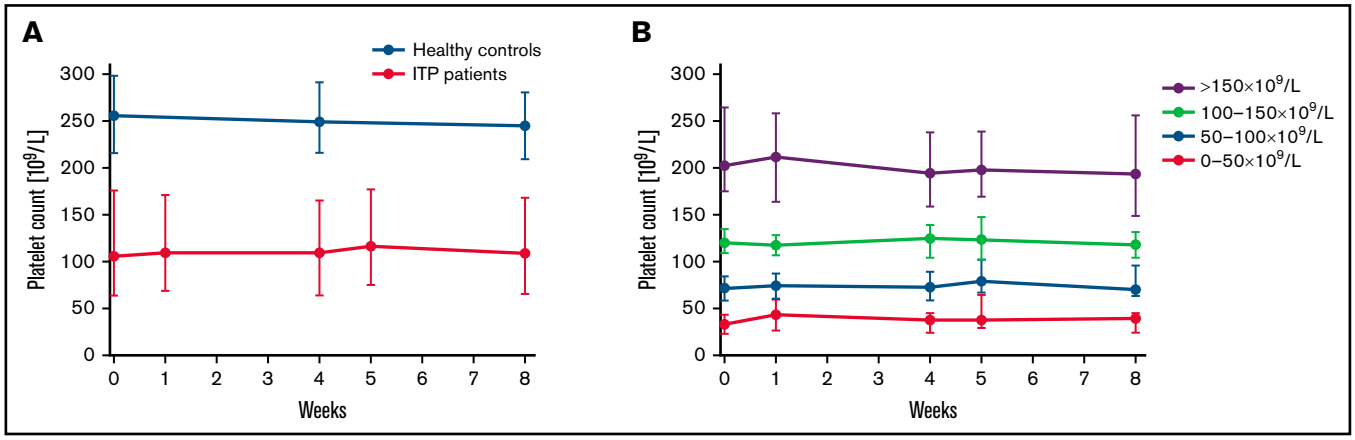

Figure 1. Platelet counts of patients with ITP and healthy controls after COVID-19 vaccination. (A) Platelet counts of patients with ITP and healthy controls over the entire study period. Platelet counts are median ± IQR. No significant difference in platelet count over time was observed between the 2 groups. (B) Platelet counts for patients with ITP grouped by baseline platelet count. Absolute platelet counts are median ± IQR.

compared with baseline and a platelet nadir $< 30 \times 10^9$/L, and 15 (6.9%) patients received rescue medication after COVID-19 vaccination (Table 2). Eleven (36.7%) of these 30 patients with ITP needed rescue medication 6 months prior to COVID-19 vaccination compared with 5 (2.7%) of the patients with ITP without exacerbation (Table 1). Of the 30 patients with exacerbation, 16 experienced it after their first vaccination, and 3 of these patients did not receive the second vaccination. Individual platelet counts of patients with ITP with rescue medication and a significant decrease in platelet count are shown in supplemental Figure 2A and supplemental Figure 2B, respectively. Six (2.8%) patients began ITP treatment after COVID-19 vaccination: 3 received glucocorticoids only, 1 received glucocorticoids with IV immunoglobulin (IVIG), 1 received IVIG, and 1 received eltrombopag. Six (2.8%) patients required intensification of current treatment with TPO RA and 1 (0.5%) switched to another TPO RA. Of these seven patients 4 used romiplostim and 3 used eltrombopag (Table 2).

Rescue medication resulted in a complete response in 7 (46.7%) patients and a partial response in 2 (13.3%) patients. One patient (6.7%) did not respond to rescue medication, and 5 (33.3%) patients had no recorded response.

