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ORIGINAL RESEARCH ARTICLE

Assessing Case Fatality on Cases of Thrombosis with Concurrent Thrombocytopenia Following COVID-19 Vaccine AstraZeneca (Vaxzevria) in the United Kingdom: A Review of Spontaneously Reported Data

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Abstract

Introduction Thrombotic thrombocytopenia syndrome (TTS) events were reported very rarely following the coronavirus disease 2019 (COVID-19) vaccine AstraZeneca (Vaxzevria). Clinical and demographic characteristics of the affected people, including the outcomes of TTS events, need to be examined using available information to better understand aspects of this association.

Objective To analyse clinical and demographic information of TTS events, including calculating the case fatality of reported cases of TTS by age and sex, using spontaneously reported data from the UK's Yellow Card spontaneous reporting system of suspected adverse drug reactions.

Methods TTS events reported to the Yellow Card scheme were extracted at weekly time points between 12 May 2021 and 25 May 2022. Cumulative numbers of TTS cases and deaths were recorded for each weekly interval, overall and stratified by age, sex, and vaccine dose.

Results To 25 May 2022, 443 cases (81 fatal, 18.28%) had been reported in the UK. Events more frequently occurred following the first vaccine dose. No trends were observed for case fatality overall, or by age or sex.

Conclusion In the UK, case fatality of TTS events reported to the Medicines and Health products Regulatory Agency (MHRA) following Vaxzevria has been approximately 17–18% since May 2021. There were no statistical differences in fatality based on age or sex. Most reports followed the first vaccine dose; none have been reported following a third dose to date, although Vaxzevria was not recommended for a third dose of COVID-19 vaccine in the UK. TTS remains very rare, and benefits of vaccination outweigh the risks.

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Key Points

In the UK, there were small but insignificant differences in cumulative case fatality of thrombosis with concurrent thrombocytopenia (thrombotic thrombocytopenia syndrome [TTS]) following the coronavirus disease 2019 (COVID-19) Vaccine AstraZeneca (Vaxzevria), by age but not sex.

Case fatality has remained stable since May 2021, at which time risk minimisation measures were implemented to prevent TTS in younger vaccine recipients.

As Vaxzevria is in wide use across the world, it is important to report on findings from the UK where a large proportion of the population were exposed. TTS is a very rare event following Vaxzevria vaccine exposure, and benefits of vaccination with Vaxzevria, like other COVID-19 vaccines used in the UK, continue to outweigh the risks.

1 Introduction

In March 2021, a signal of unusual clotting with concurrent low platelets following exposure to the coronavirus disease 2019 (COVID-19) Vaccine AstraZeneca (Vaxzevria) emerged in Europe, resulting in suspension of the vaccine in several countries while investigations commenced [1]. Subsequently 'thrombosis with thrombocytopenia syndrome' (TTS) was listed as an adverse reaction of Vaxzevria in the summary of product characteristics [2]. In the UK, this event is also known as vaccine-induced immune thrombotic thrombocytopenia (VITT) [3]. Initially, TTS was thought to most frequently affect women of younger age groups; in the first case series to be published, which outlined 11 cases from Germany and Austria, women were affected in 81.8% of cases ($n = 9$), with a median age of these patients of 36 years (range 22–49 years) [4]. Subsequently, as reports emerged of cases among other young vaccinees, the use of Vaxzevria was suspended in some countries, while its use was restricted to older vaccinees elsewhere [1]. In the UK, the Joint Committee on Vaccination and Immunisation (JCVI) decided that due to the availability of alternative vaccines, and as a precaution, all people aged 39 years and under were offered an alternative vaccine from May 2021 [5].

The aim of this study was to analyse the publicly available spontaneous reporting data from the UK's Medicines and Healthcare products Regulatory Agency (MHRA) Yellow Card Scheme, and to calculate the case fatality of reported cases of thrombosis with concurrent thrombocytopenia (TTS), stratified by age, sex, and vaccine dose.

