

Effect of inactivated and mRNA COVID-19 vaccines on thrombocytopenia in immune thrombocytopenia patients

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This retrospective observational study was aimed to address the possible effects of inactivated and mRNA vaccines in immune thrombocytopenia patients related to exacerbation. To define exacerbation, more than 30% decrease in platelet counts from baseline or platelet counts decreased to less than $30 \times 10^9/L$ and/or development of new bleeding were considered. Fifty-nine (male 30.5%, female 69.5%) out of 208 immune thrombocytopenia patients, were enrolled in the study. The median age was 47 (range 18-86). A total of 171 vaccinations were performed in 59 patients. Thirty-eight and 62% of patients were vaccinated with Sinovac[®] and BioNTech[®], respectively. Overall, 10 (16.9%) patients experienced decrease in platelet count below $30 \times 10^9/L$ after vaccination. During the last year before pandemic, 19 of the same cohort (32.2%) experienced such decrease. After first, second and booster dose vaccinations, 12.7%, 13.8% and 15% of patients experienced exacerbation respectively; exacerbation with minor bleeding was 2.3% and all bleeding episodes were successfully treated by starting with steroid or increasing the steroid dose. We did not report any severe and life-threatening bleeding. A statistical difference in exacerbation was documented in patients vaccinated with mRNA vaccine ($p = 0.041$) only after the first dose and younger patients experienced a higher rate of exacerbation without statistical significance ($p = 0.06$) after the first dose. In conclusion, both mRNA and inactivated vaccines seem to be safe for immune thrombocytopenia patients with rare bleeding complications. Especially younger patients and those vaccinated with mRNA vaccines should be followed up closely for 1-2 months post vaccination for thrombocytopenia.

Keywords: immune thrombocytopenia; SARS-CoV-2; COVID-19; vaccines; vaccination.

Introduction

Immune thrombocytopenia (ITP) is an acquired autoimmune disease diagnosed by exclusion of other causes of thrombocytopenia.⁽¹⁾ In primary ITP there is no underlying cause, whereas in secondary form, which represents approximately 20% of cases, there is an underlying cause like infections, rheumatological diseases, drugs and vaccines.⁽²⁾

Coronavirus disease of 2019 (COVID-19) is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) which mostly spreads via contact with infected secretions or aerosol droplets. COVID-19 may present in a wide range from asymptomatic disease to acute respiratory distress syndrome (ARDS).⁽³⁾ COVID-19 caused a worldwide pandemic in a short time and this abrupt course of disease was followed by rapid vaccination studies.

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SARS-CoV-2 attaches to cell membrane via ACE-2 spike protein receptor.⁽³⁾ This receptor is the antigenic target for many of the COVID-19 vaccines. Main vaccine types in use are inactivated virus, viral vector, nucleic acid and protein derived vaccines. Inactivated virus (Sinovac[®]) and nucleic acid vaccines (BioNTech[®]) are currently administered in Turkey.⁽⁴⁾

Vaccine-related side effects are mostly local injection effects and flu-like symptoms, but rare cases of myocarditis, Bell's palsy and acute ischemic stroke were reported in the literature.^(5,6) Although ITP cases were reported in the literature with COVID-19 vaccines, there is no documented data indicating an increase in the ITP cases following administration of COVID-19 vaccines compared to the number of expected ITP cases.^(7,8,9,10,11)

According to a pharmacovigilance study in France, 108 de novo ITP cases and 17 vaccine-related relapses were diagnosed after COVID-19 vaccines (1.69 cases per 1,000,000 vaccine).⁽¹⁰⁾ According to Vaccine Adverse Events Reporting System (VAERS) data, between February 2020-2021, 15 thrombocytopenia cases were documented among 18,841,309 doses of Pfizer and 16,260,102 doses of Moderna vaccines and it was comparable with normal ITP incidence.⁽⁸⁾

In this study, we aimed to analyze the exacerbations of thrombocytopenia related to COVID-19 vaccines including both inactivated virus (Sinovac[®]) and nucleic acid vaccines (BioNTech[®]) in ITP patients.

Materials and Methods

Patients and data collection

In this retrospective observational study, 208 primary and secondary ITP patients older than 18 years of age were screened from the archives of Marmara University Pendik Training and Research Hospital, Department of Hematology Clinics. ITP patients vaccinated with at least one dose of COVID-19 vaccine were enrolled in the study. The patients diagnosed as ITP after the first dose were included in the study after the second vaccination.

Data including age, ITP treatment, treatment at the time of vaccination, remission status at the time of vaccination, bleeding symptoms and severity of the

documented bleeding, date and type of vaccination and need for treatment revision after vaccination were recorded from the archives.