Bleeding complications occurred in 5 (2.3%) patients with ITP and in 0 (0.0%) healthy controls (Table 2). The first patient experienced 2 bleeding complications after the first COVID-19 vaccination. Two weeks after the COVID-19 vaccination, the patient experienced hematuria with a platelet count $< 3 \times 10^9$/L. The second bleeding was a vitreous hemorrhage and occurred 3 weeks after the first COVID-19 vaccination (platelet count, 7×10^9/L). The second patient experienced several episodes of bleeding during the study period with epistaxis, oral mucosal bleeding, and urogenital bleeding. This patient had a baseline platelet count $< 3 \times 10^9$/L and received a red blood cell transfusion and additional IVIG as the result of a severe epistaxis episode. The third patient had a bleeding event after elective vascular surgery and received a red blood cell transfusion in combination with platelet transfusion. The platelet count was 75×10^9/L, and the patient did not experience any decrease in platelet count after COVID-19 vaccination. The fourth patient had a spontaneous cerebellar bleeding 3 weeks after the first vaccination with a platelet count of 104×10^9/L. This patient did not experience a decrease in platelet count after COVID-19 vaccination. The patient was treated with additional platelet transfusion and corticosteroids. The fifth patient had a fatal esophageal bleeding 2 weeks after the first COVID-19 vaccination. This patient experienced a decrease in platelet count to 14×10^9/L after COVID-19 vaccination, for which the dosage of romiplostim was increased. However, the patient had a normal platelet count of 175×10^9/L at the time of bleeding. Despite endoscopic intervention and additional platelet transfusion, the patient died from ongoing bleeding.

The most common side effects after COVID-19 vaccination in patients with ITP were local tenderness and swelling at the site of vaccination (n = 15; 29.4%) and myalgia and arthralgia (n = 13; 25.5%). Fever was reported more often after the second vaccination (supplemental Table 2).

Risk factors for ITP exacerbation after COVID-19 vaccination

Risk factors for exacerbation of ITP after vaccination were baseline platelet count $< 50 \times 10^9$/L (odds ratio [OR], 5.33; 95% CI, 2.07-13.73), ITP treatment at start of COVID-19 vaccination (OR, 3.44; 95% CI, 1.47-8.04), and younger age (OR, 0.96 per year; 95% CI, 0.94-0.99) (supplemental Table 3). Although a longer duration of ITP was associated with a decrease in platelet counts over the entire study, in our logistic regression model it did not increase the risk of exacerbation. The type of vaccine was not associated with the risk of exacerbation, but the sample size might have been too small to detect differences between groups. The presence of antiplatelet antibodies also was not associated with exacerbation risk. However, the presence of antiplatelet antibodies was recorded in only 4.6% of patients with ITP, so our sample size might have been too small to detect differences.

Discussion

We systematically investigated the effects of COVID-19 vaccination on platelet count in a large study of patients with ITP compared with healthy controls. Only 3 of 218 patients experienced problems after the first vaccination that prohibited completion of the series. COVID-19 vaccination led to a significant (6.3%) decrease in platelet counts in patients with ITP and healthy controls. Of the patients

