Clinical Study Report Synopsis	
Drug Substance	AZD1222
Study Code	D8111R00010
Edition Number	1.0
Date	27 March 2024
ENCePP	EUPAS43687
NCT Number	NCT05252442

An assessment of a relationship between the exposure to COVID-19 vaccines and risk of thrombotic thrombocytopenia syndrome

ATTEST Study

(Association of the risk of Thrombotic Thrombocytopenia Syndrome and Exposure To COVID-19 vaccines)

Study dates: Start of data collection: 1 March 2022
End of data collection: 11 July 2023

Phase of development: Phase IV; Post Authorisation Safety Study

Principle Investigator:

PPD

Sponsor's Responsible Officer:

PPD
AZ Study Lead, PPD
AstraZeneca, Cambridge, UK
PPD

This study was performed in compliance with Good Clinical Practice, including the archiving of essential documents.

Publications

None at the time of writing this report.

Rationale and background

A very rare and serious combination of thrombosis and thrombocytopenia including thrombotic thrombocytopenia syndrome (TTS), in some cases accompanied by bleeding, was observed following vaccination with VAXZEVRIA during post-authorisation use. Large epidemiological studies have found an increased risk of TTS after VAXZEVRIA administration. The UK is exceptionally well placed to study adverse outcomes on vaccination because of its registration-based primary care system, a health systemwide unique identifier (NHS number) that links primary care to secondary care data, and high vaccination coverage.

Research questions and objectives

To evaluate an association between COVID-19 vaccine exposure and thromboembolic events occurring with thrombocytopenia (thrombotic thrombocytopenia syndrome; TTS).

Study design

The study was based in England, using data from the primary care sentinel cohort (PCSC) extracted by the Oxford-Royal College of General Practitioners (RCGP) Research and Surveillance Centre (RSC), and housed in the Oxford-Royal College of General Practitioners Clinical Informatics Digital Hub (ORCHID) trusted research environment. ORCHID was linked to secondary national datasets that contained laboratory test reports for patients tested for COVID-19, vaccination status, mortality data, and hospital admission records in England. Throughout this report when we refer to "ORCHID", we refer to the ORCHID database of primary care data linked to these datasets. A matched case-control study and a supplementary self-controlled case series (SCCS) analyses were carried out using these data to address the study objective. Data analyses comprised the following:

- ORCHID cohort description: A description of the full ORCHID population was provided after applying the inclusion criteria. Demographic and medical characteristics of the population and TTS cases were summarised separately.

- Case-control analysis: Incident TTS cases were matched to five controls without TTS at the event date and without a history of TE or TCP in the previous 12 months. Individuals were matched on age category, sex, and GP clinic. Demographic and medical characteristics of the matched case-control population were summarised. Conditional logistic regression was used to produce crude and covariate adjusted odds ratios (ORs) for the association of VAXZEVRIA and BNT162b2 exposure with TTS. Analyses were conducted separately by vaccine brand and dose (first and second dose).

- SCCS: Only incident TTS cases were included in this analysis. Conditional Poisson regression was used to estimate the crude and calendar time adjusted relative incidence ratio (RIR) for the association of VAXZEVRIA and BNT162b2 exposure and TTS across distinct risk intervals. Analyses were conducted separately by vaccine brand and dose.

Setting

The study populations consisted of eligible persons who contributed data between 2 December 2020 (approval date of the first COVID-19 vaccine in the UK by the Medicines and Healthcare products Regulatory Agency (MHRA)) and the first censoring event or end of data availability, October 2022.

Subjects and study size

Persons registered with a general practice in the ORCHID database aged ≥ 16 years with a minimum of 12 months medical history from the event date (or pseudo-event date for controls) were included. No exclusion criteria were used. Assuming 80% vaccine coverage, 78 cases and 390 controls would be required to detect an odds ratio of at least 3 in the primary case-control design with 80% power.

Variables and data sources

The primary outcome was incident TTS, defined as the co-occurrence of a thromboembolism (TE) with thrombocytopenia (TCP) with an interval of ± 7 days of the TE diagnosis. Individuals were considered exposed or unexposed based on COVID-19 vaccination in a 28-day risk window preceding the TTS event or pseudo-event date for matched controls. Exposure status was specific to vaccine brand, limited to VAXZEVRIA and Pfizer-BioNTech BNT162b2. Other COVID-19 vaccine brands were excluded from the exposed and unexposed designations. Unexposed individuals were those with no COVID-19 vaccine within the 28-day risk window.

Summary of results

The ORCHID population consisted of 7,641,136 individuals. The mean age was 46.5 years old, and half of the population were male (49.6%). The commonest Joint Committee on Vaccination and Immunisation (JCVI) risk groups were chronic heart disease and vascular disease (n=723,189, 9.5%), diabetes and other endocrine disorders (n=498,841, 6.5%) and chronic neurological disease (n=435,630, 5.7%). The commonest long-term conditions were asthma (n=1,172,250, 15.3%) and diabetes (n=493,669, 6.5%).