Thrombocyte counts were recorded as pre-vaccination and post-vaccination. Post-vaccination values were recorded two times: one measurement was documented between 1 to 2 weeks after vaccination and the second measurement was documented 1 and 2 months after vaccination. The patients with missing data including pre- and post-vaccination thrombocyte count were excluded from the study. Thrombocyte numbers of the same cohort were also recorded throughout 1 year before COVID-19 vaccination to document variations of thrombocyte numbers over time, and these data were accepted as control group.

The study was approved by Marmara University Ethics Committee (Date 22.07.2022; number 09.2022.1026) and conducted in accordance with the Declaration of Helsinki.

Definition of flare

Flare of thrombocytopenia was defined as more than 30% decrease in platelet counts from baseline or platelet counts decreased to less than $30 \times 10^9/L$ or development of a new bleeding symptom or need for new treatment.

Statistical analysis

SPSS (Statistical Package for the Social Sciences) program version 25 (SPSS Inc.; Chicago, USA) was used for statistical analysis of data. Continuous data were reported as median (range, minimum and maximum). Quantitative data were given as number of cases and percentages. For statistical analysis, chi square, Fisher's exact, and Mann-Whitney U-test were used. A p-value less than 0.05 was accepted as statistically significant.

Results

Fifty-nine ITP patients with a median age of 47 (range, 18-86) years at the time of vaccination were enrolled in the study. Eighteen (30.5%) of the patients were male and 41 (69.5%) were female. Four (6.8%) of the patients were diagnosed as ITP after the first vaccination. These patients were included in the study after the second vaccination.

Fifty-nine patients were vaccinated with median of 3 (range, 2-4) and a total of 171 doses. Sixty-five of the vaccinations (38%) were Sinovac[®], whereas 106 doses (62%) were BioNTech[®]. One, 18 and 40 patients received one dose, two doses and booster doses (three or more doses), respectively.

Regarding treatments of the patients, seventeen (28.8%) patients had splenectomy before vaccination; 30%, 17.2% and 22.5% of patients were under medical treatment during first, second and booster dose vaccinations, respectively. The most common therapy (74% of all therapies) during vaccination was eltrombopag. Other therapies were steroid (1%), azathioprine (2%), mycophenolate mofetil (MMF) (1%) and combinations (22%) of these therapies including steroid plus eltrombopag, MMF plus eltrombopag, azathioprine plus steroid or eltrombopag.

Data after first vaccination

Thrombocyte count data after the first dose was evaluated in 55 patients, since four patients, who were diagnosed as ITP after the first dose, were excluded. Median thrombocyte count was $177 \times 10^9/L$ (range, $10-594 \times 10^9/L$) and $102 \times 10^9/L$ (range, $5-868 \times 10^9/L$) before and after the first dose, respectively. Seven (12.7%) patients experienced a decrease of more than 30% in platelet number with a median of 50% (range, 34-87%). In all patients, the decreases were observed between 2 weeks and 2 months after vaccination. In two patients

the platelet count decreased below $30 \times 10^9/L$ and one of the patients had a minor bleeding episode as subcutaneous bleeding. The characteristics of the patients were summarized in Table 1.

When comparing the characteristics of patients with or without a decrease in platelet count, it was found that median age was lower in the group with a decrease in platelet count without statistical significance (39 to 57, $p=0.06$) and vaccination with mRNA (BioNTech[®]) was associated with higher incidence of more than 30% platelet decrease ($p=0.041$) (Table 2).

Data after second vaccination

Median platelet counts before and after vaccination were $284 \times 10^9/L$ (range, $25-380 \times 10^9/L$) and $118 \times 10^9/L$ ($4-793 \times 10^9/L$), respectively. A decrease of more than 30% decrease in platelet number was observed in eight (13.8%) patients after second dose. Patient characteristics are summarized in Table 3. The decrease was documented in 2 weeks to 2 months. Median platelet decrease was 51% (range 30-96%) and median age was 43 years (range, 18-69). None of the parameters (sex, age, decrease in first dose, treatment during vaccination, splenectomy status, duration between diagnosis and vaccination, platelet count before vaccination) were found to be statistically different between the groups with or without decrease. The mRNA (BioNTech[®]) vaccination predominance

Table 1. Characteristics of patients with more than 30% decrease in platelet number after first dose of vaccination.