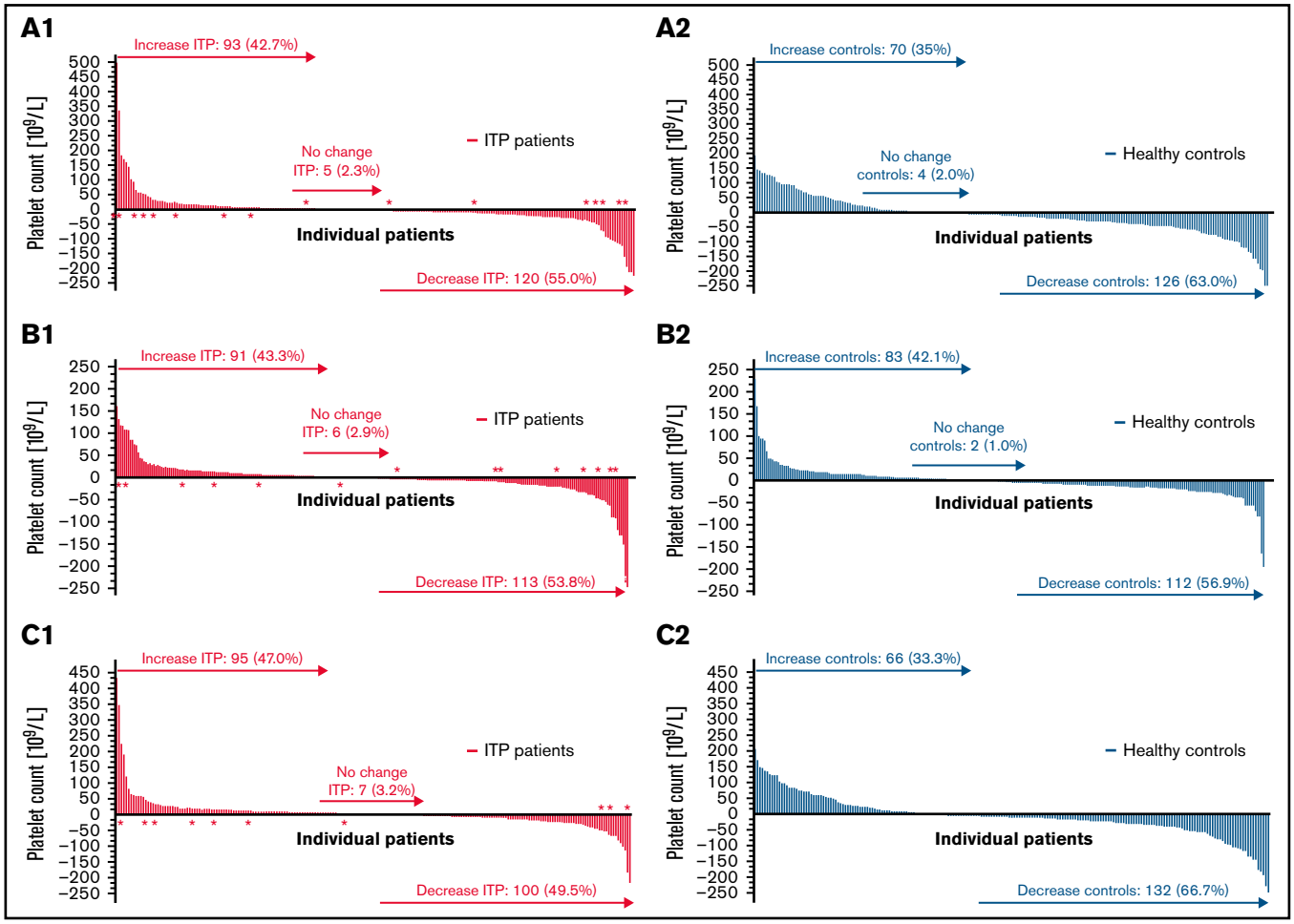

Figure 2. Individual changes in platelet count after both COVID-19 vaccinations in patients with ITP and in healthy controls. The absolute difference in platelet count is shown per individual in patients with ITP (red) and healthy controls (blue), absolute differences between baseline and 4 weeks after the second vaccination (A1-A2), between baseline and the second vaccination (B1- B2), and between the second vaccination and 4 weeks after the second vaccination (C1-C2). Every bar represents 1 subject. A positive change in absolute platelet count means an increase in platelet count after COVID-19 vaccination, whereas a negative change represents a decrease. *Subject received rescue medication during the study period.

with ITP, 13.8% exhibited an exacerbation following vaccination. Risk factors for exacerbation were baseline platelet count $< 50 \times 10^9$/L, having ITP treatment at the start of COVID-19 vaccination, and/or younger age. Nearly all patients with ITP had a (complete) response after rescue medication.

Thrombocytopenia (platelet count $< 100 \times 10^9$/L) after vaccination has been described in children, with an incidence rate of 0.087 to 2.6 per 100 000 doses.[16] After COVID-19 vaccination in adults, the incidence rate of thrombocytopenia was reported to be 1.13 to 1.33 per 100 000 ChAdOx1-S doses.[9,17,18] In our study, 63% of healthy controls experienced decreased platelet counts 4 weeks after the second vaccination, but only 1 (0.5%) had a platelet count $< 100 \times 10^9$/L.

