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LETTERS TO THE EDITOR

Acquired thrombotic thrombocytopenic purpura: A rare disease associated with BNT162b2 vaccine: Comment from Doyle et al.

We read with interest the experience of Maayan et al. describing four patients who developed clinical presentations of thrombotic thrombocytopenia purpura (TTP) within 28 days of receiving the BNT162b2 vaccine for COVID-19: two *de novo* presentations and two clinical relapses.[1] Further case reports of patients presenting with TTP following COVID-19 vaccination have also been described.[2–5] Like Israel, the United Kingdom employed an early rollout of the COVID-19 vaccination program starting in December 2020 using principally the BNT162b2 (Pfizer), an engineered mRNA vaccine coding for the spike protein and the ChAdOx1 nCov-19 (Oxford/AstraZeneca), a modified adenovirus vector vaccine. In view of these reports, clinicians routinely treating patients with TTP were contacted as part of the UK TTP Registry network to assess for clinical events.

Collaborators reviewed all diagnoses of *de novo*, clinical relapses, and ADAMTS13 relapses (ADAMTS13 activity <15% indicating consideration for elective anti-CD20 antibody therapy) of immune-mediated TTP at their centers from 1 January 2021 to 1 November 2021. The UK TTP registry is a prospective database of cases and treatment in the United Kingdom (Multicentre Research Ethics Committee: 08/H0810/54). Collaborators were asked to provide details on the patients' COVID-19 vaccination status including number of vaccines, manufacturer, and the time of vaccination in relation to presentation/treatment episode. Treatment was considered as plasma exchange with or without anti-CD20 therapy for *de novo* presentation and clinical relapse and anti-CD20 therapy alone for ADAMTS13 relapses.

We report on 90 patients requiring treatment for TTP at 10 hospital sites in England. A summary of these cases is described in Table 1. A total of 58/90 (64%) of these occurred after receiving one or more COVID-19 vaccinations (27 [47%] ChAdOx1 Oxford/Astra Zeneca; 30 [52%] BNT162b2 Pfizer; 1 [2%] unknown) and 7/90 (8%) occurred before vaccination. Nineteen of 90 (21%) patients with either new presentations or relapses of TTP had chosen not to be vaccinated against COVID-19.

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The median time from vaccination to presentation with TTP requiring treatment was 87 days (interquartile range 32–120 days). Ten of 58 (17%) occurred within 28 days of receiving COVID-19 vaccination. Of those who presented within 28 days of vaccination, five were following first vaccination and five were following second vaccination. Four of these 10 cases were new presentations, one was a clinical relapse, and five were ADAMTS13 relapses. There was no difference in cases according to vaccine type.

We also assessed if the timing of *de novo* presentations and relapse episodes correlated to the vaccination program rollout. There was a peak of *de novo* presentations in October 2021 ($n = 11$), with a median number of cases of 3 per month (range 1–11 case per month). There was a peak of relapse episodes in September 2021 ($n = 5$), with a median number of cases of three per month (range 1–5 case per month). Nationally, the highest rates of administration of first COVID-19 vaccinations were from January to March 2021 and of second vaccinations between March and June 2021.[6] Comparably, a peak in presentations was not seen in relation to these vaccination peaks in either *de novo* presentations or relapses of TTP. The proportion of *de novo*, clinical relapses, and ADAMTS13 relapses from the first half of the year (January–May 2021) were similar to those in the second half of the year (June–November 2021) (21%, 2%, and 9% vs. 38%, 5%, 14%, respectively; df = 5, $\chi^2 = 1.50$, $p = .47$).

Recognized immune-mediated complications of COVID-19 vaccinations are vaccine-induced thrombotic thrombocytopenia, Guillain-Barre syndrome, Miller-Fisher syndrome, and exacerbations of immune-mediated thrombocytopenia (ITP).[7,8] Previously, vaccination administration to other pathogens has not been recognized as a trigger factor for ITP in population-based analysis.[9] Recognized conditions associated with TTP are pancreatitis, autoimmune disease, infection, pregnancy, surgery, untreated HIV, and specific drugs. Similar to ITP, other vaccines have not been described as a trigger for TTP.