We identified 666 incident TTS cases of whom 90.7% (n=604) were unexposed to any COVID-19 vaccine within 28 days prior to TTS, 5.1% (n=34) were exposed to first dose VAXZEVRIA, 1.4% (n=9) were exposed to first dose BNT162b2 vaccine, 2.0% (n=13) were exposed to second dose VAXZEVRIA, and less than 5 individuals (n≤5)were exposed to second dose BNT162b2 vaccine. The 666 TTS cases were all successfully matched 1:5 with 3330 controls on sex, age category, and GP practice. Poor balance (SMD≥0.10) between cases

and controls was evident after matching including the majority of high-risk conditions, and prescription of drugs which are a risk factor for TCP within 90 days (SMD=0.51).

In the matched case-control study primary analysis, no association with TTS was observed between the composite first or second dose exposure levels for VAXZEVRIA or BNT162b2. However, the SCCS analysis demonstrated an increased incidence rate in days 3-28 following a first or second dose of VAXZEVRIA as compared to baseline time (RIR: 2.44, 95% CI: 1.67 to 3.56). In the dose-specific case-control analysis, we observed that TTS cases had more than double the odds of having recently received a first dose of VAXZEVRIA compared to matched controls without TTS (adjusted OR: 2.12, 95% CI: 1.14 to 3.92). Similarly, in the dose-specific SCCS analysis, we found that the relative incidence rate of TTS 3-28 days after the first dose of VAXZEVRIA administration was 3.49 times (95% CI: 2.22 to 5.49) higher compared to baseline time. In both analyses, no association was found between the second dose of VAXZEVRIA and TTS incidence. No association between BNT162b2 and TTS was observed at any exposure level in either analysis. No increased relative incidence rate after either COVID-19 vaccine at any dose was observed in the SCCS analysis in the first two days after vaccination compared to baseline.

Sensitivity definitions for case ascertainment included using a 90-day lookback for incident events, extending the time between TE and TCP to -7/+42 days, and raising the threshold for TCP from 100 x 10^9/L to 150 x 10^9/L. Sensitivity exposure definitions extended the risk period from 28 to 42 days following vaccination. The findings from these sensitivity definitions produced results similar to those using the primary case definition, demonstrating that our primary analyses were robust.

Various subgroup analyses were carried out. No sex differences were observed in either the case-control or SCCS analyses. Compared to the overall study population, the point estimates for associations between a first dose of VAXZEVRIA and TTS were numerically highest in individuals aged 16-49 (OR: 3.20, 95% CI: 1.04 to 9.83; RIR: 7.09, 95% CI: 2.78 to 18.12) than for individuals aged ≥50 (OR: 1.53, 95% CI: 0.71 to 3.27; RIR: 2.66, 95% CI: 1.58 to 4.48). While the association between TTS and a first dose of VAXZEVRIA was observed in both those aged 16-49 and ≥50 years, the overlapping 95% CIs preclude us from concluding with any certainty that the association was age dependent.

A low event number precluded the examination of vaccination and TTS in those with recent COVID-19 diagnosis or positive SARS-COV-2 infection test within 84 days in the case-control analysis. However, whilst a positive association between the first dose of VAXZEVRIA and TTS during days 3-28 in this subgroup was observed in the SCCS analysis (RIR: 5.20), the corresponding interval was imprecise (95% CI: 1.02 to 26.32).

The SCCS for individuals exposed to any anticoagulant drugs within 90 days of the event date suggested that a second homologous dose of VAXZEVRIA was associated with an increased

rate of TTS in the 3–28-day risk window (RIR: 8.76), however the corresponding confidence interval was imprecise (95% CI: 1.77 to 43.30).

Within the period sensitivity analysis (follow-up ending on 7 March 2021), we observed a reduced odds of TTS following a first dose of VAXZEVRIA though this was imprecise (OR: 0.21, 95% CI: 0.05 to 0.96). Given the low event numbers in this shorter time period, the analysis was limited to a small number of adjustment covariates. The SCCS analysis, which holds non-time varying covariates as fixed, found no association between the first dose of VAXZEVRIA and TTS in any risk period in this shorter study period.

Conclusion(s)

In our study, in the matched case-control study primary analysis, no association with TTS was observed between the composite first or second dose exposure levels for VAXZEVRIA or BNT162b2. However, a positive association was found in the corresponding composite dose analysis from the SCCS analysis for VAXZEVRIA. Furthermore, in the dose-specific case-control and SCCS analyses, an increased risk of TTS was found after the first dose of VAXZEVRIA, but not after second dose. No increased risk for TTS was found after BNT162b2 vaccination. These findings are consistent with previous studies.

Strengths of the study included the use of a case-control design, which is appropriate in the study of rare outcomes, in combination with a SCCS that has been widely used and recommended for vaccine safety monitoring by the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP). Moreover, ORCHID is a high-quality rich linked data source that is nationally representative. Weaknesses included that the algorithmic definition of TTS as a co-occurrence between TCP and TE was lacking the veracity to differentiate between the coincidental co-occurrence of TE and TCP and vaccine-induced thrombotic thrombocytopenia. Covariate imbalance remained between cases and controls after matching and even though adjusted for, the possibility of residual confounding by additional unmeasured variables remains possible. However, the SCCS design used is robust in dealing with residual (including unmeasured) confounding, so long as these covariates are not time varying. Results were similar in the case-control and SCCS analysis. Both analyses found an increased risk of TTS after the first dose of VAXZEVRIA, but not after second dose. No increased risk for TTS was found after BNT162b2 vaccination. These findings are consistent with previous studies.