In 2 small studies, a decrease in platelet counts was reported in 12% to 32% of the patients with ITP after COVID-19 vaccination.[10,11] This is in line with our observed decrease in 55% of patients with ITP after COVID-19 vaccination. In contrast, a study of 92 patients with ITP who mostly received the BNT162b2 vaccine did not report a decreased platelet count after the first and second vaccinations.[12] In our mixed-effects model, we observed a significant (6.3%) decrease in platelet counts in patients with ITP after COVID-19 vaccination. Because there is a high degree of inter- and intraindividual variability in platelet counts over time, we systemically measured patients over a longer observation period and corrected for inter- and intraindividual variability. We hypothesize that this systematic approach to monitor platelet count is essential to draw conclusions about their changes following COVID-19 vaccination.

In our study, 13.8% of patients with ITP experienced an exacerbation, defined as development of any of the following: ≥50% decline in platelet count compared with baseline, >20% decline in platelet count compared with baseline and a platelet nadir $< 30 \times 10^9$/L, or a need for rescue medication. Other observational studies found comparable incidences between 12% and 25%.[11-13] In our study, 6.9% of our patients required rescue medication compared with 8.7% in the study by Crickx et al.[12] In other autoimmune diseases, exacerbation of symptoms after COVID-19 vaccination has been described anecdotally, with rapid remission after glucocorticoids.[19,20] However, in a single-center study of 26 patients with chronic inflammatory diseases, no patient experienced a disease flare.[21]

