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SHORT REPORT

Platelets, Haemostasis and Thrombosis

Safety and efficacy of SARS-CoV-2 vaccination in patients with immune thrombocytopenia: A two-centre review

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Summary
Multiple studies have reported immune thrombocytopenia (ITP) relapse following SARS-CoV-2 vaccination, however baseline ITP relapse rate and antibody response to vaccination are not known. Patients with ITP who received at least one of the first three SARS-CoV-2 vaccination doses were included in the study. One hundred and twenty-four patients met the inclusion criteria. Relapse rate was 4.2% following a first vaccine dose, 9.1% after a second and 2.9% after a third; baseline relapse rate was 7.6%. Ninety-four per cent of patients who received three vaccine doses developed a clinical antibody response. SARS-CoV-2 vaccination appears to be safe and effective in patients with ITP.

KEYWORDS
antibodies, COVID-19, ITP, vaccines

BACKGROUND

SARS-CoV-2-related morbidity and mortality have decreased dramatically since the introduction of mass vaccination programmes.[1,2] Due to the emergence of new variants and waning immunity post-vaccination, multiple countries offer repeated vaccinations to vulnerable patients.

Several studies have reported that 8%–17% of patients with pre-existing immune thrombocytopenia (ITP) relapse following SARS-CoV-2 vaccination[3–6], however the baseline relapse rate of ITP is not known. Also, no study so far has clarified the antibody response to SARS-CoV-2 vaccination in this cohort of patients.

We aimed to explore how post-vaccine relapse rate compares to the expected monthly ITP relapse rate, and to assess the antibody response to SARS-CoV-2 vaccination in patients with ITP.

METHOD

Data from two tertiary centres, Imperial College Healthcare NHS Trust London (ICL), and Erasmus MC, University Medical Center Rotterdam (EMC), were merged to assess relapse rate and antibody response following SARS-CoV-2 vaccination in patients with ITP aged 14 years and above. Patients with primary or secondary ITP who received at least one of the first three SARS-CoV-2 vaccine doses and who had one platelet count recorded within 30 days following a dose were included in the study. Patients who were diagnosed with ITP following SARS-CoV-2 infection or vaccination were excluded.

The definition of ITP relapse following SARS-CoV-2 vaccination is heterogeneous among previously published studies; we aimed to highlight those cases of ITP relapse which might be associated with an increased bleeding risk and warrant close follow-up or rescue therapy. Relapse was therefore defined within 30 days following vaccination, as either a drop in platelet >50% with a nadir count $<30\times10^9$/L, or as a drop in platelets <50% with a nadir count $<30\times10^9$/L associated with a new bleeding event. When patients did not have a platelet count recorded within 30 days following vaccination, they were assumed not to have relapsed if they did not develop bleeding symptoms.

Those patients included in the main study who were already under follow-up at ICL in 2019 were included in the

baseline study cohort. Baseline relapse rate was calculated as relapse rate within 30 days following their first clinic appointment in 2019 using the same relapse criteria outlined above.

Antibody titres obtained 14–30 days following each vaccine dose were analysed using Abbott Alinity analyzer at ICL and LIAISON SARS-CoV-2 TrimericS IgG assay at EMC. Both laboratories provided definitions of clinical antibody response (titre >568 BAU/mL and >300 BAU/mL respectively), defined as the threshold used in clinical practice to identify those patients who might be eligible to receive anti-SARS-CoV-2 monoclonal antibodies if they were to develop severe COVID-19 disease. Patients who received Intravenous Immunoglobulin (IVIG) in the 3 months preceding SARS-CoV-2 vaccination were excluded from the antibody response analysis.

Descriptive statistics were utilised to describe the patient population and relapse frequencies. Data were presented as median and interquartile range (IQR) for continuous variables and as percentages for categorical variables. Baseline and post SARS-CoV-2 vaccination relapse rates within the same cohort of patients were compared using the McNemar test. Relation between ITP relapse and disease variables was analysed using Fisher's exact test due to the low frequency of relapse events. Continuous data were assessed for normality by the Shapiro–Wilk test and Q–Q plots. Both platelet count and antibody titre did not conform to normal distribution; paired data were therefore analysed by the Wilcoxon signed-rank test and unpaired data by the Mann–Whitney *U* test. Significance was set at $p < 0.05$.