Patient number	Sex	Age	Type of vaccine	Platelet number before vaccination ($\times 10^9/L$)	Platelet number after vaccination ($\times 10^9/L$)	Treatment during vaccination	Treatment modification after vaccination
4	Female	24	BioNTech [®]	215	25	No	No
17	Female	51	BioNTech [®]	177	104	Eltrombopag 50 mg/day	No
18	Female	38	BioNTech [®]	192	95	Eltrombopag 50 mg/day	No
22	Male	39	BioNTech [®]	172	45	No	No
26	Male	37	BioNTech [®]	413	272	No	No
31	Female	53	Sinovac [®]	87	52	No	No
51	Female	18	BioNTech [®]	40	5	Eltrombopag 50 mg + steroid 8 mg/day	Increase in steroid dose to 0.5 mg/kg/day

Table 2. Comparison of patients with or without a decrease >30% in platelet number after first dose.

Characteristic	With decreasing platelets n, (%)	Without decreasing platelets n, (%)	P value
Age (median)	39	57	P=0.06
Gender:			
Female	5 (13.2%)	33 (86.8%)	P=0.88
Male	2 (11.8%)	15 (88.2%)	
Vaccine:			
Sinovac®	1 (3.7%)	26 (96.3%)	P=0.04*
BioNTech®	6 (21.4%)	22 (78.6%)	
Time from diagnosis to vaccination (month)	71	62	P=0.78
Treatment during vaccination:			
Yes	3 (17.6%)	14 (82.4%)	P=0.44
No	4 (10.5%)	34 (89.5%)	
Splenectomy before vaccination:			
Yes	2 (11.8%)	15(88.2%)	P=0.86
No	5(13.2%)	33 (86.8%)	
Eltrombopag treatment during vaccination:			
Yes	3(21.4%)	11 (78.6%)	P=0.25
No	4 (9.8%)	37 (90.2%)	
Platelet count before vaccination (median)	175×10 ⁹ /L	174×10 ⁹ /L	P=0.82

could not be documented in second dose analysis ($p=0.38$). Three of the patients experienced a decrease below $30 \times 10^9/L$. Two of them had mild bleeding episodes including epistaxis, gingival bleeding and subcutaneous bleeding. These patients were treated with 1 mg/kg/day steroid and remission was achieved in both patients in 10 days. The platelet count increased above $50 \times 10^9/L$ in 1 week without any treatment modification in the third asymptomatic patient.

Data after booster vaccination

Forty (67.8%) of 59 patients were vaccinated with a booster dose. Ten (25%) patients received inactivated (Sinovac®) vaccines and 30 (75%) patients, mRNA vaccines (BioNTech®). A decrease of more than 30% in platelet number was observed in 6 (15%) patients after booster dose, but none of the patients had a platelet count less than $30 \times 10^9/L$. Platelet decrease was statistically higher in younger patients after booster dose (8.7% to 33.3%, $p=0.04$). Other parameters were

statistically insignificant between the two groups with or without decrease. When the overall vaccination data were considered, after 171 doses of vaccinations 21 (13.7%) exacerbations were recorded. Seven (12.7%), 8 (13.8%) and 6 (15%) patients had exacerbation following first, second and booster dose, respectively. In addition, 10 (16.9%) patients experienced a decrease in platelet count to a level of less than $30 \times 10^9/L$ after vaccination and only four (2.3%) patients had minor bleeding episodes, all of which were successfully treated. When we compared the platelet number variations of the same cohort during the last year before the COVID-19 vaccination, 19 patients (32.2%) experienced such a decrease.

Data of patients diagnosed as ITP after vaccination

Four patients (6.7%, three patients after mRNA vaccine and one patient after inactivated vaccine) were diagnosed as ITP after vaccination. The median age of patients was 34 years (range 18-22). Complete remission

Table 3. Characteristics of patients with a decrease of more than 30% in the number of platelets after the second vaccination dose.

Patient number	Sex	Age	Type of vaccine	Platelet number before vaccination ($\times 10^9/L$)	Platelet number after vaccination ($\times 10^9/L$)	Platelet decrease (%)	Treatment during vaccination	Treatment modification after vaccination	Platelet decrease after first vaccine
8	Female	35	Sinovac [®]	403	17	96%	Eltrombopag 25 mg	Steroid 1mg/kg	No
14	Male	41	BioNTech [®]	153	74	51%	None	None	No
25	Female	22	Sinovac [®]	18	4	96%	Azathioprine	Steroid 1 mg/kg/day	No
45	Female	19	Sinovac [®]	380	174	54%	Eltrombopag+ Steroid	None	No
47	Male	44	BioNTech [®]	316	178	43%	None	None	No
51	Female	18	BioNTech [®]	348	21	93%	Steroid 0.5 mg/day	None	Yes
54	Female	69	Sinovac [®]	112	66	41%	None	None	No
55	Male	40	Sinovac [®]	53	37	30%	None	None	No

was achieved in all of patients. Among four patients, only one had exacerbation of ITP after booster dose with mRNA vaccination without any symptom or treatment modification.