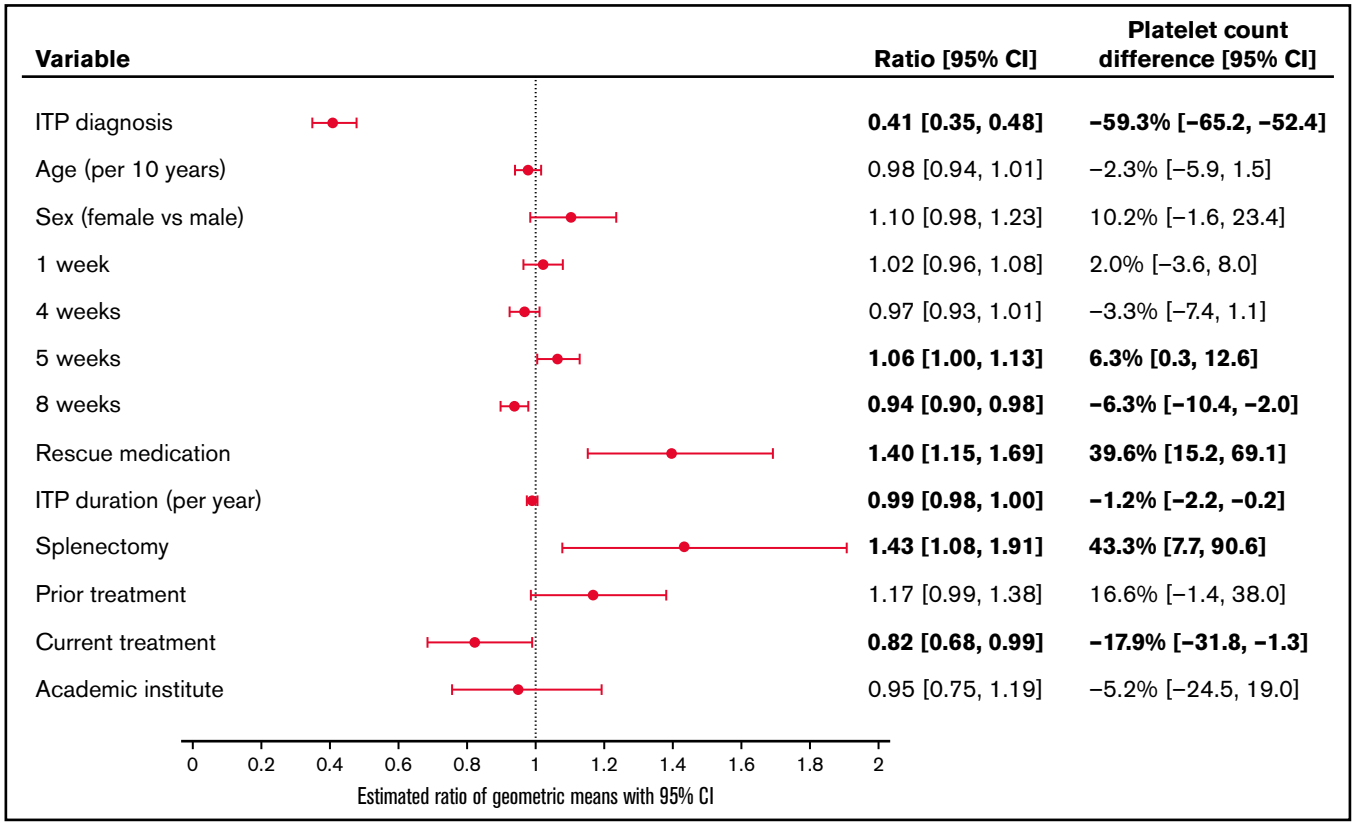

Figure 3. Effect of COVID-19 vaccination on platelet count. Forest plot for estimated ratios of geometric means with 95% CI for the effect on platelet count. Time points 1 week, 4 weeks, 5 weeks, and 8 weeks after the first COVID-19 vaccination are compared with T = 0 (baseline), ITP diagnosis is the comparison of patients vs healthy subjects, and other variables are reported as comparisons of yes vs no. *Percentage difference and 95% CI were calculated from the ratio of geometric means.

Furthermore, a large cohort study did not show any significant difference in the exacerbation of autoimmune rheumatic disease compared with non–autoimmune rheumatic disease after COVID-19 vaccination.[22]

Based on our current understanding, we speculate that ITP stems from a propensity to autoimmunity in combination with a triggering event, such as infection or vaccination.[7] Intriguingly, in our systematic evaluation of platelet counts in patients with ITP and healthy individuals, we found that both groups had significantly decreased platelet counts as a result of COVID-19 vaccination. This suggests that exacerbation or development of thrombocytopenia because of (COVID-19) vaccination might be unrelated to ITP, as evidenced by the fact that we could not find an interaction between platelet counts over time and whether a subject had ITP. This observation is also underscored by the high degree of interindividual variability in patients with ITP and healthy controls, suggesting no universal mechanism leading to lower or higher platelet counts. We also did not find a correlation between platelet counts and anti–SARS-CoV-2 immunoglobulin G levels in the healthy controls (data not shown), suggesting that, at least in healthy individuals, changes in platelet count are unrelated to vaccine response. On the other hand, we found a significant negative association between platelet counts and ITP duration, as well as between platelet counts and current ITP treatment. Also, patients with ITP with exacerbation needed more frequent rescue medication prior to COVID-19 vaccination compared with patients with ITP without exacerbation. These data may suggest that the hardest-to-treat patients with chronic ITP are more susceptible to develop thrombocytopenia after vaccination in comparison with a group not currently requiring treatment for ITP. Additionally, previous splenectomy was positively associated with platelet counts over time, signifying that this potential lack of acute immune response is directly favorable for platelet counts in these individuals. To summarize, it remains unclear whether COVID-19 vaccination has a differential effect on patients with ITP and healthy controls. Our associative findings warrant further investigation to firmly establish whether patients with ITP are more prone to platelet count changes resulting from COVID-19 vaccination.

