Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Very rare thrombosis with thrombocytopenia after second AZD1222 dose: a global safety database analysis

Since COVID-19 vaccine roll-out, very rare cases of thrombosis with thrombocytopenia syndrome (TTS), which has been referred to as vaccine-induced immune thrombotic thrombocytopenia, have been reported. Here we describe case details of TTS identified in the AstraZeneca global safety database, which captures all spontaneously reported adverse events from real-world use of its medicines and vaccines worldwide.

All cases of TTS occurring within 14 days of intramuscular administration of first or second AZD1222 (ChAdOx nCoV-19) dose up to April 30, 2021, were included. In alignment with the Brighton Collaboration definition of TTS,[1] TTS cases were searched using standardised Medical Dictionary for Regulatory Activities (version 23.1) queries "embolic and thrombotic events", "hematopoietic thrombocytopenia", and high-level term "thrombocytopenias". The understanding of the role of anti-platelet factor 4 (PF4) antibodies in TTS is still evolving, so in line with the Brighton criteria, all cases meeting the above definition, irrespective of anti-PF4 antibodies, were included. This research was led and funded by AstraZeneca.

At data cutoff, 13 cases of TTS were identified after the second AZD1222 dose, occurring 1–13 days post-vaccination (appendix p 1; no cases were observed outside the 14-day window). The reported events included eight individuals with pulmonary embolism, co-occurring with cerebral venous sinus thrombosis (CVST) in two individuals; one individual with CVST occurring alone; one individual with deep vein thrombosis; one individual with thrombotic stroke; and two individuals with unspecified embolisms. The 13 vaccinees reporting TTS were aged 45–85 years (one age unknown); eight were female (a lower proportion than in initial TTS reports[2]). Medical history was available for 11 vaccinees; one had previous pulmonary embolism, one had thrombocytopenia, three had cancer, and one had COVID-19. Other medication details were available for seven vaccinees and included cancer treatments, antihypertensives, anticoagulants, and statins. Anti-PF4 test results were available for three of 13 cases, all of which were negative (appendix p 1). At data cutoff, six vaccinees were reported as "not recovered", three were "recovering", three died, and one "recovered with sequalae".

Based on weekly data from the European Centre for Disease Prevention and Control and the UK Department of Business Energy and Industrial Strategy, as of April 25, 2021, approximately 5·62 million people were estimated to have received the second AZD1222 dose in the EU/EEA and in the UK (93·5% administered in the UK). Based on this exposure level, the estimated rate of TTS within 14 days of the second AZD1222 dose was 2·3 per million vaccinees.

By comparison, within the same timeframes, the estimated rate of TTS within 14 days of the first dose was 8·1 per million vaccinees, based on 399 cases of TTS identified after the first AZD1222 dose and approximately 49·23 million first doses administered, with 45·2% of doses administered in the UK and 54·8% in the EU/EEA.

We estimated background TTS rates using two analysis methods with the US Truven MarketScan Commercial Claims and Encounters database from Jan 1, 2019, to Dec 31, 2019. The very low rate of TTS reported following a second AZD1222 dose is within preliminary estimates of the background range in an unvaccinated population pre-COVID-19 (appendix p 4).[3]

Limitations of this safety database analysis include a reliance on healthcare provider-reported and vaccinee-reported data, which might result in event under-reporting. Furthermore, heightened media attention might have led to event misclassification. Therefore, to provide a cautious estimate for the event rate, data used for the number of doses administered was limited to the EU/EEA and the UK, while all cases reported globally were included.

As common in post-market reporting, limited information was provided in many cases, including medical history and concomitant medication. Additionally, comparing incidence rates, including background rates, can be challenging due to dependence on data sources, event definitions, data collection method, timeframe, and the patient population. The TTS background event rate reported here was derived from a large US population with health insurance in 2019, prior to the emergence of COVID-19, a disease which itself has been associated with thrombotic events.[4]

Although post-marketing surveillance reporting does not enable full characterisation and contextualisation of each case, overall results support the continued administration of AZD1222 in a two-dose schedule, as indicated.[5] This is particularly relevant in light of recent data demonstrating the efficacy of two doses of AZD1222 against SARS-CoV-2 variants of concern, including protection against hospitalisation with the Delta variant.[6,7]

We are employees of AstraZeneca and might have stock or options, or both. Details of contributions are shown in the appendix.