RESULTS

One hundred and twenty-four patients were included in the study: 102 from ICL and 22 from EMC. Median age was 47 (IQR 31–60) and 82 (66%) were female. Median time since ITP diagnosis was 5 years (IQR 2–10) and 36 patients (29%) had at least one platelet count below 30×10^9/L in the 12 months preceding their first SARS-CoV-2 vaccination.

Thirty-nine patients (31%) were not receiving any ITP treatment when they had their first SARS-CoV-2 vaccine. Fifty-two patients (42%) were on thrombopoietin receptor agonists: 36 (29%) were receiving eltrombopag and 16 (13%), romiplostim. Fifty patients (40%) were on immunomodulators: 11 of these (9%) were on tacrolimus, 11 (9%) on MMF, 5 (4%) on hydroxycarbamide, 1 on azathioprine, 1 on sirolimus, 1 on methotrexate, 1 on fostamatinib, and 1 on ciclosporin. Nine patients (7%) were on steroids and 9 (7%) had received rituximab in the 12 months preceding their first SARS-CoV-2 vaccination. Eleven patients (9%) had undergone a splenectomy. Around 25% of the patients included in this study were on dual or triple ITP therapy when they received their first SARS-CoV-2 vaccine.

One hundred and seventeen patients received a first SARS-CoV-2 vaccine dose; 54 (47%) had Pfizer-BioNTech, 35 (30%) ChAdOx1 nCoV-19 and 21 (18%) Moderna mRNA-1273. No vaccine type was recorded for seven patients. Median platelet count was 117×10^9/L (IQR 69–187) before and 122×10^9/L (IQR 74–176) after the first vaccine. Five patients (4.2%) relapsed within 30 days following vaccination. The median platelet count of those five patients was 31×10^9/L (IQR 14–55) before and 13×10^9/L (IQR 7–14) after vaccination. Three patients developed bleeding symptoms (petechiae, PV bleeding) and received rescue therapy. Relapses were identified between 2 and 24 days following vaccination (median 16 days).

Of 113 patients who received a second SARS-CoV-2 vaccine, 53 (47%) had Pfizer-BioNTech, 35 (31%) ChAdOx1 nCoV-19 and 20 (18%) Moderna mRNA-1273. No vaccine type was recorded for five patients. Median platelet count was 124×10^9/L (IQR 65–193) pre-vaccination and 113×10^9/L (IQR 64–185) post-vaccination. Ten patients (9.1%) relapsed following the second vaccine; six experienced bleeding symptoms and received rescue therapy or modifications of long-term therapy. The median platelet count of those 10 patients was 63×10^9/L (IQR 28–105) before and 18×10^9/L (IQR 12–28) after vaccination. Relapses were identified between 3 and 26 days following vaccination (median 6 days).

Sixty-eight patients received a third SARS-CoV-2 vaccine dose: 29 (43%) received Pfizer-BioNTech, 10 (15%) Moderna mRNA-1273 and 42% either Moderna mRNA-1273 or Pfizer-BioNTech (not specifically recorded). Median platelet count was 120×10^9/L (IQR 75–202) before and 113×10^9/L (IQR 60–203) after vaccination. Two patients (2.9%) relapsed following vaccination. There were no bleeding complications, however both received rescue treatment. Both patients relapsed within 7 days of vaccination.

Three out of five patients who relapsed following a first SARS-CoV-2 vaccine dose received a second dose: two of these relapsed. Four of 10 patients who relapsed following a second vaccine went on to receive a third dose: one of these four relapsed. No patient in our cohort relapsed after all three vaccination doses. The only predictor of relapse following SARS-CoV-2 vaccination was severe thrombocytopenia ($<30 \times 10^9$/L) in the 12 months preceding the first vaccine dose.