Our study aimed to provide a better understanding of the effect of COVID-19 vaccination in patients with ITP. The strengths of this study are the prospective and systematic evaluation of real-world data on platelet counts, bleeding complications, and the need for rescue medication in patients with ITP. Furthermore, we used a healthy control group to interpret results from patients with ITP accordingly. However, there are also some limitations. First, almost all patients with ITP received the mRNA vaccine, so caution is warranted when generalizing our results to other vaccines. Still, mRNA vaccines are the most frequently used globally, with >80% of European vaccine recipients and >90% of US vaccine recipients getting this type of vaccine.[23,24] One patient with ITP received the adenoviral vector vaccine (ChAdOx1-S vaccine) without any significant changes in platelet count. Although thrombocytopenia after COVID-19 vaccination is primarily associated with ChAdOx1-S vaccination,

Table 2. Complications after COVID-19 vaccination in patients with ITP

	Total (N = 218)	After first vaccination (n = 218)	After second vaccination (n = 213)	Healthy controls (n = 200)
Bleeding	5 (2.3)	5 (2.3)	0 (0.0)	0 (0.0)
WHO grade 2	2 (0.9)	2 (0.9)	0 (0.0)	
WHO grade 3	1 (0.5)	1 (0.5)	0 (0.0)	
WHO grade 4	2 (0.9)	2 (0.9)	0 (0.0)	
Exacerbation	30 (13.8)	16 (7.3)	14 (6.6)	2 (1.0)
≥50% decline in platelet count compared with baseline	18 (8.3)	8 (3.7)	10 (4.7)	2 (1.0)
>20% decline in platelet count compared with baseline and platelet nadir $< 30 \times 10^9$/L	18 (8.3)	6 (2.8)	12 (5.6)	0 (0.0)
Use of rescue medication	15 (6.9)	8 (3.7)	6 (2.8)	0 (0.0)
Intensification of treatment	6 (2.8)	4 (1.8)	1 (0.5)	
Addition of extra medication	4 (1.8)	2 (0.9)	2 (0.9)	
Switch medication	1 (0.5)	1 (0.5)	0 (0.0)	
Start new medication	4 (1.8)	1 (0.5)	3 (1.4)	
Transfusion	4 (1.8)	4 (1.8)	0 (0.0)	0 (0.0)
Red blood cell transfusion	3 (1.4)	3 (1.4)	0 (0.0)	
Platelet transfusion	2 (0.9)	2 (0.9)	0 (0.0)	

All data are n (%).

conclusions cannot be made with regard to ChAdOx1-S vaccination in patients with ITP.[9] Second, although we cannot exclude that exacerbation after COVID-19 vaccination is due to a natural course of ITP, half of the patients with ITP with exacerbation did not require treatment for ITP before COVID-19 vaccination. In these patients, COVID-19 vaccination seems to be a plausible cause of exacerbation. Third, we did not assess anti–SARS-CoV-2 immunoglobulin G levels in patients with ITP as a measure of vaccine response, so no firm conclusions can be made about the direct effect of COVID-19 vaccination on platelet count; however, no association between platelet count and antibody levels was noted in healthy controls. Finally, platelet count and bleeding complications in healthy controls were obtained from the RECOVAC IR study. Because bleeding complications were not a primary outcome in this study, their underestimation might have occurred, although bleeding scores were similar (eg, WHO criteria National Cancer Institute's Common Terminology Criteria ≥ grade 2). Also, the RECOVAC-IR study did not measure platelet count 1 week after each COVID-19 vaccination. A temporary decrease in platelet counts may be missed in healthy volunteers. In contrast, however, we observed an increase in overall platelet count in patients with ITP 1 week after the first and second vaccinations.

To conclude, our study highlights the safety of COVID-19 vaccination in patients with ITP and the importance of close monitoring of platelet counts in a subgroup of patients with ITP. Patients with ITP with an exacerbation responded well to therapy.

Authorship

Contribution: H.N.-N., M.E., S.M.L.-K., C.I., M.-D.L., and A.J.G.J. designed the study protocol; C.V. and E.D.v.W. analyzed data; E.D.v.W. created the linear mixed-effects model; F.N.C., H.N.-N., M.E., S.M.L.-K., C.I., P.E.W., B.S., P.A.J., F.B., P.A.W.t.B., F.W.G.L., M.J.H.A.K., and A.J.G.J. enrolled and treated patients; the RECOVAC-IR Consortium provided data for healthy controls; and C.V., M.S., and A.J.G.J. wrote the manuscript. All authors reviewed and provided feedback on the drafts and approved the final manuscript for submission.

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