2 Methods

Due to the unusual nature of TTS, we analysed the publicly available data from the UK's Yellow Card spontaneous reporting scheme (extracted from the 'Coronavirus vaccine—weekly summary of Yellow Card reporting' [6]). We calculated the proportion of events with a fatal outcome (case fatality) for cases of TTS that had been spontaneously reported in the UK following any dose of Vaxzevria. Data were obtained at weekly timepoints between 12 May 2021 (when publicly available data were released by the MHRA) and 25 May 2022. Data were stratified by age, sex, and Vaxzevria vaccine dose. Ten-year age bands were used, per the outputs of Yellow Card data, for adults aged 18 years and older. For the purposes of this analysis, it was assumed that all clotting events with concurrent thrombocytopenia reported by the MHRA met the definition for thrombosis with thrombocytopenia syndrome (TTS) [7–9]. Insufficient data are available to determine whether reported cases were vaccine-induced and thus met the criteria for VITT.

Ethics approval was not required for this research due to the nature of the data source.

3 Results and Discussion

To 25 May 2022, 443 cases of thrombosis with concurrent thrombocytopenia had been reported to the Yellow Card scheme (Table 1), of which 81 were fatal cases (Table 1). Therefore, the overall cumulative case fatality was estimated at 18.28% (95% confidence interval [CI] 14.79–22.20%) (Table 1). To the same date, 24.9 million first doses and 24.1 million second doses of Vaxzevria had been administered in the UK [6]. The reporting rate of TTS is therefore estimated at 15.74 cases reported per million first doses of Vaxzevria and 2.12 cases of TTS reported per million second doses of Vaxzevria administered in the UK population, indicating that this is a very rare event. Due to the lack of accurate numerator and denominator data within spontaneous reports databases, it was not possible to estimate the incidence of TTS following Vaxzevria for this population. The true incidence of TTS is not known and varies per region, however published estimates suggest that incidence ranges from 1 case per 26,500–137,000 first doses of Vaxzevria administered [10, 11]. Further research is required to establish the true incidence of TTS following Vaxzevria.

When considering the age of vaccinees who had reported a case of TTS to the Yellow Card scheme, there were no

Table 1 Overall number of events (cumulative) of thrombosis with concurrent thrombocytopenia reported to the MHRA, cumulative number of fatal cases reported, and cumulative case fatality (%) at weekly intervals [6]

Date	Cases reported (cumulative)	Fatal events (cumulative)	Cumulative case fatality		
			Case fatality (%)	Lower 95% CI (%)	Upper 95% CI (%)
12 May 2021	262	51	19.47	14.85	24.79
19 May	332	58	17.47	13.54	21.99
02 Jun	372	66	17.74	14.00	22.01
09 Jun	390	71	18.21	14.50	22.40
16 Jun[a]	389	68	17.48	13.84	21.62
23 Jun	395	70	17.72	14.08	21.85
30 Jun	399	71	17.79	14.17	21.91
14 Jul	411	71	17.27	13.74	21.28
18 Aug	417	72	17.27	13.76	21.24
25 Aug	415	72	17.35	13.82	21.34
01 Sep	416	72	17.31	13.80	21.30
08 Sep	419	72	17.18	13.69	21.14
15 Sep	419	72	17.18	13.69	21.14
29 Sep	421	72	17.10	13.63	21.05
06 Oct	424	72	16.98	13.53	20.90
13 Oct	421	72	17.10	13.63	21.05
20 Oct	423	72	17.02	13.56	20.95
27 Oct	424	72	16.98	13.53	20.90
03 Nov	425	73	17.18	13.71	21.11
10 Nov	425	73	17.18	13.71	21.11
17 Nov	426	73	17.14	13.68	21.06
01 Dec	428	74	17.29	13.83	21.21
08 Dec	428	74	17.29	13.83	21.21
15 Dec	429	75	17.48	14.01	21.41
22 Dec	430	75	17.44	13.97	21.37
05 Jan 2022	433	76	17.55	14.09	21.47
12 Jan	435	76	17.47	14.02	21.37
19 Jan	435	77	17.70	14.23	21.62
25 Jan	436	78	17.89	14.41	21.82
02 Feb	437	78	17.85	14.37	21.77
09 Feb	438	79	18.04	14.55	21.96
16 Feb	438	79	18.04	14.55	21.96
23 Feb	438	79	18.04	14.55	21.96
02 Mar[a]	437	78	17.85	14.37	21.77
09 Mar	438	79	18.04	14.55	21.96
16 Mar	438	79	18.04	14.55	21.96
23 Mar	438	79	18.04	14.55	21.96
30 Mar	439	79	18.00	14.51	21.91
06 Apr	440	79	17.95	14.48	21.87
04 May	443	81	18.28	14.79	22.20
11 May	443	81	18.28	14.79	22.20
18 May	443	81	18.28	14.79	22.20
25 May	443	81	18.28	14.79	22.20