Discussion

In this retrospective study, we aimed to identify the effect of both inactivated and mRNA vaccines in ITP patients. There was no consensus in the literature on the definition of ITP exacerbation after vaccination. There was a wide decrease in platelet count ranging between 20% and 60%.^(11,12,13)

Overall, patients who had a decrease in platelet number in our cohort was nearly 16,9 % after vaccination, whereas 32.2% of the same cohort also had a decrease in platelet count before the pandemic and not related to vaccination in the previous year. Only three patients with ITP exacerbations had mild bleeding episodes after the first and second dose.

Depending on including criteria such as definitions of exacerbations, type of vaccines, the exacerbation rate ranges between 5-15% in the literature after COVID-19 vaccination in ITP patients.⁽¹⁴⁾

Visser et al, conducted a study including 218 ITP patients and 200 controls for determining the effect of vaccination on ITP exacerbation.⁽¹²⁾ In their study, only 2.2% (5 patients) of patients experienced bleeding episodes and reported that they did not observe any difference between groups; in conclusion, they considered COVID-19 vaccines as safe. These results were also compatible with our results. Another study reported a higher rate of severe exacerbation along with worsening bleeding symptoms.⁽¹³⁾ In that study, 12% of all patients experienced severe exacerbation. Since the cohort of this prospective study was relatively small, six patients accounted for 12% of the cohort and this might be the fact under higher exacerbation rate. Secondly, although the median platelet count of six patients was $164 \times 10^9/L$ there were also patients with low platelet count such as $12 \times 10^9/L$ which would increase the rate of adverse events related to bleeding. Thirdly this was a prospective study and all the patients were followed up closely and patients with less severe exacerbations and less severe bleeding symptoms including only petechias

and ecchymoses were reported in details. In this study like other studies, there was no life threatening bleeding episodes.⁽¹³⁾

In another study including de novo ITP after COVID-19 vaccines,⁽⁶⁾ the median time to thrombocytopenia was 5.5 days but the cases were also reported up to 23 days after vaccination. Unlike their study, in the present research no decrease in platelet number was documented in the first week and all decreases were documented between the second week and second month post-vaccination in our cohort. Also, symptomatic exacerbations were less common in this study compromising four minor bleeding episodes in 171 vaccinations.

In the present study, inactivated and mRNA vaccines could also be compared. A statistical difference in ITP exacerbation could be documented after the first dose in patients who were vaccinated with the mRNA vaccine, but no significant differences were demonstrated for subsequent doses.

Other parameters including sex, decrease in platelet count after the first dose, treatment during vaccination, splenectomy status, duration between diagnosis and vaccination and platelet count before vaccination were not found to be statistically different between the patients with or without a decrease in platelet number.

There was no consensus in the literature on the risk factors for ITP exacerbations. Lee et al,⁽¹⁵⁾ reported that splenectomized patients and those who received five or more prior lines of therapy were at the highest risk for ITP exacerbation; but no difference in age, gender, vaccine type between those who did and did not develop an ITP exacerbation was documented. Another study including 218 ITP patients, reported platelet count $<50 \times 10^9/L$, ITP treatment at the time of vaccination and younger age as risk factors for ITP exacerbation.⁽¹¹⁾ In another prospective study, age, sex, duration of ITP, baseline platelet level, remission status, concurrent ITP treatment and vaccine type seemed to be no predictors for exacerbation.⁽¹²⁾ Concerning age, in this study, the median age was lower in the group with decreasing platelet count after the first dose, but this difference did not reach statistical significance ($p=0.06$) and could not be confirmed in subsequent doses.

