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Epidemiology of thrombotic thrombocytopenia syndrome in integrated health-care database in England

Secondary data analysis using a cohort design

Study dates: Start of data collection: 1 March 2022
End of data collection: 25 May 2023

Phase of development: Phase IV; Post Authorisation Safety Study

Principle Investigator:

PPD

Sponsor's Responsible Officer:

PPD

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

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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, has been observed following vaccination with VAXZEVRIA (ChAdOx1-S [recombinant]) during post-authorisation use. Although initial reports indicated more cases of TTS being identified in females and younger age groups, potential factors, or conditions such as age, gender, and history of blood clotting disorders have not been confirmed as risk factors.

Research questions and objectives

The overall objective of this study was to estimate event rates and describe characteristics of patients with a record for TTS, or thromboembolism (TE), or thrombocytopenia (TCP), in the general population of England.

Specific objectives were to:

1 Estimate occurrence of, and describe patients with TTS, or TE, or TCP (definitions may subset for specific diagnostic units described in the Case Definitions section), overall and split by age, gender, and known risk factors.

2 Estimate occurrence of, and describe patients with TTS, TE, and TCP within a pre-defined time interval of receiving COVID-19 vaccination overall and split by age, gender, and known risk factors.

3 Evaluate associations of TTS and pre-defined risk factors.

Study design

The objectives were addressed through a cohort study using the Oxford-Royal College of General Practitioners Clinical Informatics Digital Hub (ORCHID), linked to nationwide data containing COVID-19 data including diagnosis, polymerase chain reaction (PCR) tests and vaccinations (hereafter when we refer to "ORCHID" we refer to the ORCHID database linked to these datasets). Unadjusted incidence rates of TCP, TE, and TTS were calculated with associated Poisson exact 95%-confidence intervals by dividing the number of incident events by the person-time at risk (presented per 100,000 person years). Multivariable logistic regression analyses was carried out to investigate the association between risk factors and the occurrence of a TTS event.

Setting

The study dataset was from England, UK.

Subjects and study size

Three study cohorts were extracted from the data sources based on calendar time and exposure to COVID-19 vaccination/confirmed COVID-19. As cohorts were non overlapping in terms of calendar time, an individual can contribute to multiple cohorts where conditions are met. The following periods were defined as the study dates:

- Pre-COVID-19 period: 01 January 2011 to 31 December 2019 (inclusive). Index date was defined as the date when 365 days history was available during the study period and age eligibility criteria were met.

- COVID-19 period: 01 January 2020 to 31 December 2020 (inclusive). This cohort included individuals with COVID-19 defined by diagnostic code for COVID-19 together with the record of a positive PCR test within 10 days of each other. The index date was defined as the earliest of COVID-19 diagnosis date or positive PCR date.

- COVID-19 vaccination (VAXZEVRIA) period: 1 January 2021 until 4 July 2022 (inclusive). This cohort included individuals with VAXZEVRIA vaccination record/s. Index date was defined as the date of first VAXZEVRIA vaccination**.** The end date of the COVID-19 vaccination cohort study periods reflects the end of data availability.

All follow-up time started at the index date and ended at the earliest of outcome occurrence, death, deregistration, end of relevant study period, there were bespoke censoring criteria applied, namely follow-up could end 42 days after COVID-19 infection (COVID-19 confirmed cohort) or 28 days after vaccination, and when receiving another COVID vaccine dose (COVID-19 vaccination cohort).

Variables and data sources

All variables were taken from ORCHID. TE was defined as a code in the primary record of thromboembolism, including:

- Cerebral venous sinus thrombosis (CVST), including cerebral venous thrombosis (CVT)

- intracranial venous thrombosis

- intracranial thrombophlebitis

- splanchnic venous thrombosis (SpVT)

- deep venous thrombosis (DVT) including:
- DVT of limb
- pulmonary embolism

Only patients without a prevalent TE in the 365 days before index were included in the incident event rates. For patients with thrombosis in multiple sites, we considered the time to the first thrombotic event.