CI confidence interval, *MHRA* Medicines and Health products Regulatory Agency

[a]Due to the MHRA merging cases and further reviewing events reported during follow-up, the counts decreased for this week

clear trends. Among the TTS cases reported to the Yellow Card scheme, people aged ≥ 80 years seemed to have the highest case fatality of all other age groups, with 50.00% (95% CI 15.70–84.30%) of the eight cases reported to have a fatal outcome. The 18–29 years age group had the next highest cumulative case fatality of all reported TTS events, with 22.58% (95% CI 9.59–41.10%) of reports having a fatal outcome ($n = 7$ of 31 reports for this age group). The highest number of reports received were for the 40–49 years age group ($n = 111$, of which 15 were fatal [13.51%, 95% CI 7.77–21.31%]). This was the youngest age group in the UK population routinely offered Vaxzevria [12]. CIs were calculated for case fatality for each age group at data lock (Table 2); although imprecise due to small numbers of reported cases, 95% CIs overlap for all age groups, suggesting no statistical difference in case fatality depending on age.

Reports were approximately balanced between males and females, with 221 reported events from females and 217 reports from males to 25 May 2022. Females had a higher cumulative case fatality at each weekly time point examined. As of 25 May 2022, case fatality was 20.36% ($n = 45$ fatal cases [95% CI 15.26–26.28%]) for females and 16.13% ($n = 35$ fatal cases [95% CI 11.45–21.71%]) for males, suggesting no statistical difference in fatality of TTS depending on sex.

The majority of events had been reported following the first or unknown dose ($n = 392$ of 443 reports, 88.49% [95% CI 85.14–91.31%]). Cumulative case fatality was higher for events reported following the first or unknown dose (19.13% [95% CI 15.36–23.38%]) than reports following a second dose of Vaxzeria (11.76% [95% CI 4.44–23.87%]). The considerably smaller number of reported TTS events following a second vaccine dose may be due to the phenomenon 'depletion of the susceptibles', whereby the risk of an event is higher in the earlier period of exposure and decreases thereafter [13]. In this study, 'depletion of the susceptibles' bias may have affected the results, as the majority of people who were at risk of the event experienced TTS on their first exposure to the vaccine. It was therefore expected that a smaller number of cases would be reported following the third dose of Vaxzevria compared with the first and second doses. To 25 May 2022, there had been no reports of TTS after a third dose of Vaxzevria in the UK [6].

In the UK, Vaxzevria is not routinely used in the booster vaccination programme; only those for whom messenger RNA (mRNA) vaccines (COVID-19 Vaccine Pfizer/BioNTech [Comirnaty] or Moderna [Spikevax]) are clinically contraindicated should be offered Vaxzevria, provided they had received at least one dose of this vaccine previously [14]. Due to this, use of Vaxzevria as a third dose is small, however the vaccine is expected to remain one of the main choices for COVID-19 vaccination programmes in other countries, particularly where health and logistical infrastructure limits cold storage of vaccines [15]. Therefore, it remains important to report on case fatality of TTS events observed in the UK population where there was wide use of the vaccine in the primary COVID-19 vaccination programme.