Another parameter for the risk of exacerbation of thrombocytopenia was the duration of ITP defined as the time between ITP diagnosis and COVID-19 vaccination. Although in this study there was no statistical significance between the groups with or without decrease in platelet in terms of ITP duration, Visser et al,⁽¹¹⁾ documented that it had an association with a decreased platelet counts, but this could not be confirmed in other studies.⁽¹²⁾

In this study, 21 (13.7%) exacerbations were observed after vaccinations, but bleeding was documented in only four patients. All bleeding episodes were mild. Similarly, mild bleeding episodes were mostly reported in the literature, but rarely severe and life threatening bleeding episodes including gastrointestinal and central nervous system bleedings were also reported.^(8,11,15,16) All the patients with ITP exacerbations and bleeding episodes were treated with an increase in steroid dose and all of the patients got complete remission through steroid therapy. Similar to our results, the remission rates were up to 95% after starting the therapy including steroids, intravenous immunoglobulin and thrombopoietin receptor agonists.^(9,11,12,13)

This study also had some limitations. First, this was a retrospective study, thus we could not reach all the data, including other adverse events; losing the follow-up was another problem. Second, we excluded the patients with missing data. Since asymptomatic ITP patients may have chosen not to obtain pre- and post-vaccination platelet counts, the exclusion of these patients may have resulted in an overestimation of platelet decrease postvaccination. Third, we could not obtain the platelet counts in a fixed time interval in the pre or post-vaccination period. Instead, we obtained the measurements retrospectively within a relatively wide time interval so the exact time of decrease could not be documented. One of the most important strengths of this study was the comparison between two different types of vaccines, inactivated and mRNA. This study documented preliminary data related to thrombocytopenia risk in these new vaccines.

Conclusions

Both COVID-19 vaccines, Sinovac[®] and BioNTech[®], seem to be safe in patients with ITP with rare and

mostly non-severe bleeding complications. Although the risk groups could not be documented well, the ITP patients especially younger patients and patients vaccinated with mRNA vaccines should be followed up closely for 1-2 months post-vaccination for any severe decrease in platelet count and they should be informed about any bleeding symptoms. This preliminary data demonstrated that both mRNA and inactivated vaccines could be used in ITP patients.

Conflict of interest

The authors declare that there is no conflict of interest.

Author's contributions

Duygu Abdurakhmanov: original drafting, research and data curation.

Ahmet Mert Yanik: formal analysis and data curation.

Meral Menguc: data curation and research.

Fatma Arikan: data curation and research.

Tayfur Toptas: methodology, editing and visualization.

Isik Kaygusuz Atagunduz: project management.

Tulin Tuğlular: supervision.

Asu Fergun Yilmaz: research, conceptualization, draft revising, editing and supervision.

All authors have read and agreed to the published version of the manuscript.

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Efecto de las vacunas inactivada y de ARNm contra la COVID-19 sobre la trombocitopenia en pacientes con trombocitopenia inmunitaria

Resumen

Este estudio observacional retrospectivo tuvo como objetivo abordar los posibles efectos de las vacunas inactivada y de ARNm en pacientes con trombocitopenia inmunitaria relacionados con la exacerbación. Para definir exacerbación, se consideró una disminución de más del 30% en el recuento de plaquetas con respecto al valor basal o un recuento de plaquetas disminuido a menos de $30 \times 10^9/L$ o el desarrollo de una nueva hemorragia. Cincuenta y nueve (hombres 30,5%, mujeres 69,5%) de 208 pacientes con trombocitopenia inmunitaria, se inscribieron en el estudio. La mediana de edad fue de 47 años (rango 18-86). Se realizó un total de 171 vacunaciones en 59 pacientes. El 38% y el 62% de los pacientes fueron vacunados con Sinovac® y BioNTech®, respectivamente. En total, 10 (16,9%) pacientes experimentaron una disminución del recuento de plaquetas por debajo de $30 \times 10^9/L$ tras la vacunación. Durante el último año antes de la pandemia, 19 de la misma cohorte (32,2%) experimentaron dicha disminución. Después de la primera, segunda y la dosis de refuerzo de la vacunación, el 12,7%, 13,8% y 15% de los pacientes experimentaron exacerbaciones, respectivamente; las exacerbaciones con hemorragias leves fueron del 2,3% y todos los episodios hemorrágicos se trataron con éxito comenzando con esteroides o aumentando la dosis de esteroides. No se registró ninguna hemorragia grave o potencialmente mortal. Se documentó una diferencia estadística en la exacerbación en los pacientes vacunados con la vacuna de ARNm ($p = 0,041$) sólo después de la primera dosis y los pacientes más jóvenes experimentaron una mayor tasa de exacerbación sin significación estadística ($p = 0,06$) después de la primera dosis. En conclusión, tanto la vacuna de ARNm como la inactivada parecen ser seguras para los pacientes con trombocitopenia inmunitaria con complicaciones hemorrágicas poco frecuentes. Especialmente los pacientes más jóvenes y los vacunados con vacunas de ARNm deben ser objeto de un seguimiento estrecho durante 1-2 meses después de la vacunación para detectar trombocitopenia.

Palabras clave: púrpura trombocitopénica; SARS-CoV-2; COVID-19; vacunas; vacunación.

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