Maayan et al. have expressed concern that the four cases of TTP they report are temporally related to COVID-19 vaccination, with two being *de novo*. They also highlight that there is a greater incidence of TTP cases than expected presenting in their health care system. From our UK experience, we identified four *de novo* presentations within 28 days of receiving vaccination in a much

TABLE 1 Clinical features of patients requiring treatment for immune thrombotic thrombocytopenic purpura in relation to COVID-19 vaccination status

Clinical features	Frequency
Type of TTP presentation	*De novo* 59 (66%)
	Clinical relapse 7 (8%)
	ADAMTS13 relapse 24 (27%)
Timing of TTP presentation in relation to COVID-19 vaccination	Unvaccinated 19 (21%)
	Before receiving vaccination 7 (8%)
	After receiving vaccination 58 (64%)
	Unknown 6 (7%)
Type of vaccine used	ChAdOx1 nCov-19 (Oxford/AstraZeneca) 27 (47%)
	BNT162b2 (Pfizer) 30 (52%)
	Unknown 1 (2%)
Total number of doses received per patient[a]	No doses 19
	One dose 12
	Two doses 47
	Three doses 4
	Unknown 8

TTP, thrombotic thrombocytopenia purpura.

[a]Includes doses received before and after episode of treatment for TTP.

larger population. Disease relapse, either frank clinical relapse or ADAMTS13 relapse, is recognized as a feature in the clinical course of TTP occurring in at least 30% of patients during long-term follow-up. In the series we describe here, this consisted of 31/90 (34%) cases. There were higher numbers of treatment episodes in the second half of 2021; however, the types of treatment episodes were not different between the two periods. This may be due to clinicians preferring to avoid immunosuppressants such as rituximab and steroids during the second wave of COVID-19 in early 2021 in the UK or allowing for an optimal immune response following vaccination which again was predominantly in early 2021.

Although we cannot exclude a causal relationship between TTP in four *de novo* patients seen in our described cohort similar to Maayan et al., reassuringly we did not see an increased number of presentations of TTP during the peak of the vaccination program when a larger and nationwide patient cohort was reviewed. Additionally, the incidence of *de novo* cases of TTP was within an expected range of the population of England in 2021 with no perceived increased in demand for treatment of TTP by the authors.

Although we cannot exclude a link between COVID-19 vaccination and a small number of *de novo* presentations, it appears unlikely based upon these data. We would therefore support the ongoing use of COVID-19 vaccines in patients with TTP, particularly in those who have ongoing or an anticipated need for immunosuppression. We would also support the further reporting of *de novo* presentations of TTP within 1 month following COVID-19 vaccination to national reporting schemes to ensure detection of any future concerns.

CONFLICT OF INTEREST

A.J.D., D.S., J.K., J.H., J.V., and W.L. have nothing to disclose. T.D. reports speaker fees from Sanofi and Alexion. G.L. reports speaker fees from Roche and Novo Nordisk. M.D. reports speakers/advisory boards for Takeda, Portola, Pfizer, Sanofi, and Amgen. W.T. reports speaker fees from Pfizer and advisory boards for Sanofi and Ablynx. T.C. reports and educational grant from AbbVie. E.B. reports educational grants from Abbvie and Celgene. Q.H. reports speaker or advisory fees from Alexion, Amgen, Apellis, Argenx, Grifols, Novartis, ReAlta, Sanofi, and Shire. M.S. reports speaker fees and advisory boards for Novartis, Takeda, Sanofi, and Octapharma and grants from Shire and Alexion.

AUTHOR CONTRIBUTIONS

A.J.D. designed the study, organized data collection, analyzed the data, and wrote the manuscript. M.S. designed the study, organized data collection, and reviewed the manuscript. All other authors collected data and reviewed the manuscript.

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Acquired thrombotic thrombocytopenic purpura: A rare disease associated with BNT162b2 vaccine: Reply to comment from Doyle et al.

To the Editor,

We thank Dr. Doyle and colleagues for sharing their national data on de novo/relapsed acquired thrombotic thrombocytopenic purpura (aTTP) in the UK from January to November 2021. According to their report, there was no increased number of aTTP presentations during the peak of the UK vaccination program, and the incidence of aTTP cases was within the expected range of England's population, with no increase in treatment demand for aTTP during 2021. In contrast, we have reported on a cluster of aTTP patients presenting on average 14 days after the BNT162b2 vaccine.[1] The 1-month occurrence

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