It should be noted that it is unclear whether the cases reported to the Yellow Card scheme, and subsequently included in the MHRA's weekly summary of Yellow Card reports, met the criteria for TTS. According to case definitions, a platelet count $< 150 \times 10^9$/L meets the criteria for TTS [3, 8]. No definition has been provided within the MHRA's weekly summary, only that reports concern thromboembolic events with concurrent low platelets [6]. This should be noted when interpreting the results of this analysis. It is also possible that results may be affected by causality assessment of the TTS events that have been reported; details on causality assessments made by the MHRA are not available. Furthermore, the outputs from the MHRA do not report sufficient clinical information that would be required to determine the number of reported events that met the case definition for TTS; verification using medical records is also

Table 2 Cumulative case fatality of thrombosis with thrombocytopenia events reported to the Yellow Card Scheme to 25 May 2022

Age group (years)	No. of reported TTS events submitted to the Yellow Card Scheme	Cumulative case fatality of TTS (%)	Lower 95% CI	Upper 95% CI
18–29	31	22.58	9.59	41.10
30–39	49	20.41	10.24	34.34
40–49	111	13.51	7.77	21.31
50–59	108	20.37	13.24	29.20
60–69	11	17.74	9.20	29.53
70–79	40	17.50	7.34	32.78
80–89	6	50.00	11.81	88.19
90+	2	50.00	1.26	98.74
Not specified	34	14.71	4.95	31.06

TTS thrombotic thrombocytopenia syndrome, *CI* confidence interval

not possible. Indeed, one important limitation of spontaneously reported data is the extent of missing data on possible factors contributing to, or allowing further verification of, the event. Furthermore, our period of observation started in May 2021, while TTS began to be reported earlier in 2021. Conversely, it is possible that media attention surrounding TTS following Vaxzevria led to inflated reporting; a paper by Ferner et al. concluded that most cases of cerebral sinus thrombosis had occurred after the event had been publicised [16]. It was not possible to determine the date of onset for each case reported to the Yellow Card scheme that had been included in this analysis, as we were limited to data being made available by MHRA. Therefore, case fatality of TTS prior to the start of our observation period may have been different.

In the UK, guidelines are available for the treatment of TTS; however, we cannot be certain that all patients reporting events included in this analysis received any treatment. While it could be assumed that patients diagnosed in a British hospital under the care of a haematologist would receive treatment per the guidelines, it is possible that factors such as death before treatment initiation meant the patient did not receive treatment for TTS. Therefore, it has not been possible to comment on whether treatment of TTS has any effect on case fatality.

Further research into risk factors for TTS following adenovirus vector vaccines, including Vaxzevria, is required.

4 Conclusion

In the UK, case fatality of TTS following Vaxzevria reported to the Yellow Card scheme has remained stable at approximately 17–18% since May 2021. Of the events reported to the MHRA, no statistical differences in fatality were observed based on age or sex. Reports of TTS following Vaxzevria to the Yellow Card scheme are highest following a first vaccine dose. TTS is very rare and the benefits of COVID-19 vaccination continue to outweigh the risks.

Declarations

Competing interests The Drug Safety Research Unit (DSRU) receives donations and grants from pharmaceutical companies; however, the companies have no control over the conduct or publication of its studies. The DSRU has received grants to conduct unconditional studies on the Oxford/AstraZeneca COVID-19 vaccine and for conducting Clinical Practice Research Datalink (CPRD) studies for Pfizer, Moderna, and Janssen COVID-19 vaccines. The DSRU has conducted benefit–risk studies on products for COVID-19, including remdesivir, lopinavir/ritonavir, chloroquine and hydroxychloroquine, and convalescent plasma. Professor Shakir is the principal investigator for an active surveillance study for the Oxford/AstraZeneca vaccine, but this assessment is unrelated to this study. Professor Shakir has been a member of Data Safety Monitoring Boards for Ipsen, Biogen, and Diurnal. None of these companies have any involvement with COVID-19 vaccines. Professor Shakir was also invited by AstraZeneca to advise on the events of thrombosis with thrombocytopenia with the COVID-19 vaccine and to be a member of an advisory committee on a safety study of the Oxford/AstraZeneca vaccine in Europe. Samantha Lane has no conflicts of interest with regard to this study.

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Availability of data and material No additional data are available.

Code availability Not applicable.

Patient and public involvement Patients and the public were not consulted during the course of this study.

Ethics approval Ethics approval was not required for this research due to the nature of the data source.

Consent to participate Not applicable.

Consent for publication Not applicable.

Authors' contributions Samantha Lane was responsible for data acquisition, analyses, and interpretation. Samantha Lane and Saad Shakir were responsible for study conception, drafting and reviewing the manuscript, and approval of the final version for publication.

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