TCP was defined as all cause TCP using recorded medical diagnosis codes in primary care data and/or platelet count between 10 and 100 x 109/L. The first of the 2 events (medical diagnosis or platelet count meeting criteria) were considered as the TCP event date if both were present. Events separated by more than 90 days were considered separate events.

Only patients without TTS, TE or TCP in the 365 days before index were included in the incident event rate.

Summary of results

In the pre-COVID-19 Cohort (n= 9 062 313), the crude incidence rate of TE was 231.3 (95%CI: 229.9 to 232.6) per 100,000 person years. The crude incidence rate of TCP was 132.5 (95%CI: 131.5 to 133.5) per 100,000 person years, and the crude incidence rate of TTS was 0.42 (95%CI: 0.36 to 0.48) per 100 000 person years. The crude incidence rate of TE increased with age from 22.8 (95%CI: 21.3 to 24.4) per 100,000 person-years in the 16-17 age group to 704.5 (95%CI: 698.6 to 710.4) 100 000 person-years in those 65 years of age or older. The crude incidence of TCP also increased with age from 29.6 (95%CI: 27.9 to 31.5) per 100,000 person-years in those 16-17 to 374.8 (95%: 370.5 to 379.0) per 100,000 person-years in those 65 or older. TCP was more common in men (confidence intervals did not overlap) and the crude incidence rate for men was almost double that of in women from age 65 (crude IR 509.9 vs 268.0 per 100,000).

In the COVID-19 confirmed cohort (n= 39 448) with 42 days following COVID-19, there were ≤5 cases of TTS, whereof none were incident. The crude incidence rate of TE was 7538.0 (95%CI: 6597.2 to 8575.3) per 100 000 person-years. The most common type of TE after confirmed COVID-19 infection was PE (representing more than 80% of the TEs). The crude incidence rate of TCP after COVID-19 infection was 809.4 (95%CI: 523.8 to 1194.9) per 100 000 person-years. The crude incidence rate of TE increased with age, ranging from 3344.8 (95%CI: 1911.8 to 5431.7) per 100,000 person-years in those 30-39 (which was the youngest age group a rate could be calculated) to 17483.7 (95%CI: 14145.4 to 21373.0) per 100,000 person-years in those 65 or older. The crude incidence rate of TCP could only be calculated in the 65+ age group (2851.8 per 100 000 person-years; 95%CI: 1046.6 to 6207.2), whilst the crude incidence rate of TTS stratified by sex and age could not be calculated due to no cases being identified.

In the Vaccination cohort (n= 5 544 761) the crude incidence rate of TTS within 28 days after vaccination with VAXZEVRIA was 2.41 (95%CI: 1.47 to 3.72) per 100 000 person years

based on 20 cases. The crude incidence rates of TTS within 28 days of vaccination with VAXZEVRIA higher in men (2.95 (95%CI: 1.52 to 5.15)) than women (1.89 (95%CI: 0.81 to 3.72)), however confidence intervals were wide and overlapped. There were too few TTS cases to stratify the rates by age groups. The crude incidence rate of TE within 28 days of vaccination with VAXZEVRIA increased with age from 105.3 (95%CI: 76.5 to 141.3) in those 18-29 to 690.7 (95%CI:656.2 to 726.5) in those 65 year or older. The TE crude incidence rate within 28 days of vaccination with VAXZEVRIA was somewhat higher among men in the 50-64 age group (313.4 (95%CI: 287.3 to 341.3) vs 228.9 (95%CI: 205.8 to 253.9) in women. Similarly, TCP crude incidence rate increased with age from 86.1 (95%CI: 60.3 to 119.1) in those aged 18-29 years to 381.8 (95%CI: 356.4 to 408.6) in those 65 years or older. TCP within 28 days of vaccination with VAXZEVRIA was more frequent in men with a crude incidence rate of 472.8 (95%CI: 431.3 to 517.1) than in women in the 65+ age group 303.6 (95%CI: 272.9 to 336.8) (confidence intervals not overlapping).