We performed a sub-analysis focussing solely on those patients who had a platelet count recorded within 30 days following vaccination. Of 91 patients who received a first SARS-CoV-2 vaccine, 5 experienced a relapse (5.49%). Of 84 patients who received a second vaccine, 10 relapsed following vaccination (11.90%). Two out of 41 patients who received a third vaccine dose experienced a relapse within 30 days following vaccination (4.87%).

Sixty-five patients were under follow-up at ICL in 2019 and were included in the baseline study cohort. Five of these patients relapsed within 30 days following their first clinic appointment in 2019; their baseline monthly relapse rate was calculated as 7.6%. Fifty-nine patients included in the baseline cohort received a first SARS-CoV-2 vaccine dose; their relapse rate following vaccination was 5.2%. Sixty-three patients included in the baseline cohort received a second vaccination dose; their post-vaccination relapse rate was 6.3%. There was no statistically significant difference between the

relapse rate before and after vaccination within the same cohort of patients.

Three of nine patients (33.3%) who had an antibody titre recorded following a first SARS-CoV-2 vaccination dose developed a clinical antibody response. Their median antibody titre was 157 BAU/mL (IQR 35–3883) as measured by the Abbott Alinity analyzer. All patients in this group received Pfizer-BioNTech.

Twelve of the 22 patients (54.4%) who had an antibody titre recorded following a second vaccination dose developed a clinical antibody response. Their median antibody titre was 972 BAU/mL (IQR 95–3607) as measured via Abbott Alinity analyzer. No patient who was on steroids, or had received rituximab in the previous 12 months, or had a prior splenectomy, developed a clinical antibody response after two vaccine doses. The median antibody titre of patients who received two doses of ChAdOx1 nCoV-19 was 109 BAU/mL (IQR 50–2016), whilst the median antibody titre of those who received two doses of Pfizer-BioNTech was 2751 BAU/ml (IQR 877–5016), $p < 0.01$. Focussing on patients under follow-up at ICL, those who relapsed following the second vaccine had a median antibody titre of 4311 BAU/mL (IQR 965–5481) compared to 972 BAU/mL (IQR 107–2892) among those who did not relapse. Patients who received rituximab were excluded from this analysis.

Seventeen out of 18 patients (94.4%) who received a third SARS-CoV-2 vaccination dose developed a clinical antibody response, including two patients who had undergone a splenectomy. Their median antibody titre was 5237 BAU/mL (IQR 838–86900) for patients under follow-up at EMC and 2380 BAU/mL (IQR 724–11260) for those under follow-up at ICL, although the two assays are not directly comparable. The one patient who did not achieve a clinical antibody response had received rituximab 3 months before vaccination.

None of the patients who received rituximab in our cohort developed severe COVID-19 disease, despite not developing an antibody response to vaccination.

DISCUSSION

Our study has shown a relapse rate of 3%–9% following SARS-CoV-2 vaccination, which was not significantly different from the baseline relapse rate in 2019 (7.6%) (Figure 1).

Unfortunately, it was not possible to study the relapse rate of patients with ITP who did not receive SARS-CoV-2 vaccination within the same time period as the study cohort; this was because by the end of the study period the overwhelming majority of patients under follow-up at both centres had received the vaccine. By assessing ITP baseline relapse rate in 2019, we obtained a figure which was completely independent from both COVID-19 disease and vaccination; calculating baseline relapse rates over multiple years might have increased the accuracy of our estimate.