*Prakash Bhuyan, Jennie Medin, Hugo Gomes da Silva, Madhavi Yadavalli, Nirmal Kumar Shankar, Hana Mullerova, Matthew Arnold, *Magnus Nord*
magnus.nord@astrazeneca.com

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See **Online** for appendix

Global Clinical Development Late R&I (PB) and Global Patient Safety BioPharmaceuticals (MY), AstraZeneca, Gaithersburg, MD, USA; Global Medical BioPharmaceuticals (JM) and Global Patient Safety BioPharmaceuticals (MN), AstraZeneca, Gothenberg SE431 83, Sweden; Global Medical BioPharmaceuticals, AstraZeneca, Cambridge, UK (HGdS, HM, MA); Global Patient Safety BioPharmaceuticals, AstraZeneca, Bangalore, India (NKS)

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Voriconazole pharmacogenetics

See **Online** for appendix

In their Article, Johan Maertens and colleagues[1] showed the results of a randomised, controlled, phase 3 trial comparing posaconazole versus voriconazole for the primary treatment of invasive aspergillosis. Mortality up until day 42 (the primary endpoint) was 44 (15%) of 288 patients for posaconazole versus 59 (21%) of 287 patients for voriconazole.[1] The overall incidence of treatment-related adverse events was 10% higher with voriconazole than with posaconazole.[1]

Therapeutic drug monitoring was not done, and the CYP2C19 phenotype status of the patients was unknown. However, voriconazole (unlike posaconazole) is metabolised by CYP2C19,[2] and there is substantial evidence linking the *CYP2C19* genotype with phenotypic variability in voriconazole pharmacokinetics.[3,4]

In patients for whom a rapid or ultrarapid metaboliser genotype is identified (carriers of one or two *CYP2C19*17* alleles; 5–30% of patients), the probability of reaching therapeutic voriconazole concentrations is very low. In such cases, use of an alternative antifungal agent, such as posaconazole, is recommended.[3] A strong association between individuals who are slow metabolisers (carriers of two no-function *CYP2C19*2* or *CYP2C19*3* alleles; 2–15% of patients) and increased voriconazole concentrations resulting in adverse events is also documented, which provides the basis for recommending use of alternative agents (eg, posaconazole) in these patients.[3]

Considering the prevalence of rapid and slow metaboliser phenotypes within the general population, it is likely that a sizeable proportion of patients receiving voriconazole in this study metabolised either rapidly or slowly, which partly explains the lower therapeutic response or more frequent side-effects seen with voriconazole compared with posaconazole.

We declare no competing interests.

*Nicolas Pallet, Marie Anne Loriot
nicolas.pallet@aphp.fr

Service de Biochimie, Assistance Publique Hôpitaux de Paris, Hôpital Européen Georges Pompidou, F-75015 Paris, France

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Authors' reply

Nicolas Pallet and Marie Anne Loriot postulate that the CYP2C19 metaboliser phenotype might contribute to lower therapeutic response, or to more treatment-related adverse events, or both, with posaconazole than with voriconazole.[1]

Here we summarise the exploratory pharmacogenetic testing, as described in the Article.[1] Germline DNA was obtained from consented participants genotyped for *CYP2C19* alleles *CYP2C19*2–CYP2C19*8* and *CYP2C19*17*. Participants with a transplant history were excluded because of the potential for a confounding genotype, leaving 149 (52%) of 287 voriconazole participants for analyses. The objectives of the analyses included determining the contribution of CYP2C19 metaboliser phenotype status to variability in the efficacy and safety findings. The primary efficacy measure was day 42 mortality, whereas the safety measure was the rate of treatment-related adverse events. The CYP2C19 phenotypes for posaconazole and voriconazole are listed in the appendix. Among participants in the voriconazole group, only one person was identified as a poor metaboliser. Given the very low number of poor metabolisers, it was unlikely that the reason for the more frequent side-effects seen in this study could be