In the pre-COVID-19 Cohort younger age groups were significantly associated with a reduced risk for incident TTS. The lowest odds was in those aged 18-29 (OR: 0.29 (95%CI: 0.16 to 0.55)) while being in the middle age groups was associated with higher odds (OR:1.73 (1.19 to 2.51) and 2.36 (95%CI: 1.82 to 3.07). Females presented with a slightly reduced odds of incident TTS; however, this was not statistically significant (OR: 0.82 (95%CI: 0.66 to 1.01)). There was no significant association between TTS and ethnicity other than a reduced odds of TTS for those with missing ethnicity data as compared to those of white ethnicity (OR:0.65, 95% CI 0.49 – 0.85). Being less deprived than the most deprived quintile was associated with a higher risk of incident TTS (ORs ranging between 1.89 and 2.37, quintile 3 not statistically significant). Being overweight was associated with a decreased odds of incident TTS (OR: 0.68 (95%CI: 0.46 to 0.99)) compared to normal weight, although the upper confidence interval was close to 1. Missing obesity information was highly associated with TTS (OR: 25.22, 95% CI 18.44 to 34.50). For the JCVI risk groups, Chronic heart disease and vascular disease (OR: 2.35 (95%CI: 1.79 to 3.07)), Chronic kidney disease (OR: 1.47 (95%CI: 1.08 to 2.00)), Chronic liver disease (OR: 5.75 (95%CI: 3.82 to 8.65)), Chronic neurological disease (OR: 1.54 (95%CI: 1.14 to 2.09)), Chronic respiratory disease (OR: 2.45 (95%CI: 1.78 to 3.36)), Diabetes mellitus and other endocrine disorder (OR: 2.70 (95%CI: 2.00 to 3.63)), and Immunosuppression (OR: 2.71 (95%CI: 1.89 to 3.88)) were found to be associated with increased odds of TTS compared to those not in these risk groups. A medical history of solid tumour (OR: 4.24 (95%CI: 3.30 to 5.45)), or that of chemotherapy of radiotherapy (OR: 2.41 (95%CI: 1.64 to 3.55)) was associated with higher odds of incident TTS. A history of Asthma (OR: 0.41 (95%CI: 0.26 to 0.63)), Atrial fibrillation (OR: 0.34 (95%CI: 0.20 to 0.57)), Dementia (OR: 0.30 (95%CI: 0.13 to 0.71)), Myocardial Infarction (OR: 0.20 (95%CI: 0.09 to 0.45)), and Disorder of Immune Function OR: 0.14 (95%CI: 0.08 to 0.23) was associated with reduced odds of incident TTS. Being on Anticoagulant drugs (OR: 7.93 (95%CI: 5.63 to 11.16)), oral hormonal contraception (OR: 2.70 (95%CI 1.09 to 6.67)), drugs associated with TCP (OR: 11.46 (95% 8.26 to 15.90)), and drugs used to treat TCP (OR: 5.68 (95% 4.39 to

7.34)) was associated with increased odds of TTS. Over 85% of incident TTS events (311/363) occurred in patients receiving drugs associated with TCP.

Conclusions

TTS was very rare in all cohorts. The crude incidence rate of TTS after VAXZEVRIA administration was found to be lower that found in other studies. Initial reports showed that most TTS cases occurred in women, however our results found numerically higher incidence rates of TTS in men after vaccination, though the confidence intervals were overlapping. Incidence rates of TTS were similar for women and men and increased with age in the pre-COVID-19 and COVID-19 periods, again similar to previous findings. In all cohorts the crude incidence rates of TE and TCP also increased with age and TCP was more common among men than women in the older age groups. Owing to a small number of events, the association of TTS could not be examined in a multivariable logistic regression model in the COVID-19 and Vaccination cohorts. Our study adds a report of the association of sociodemographic, clinical risk group and medication use with TTS, which may contribute to a better understanding of this rare condition. TTS is an identified Adverse Drug Reaction (ADR) in the VAXZEVRIA Core Data Sheet (CDS) and Summary of Product Characteristics (SmPC). Information on TTS is also included in the ‘contraindications and special warnings and precautions for use’ sections.