The rate of relapse following the second vaccination dose was almost double the relapse rate following the first vaccine, possibly reflecting a stronger immunogenic response. It is also possible that the vaccine safety strategy implemented by ICL since mid-2021, whereby patients with pre-existing ITP had a platelet count recorded at 1, 2, and 4 weeks

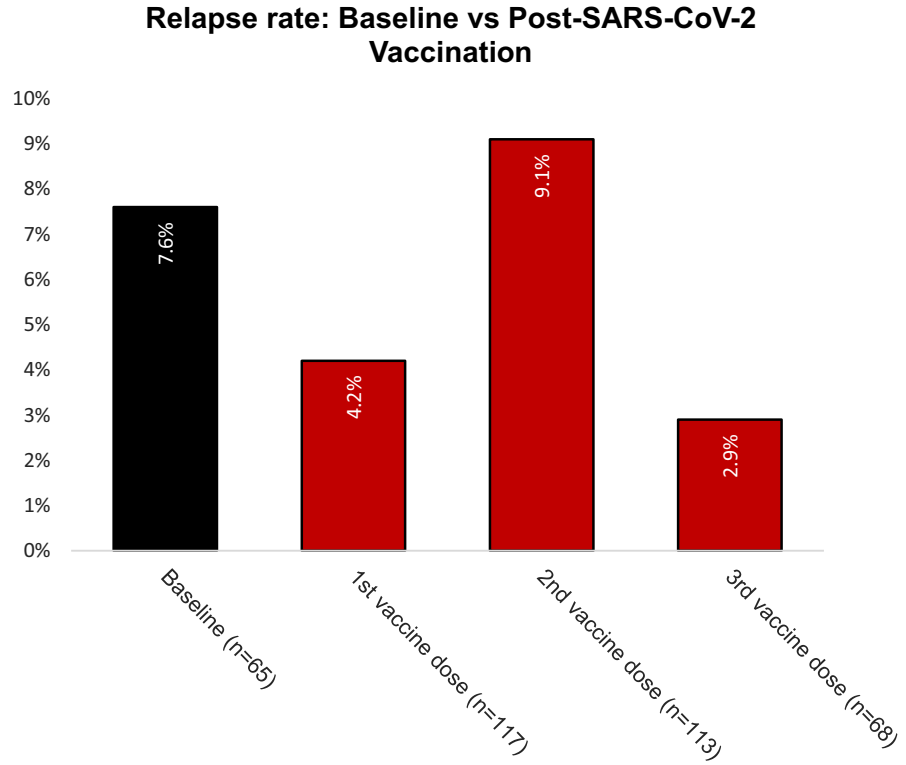

FIGURE 1 Comparison of baseline versus post-vaccination relapse rate in patients with ITP.

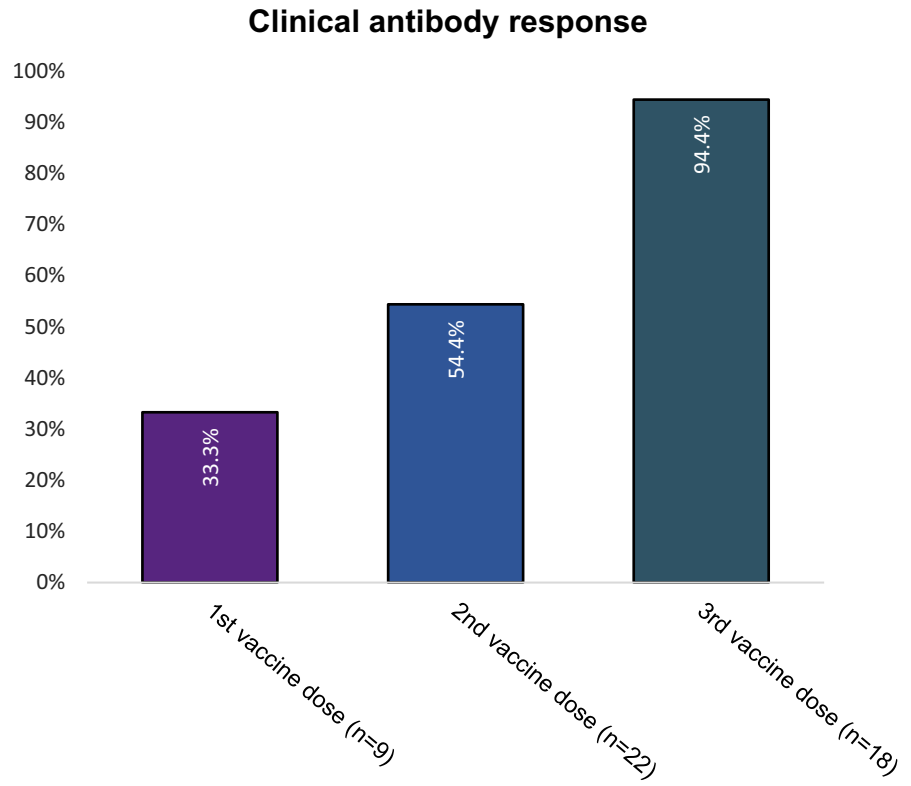

FIGURE 2 Percentage of patients who developed a clinical antibody response 14–30 days following SARS-CoV-2 vaccination.

post-vaccination, might have resulted in higher chances of identifying a relapse.

Our results suggest that patients with more severe disease at baseline are at higher risk of relapse; this is consistent with findings from other studies.[5,6] Patients under follow-up at ICL experienced a higher rate of relapse compared to those at EMC; this appears to be due to these patients having more severe disease at baseline.

Only around half of the patients who relapsed in our cohort experienced bleeding symptoms; these were all minor to moderate events with no patient in our cohort suffering major or catastrophic bleeding. All patients who relapsed post-vaccination recovered a platelet count close to their baseline either spontaneously or following rescue treatment. None of the patients included in this study developed thrombotic complications including VITT following SARS-CoV-2 vaccination.

Median antibody titres increased with each vaccination, resulting in a higher proportion of patients achieving a clinical antibody response with each vaccine dose. Patients who received rituximab did not mount an antibody response, in line with previously published studies.[7] Apart from those receiving rituximab, all patients achieved a clinical antibody response following three vaccine doses (Figure 2).

Patients who received Pfizer-BioNTech vaccination developed much higher antibody titres compared to those receiving ChAdOx1 nCoV-19, in keeping with previously published research.[8] Only a minority of patients in our study had an antibody titre recorded before vaccination; we cannot exclude that this differential response might be secondary to SARS-CoV-2 infection, rather than vaccination alone.

Patients who relapsed following two vaccine doses tended to have a higher antibody titre compared to those who did not relapse. Although this did not reach statistical significance, it is possible that ITP relapse following SARS-CoV-2 vaccination might be related to a heightened immune response to the vaccine.

CONCLUSION

In this cohort of patients, there was no increase in post-vaccination relapse rates compared to baseline levels. This does not negate the fact that some patients might develop an ITP relapse after SARS-CoV-2 vaccination; however, this may be no different to relapse risk following other vaccines and infections.

Overall, SARS-CoV-2 vaccination appears to be safe and effective in patients with ITP; however three vaccine doses may be required.

AUTHOR CONTRIBUTIONS

Sara Stefani designed the study, collected data, performed the analysis and wrote the paper. Noora Buti contributed to research design and data collection. Alice Hart and Christin Ademokun contributed to research design. Deena Paul, Naghma Rizvi, Vashti Ragoonanan and Camelia Vladescu contributed to data collection. Richard Szydlo assisted with statistical analysis.

Gerard Jansen contributed to research design, provided data for EMC patients and supervised the writing of the manuscript. Nichola Cooper designed the study, supervised the project and supervised the writing of the manuscript.

CONFLICT OF INTEREST STATEMENT

A. J. Gerard Jansen, MD: Speaker's fees and travel cost payments from 3SBio, Amgen, Sobi and Novartis; international advisory board member of Novartis; received research funding from CSL Behring, Principia, Sobi and Argenx (all not applicable to this study). Nichola Cooper, MD: Consultancy/Honoraria for Sanofi, Principia, Novartis, Grifols, Sobi, Argenx, UCB, Rigel (not applicable to this study).

DATA AVAILABILITY STATEMENT

Erasmus MC data can be made available upon request.

ETHICS STATEMENT

Erasmus MC: Ethics approval number MEC-2021-0238. Imperial College London: Audit registration number HAE_020.

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