Position paper

Management of cerebral and splanchnic vein thrombosis associated with thrombocytopenia in subjects previously vaccinated with Vaxzevria (AstraZeneca): a position statement from the Italian Society for the Study of Haemostasis and Thrombosis (SISET)

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ChAdOx1 nCOV-19 (Vaxzevria) is a vaccine against SARS-CoV-2 infection (COVID-19) developed by Oxford University and AstraZeneca that uses a replication-deficient chimpanzee adenoviral vector (ChAdOx1) containing the SARS-CoV-2 structural surface glycoprotein antigen (spike protein; nCoV-19) gene[1].

Over the last few weeks, there have been several reports of thromboembolic events in subjects who had been administered Vaxzevria in the previous weeks. This led several European countries to decide to suspend its administration or, more recently, to limit it to subjects over 60 years of age[2,3].

While the incidence of venous thromboembolism (VTE) at usual sites in vaccinated subjects has not exceeded that in the non-vaccinated population[4,5], a rare and particular type of event has been described following vaccination. This is characterised by cerebral and/or splanchnic vein thrombosis, often associated with multiple thromboses, with thrombocytopenia and bleeding, and sometimes disseminated intravascular coagulation (DIC), occurring in otherwise healthy subjects. This syndrome was mainly observed in females under 55 years of age, and the events occurred between 4 and 16 days after receiving the Vaxzevria vaccine, with a high fatality rate. It is known that it may be extremely difficult to prove that an adverse event following immunisation is actually caused by the vaccine itself when its occurrence is extremely rare[6]. However, the described clinical picture requires attention and it is emerging as a likely, although very rare, complication of vaccination with Vaxzevria[7].

Several scientific societies and experts have concluded for a causative role of Vaxzevria vaccination in these peculiar thrombotic events and two groups of investigators independently described this condition as a prothrombotic disorder resembling heparin-induced thrombocytopenia[8,9] issuing a number of recommendations for its management[10-12]. However, some other cases recently reported were tested for anti PF4/heparin antibodies and found negative (*manuscript in preparation*).

While awaiting a conclusive demonstration of causation and a more complete understanding

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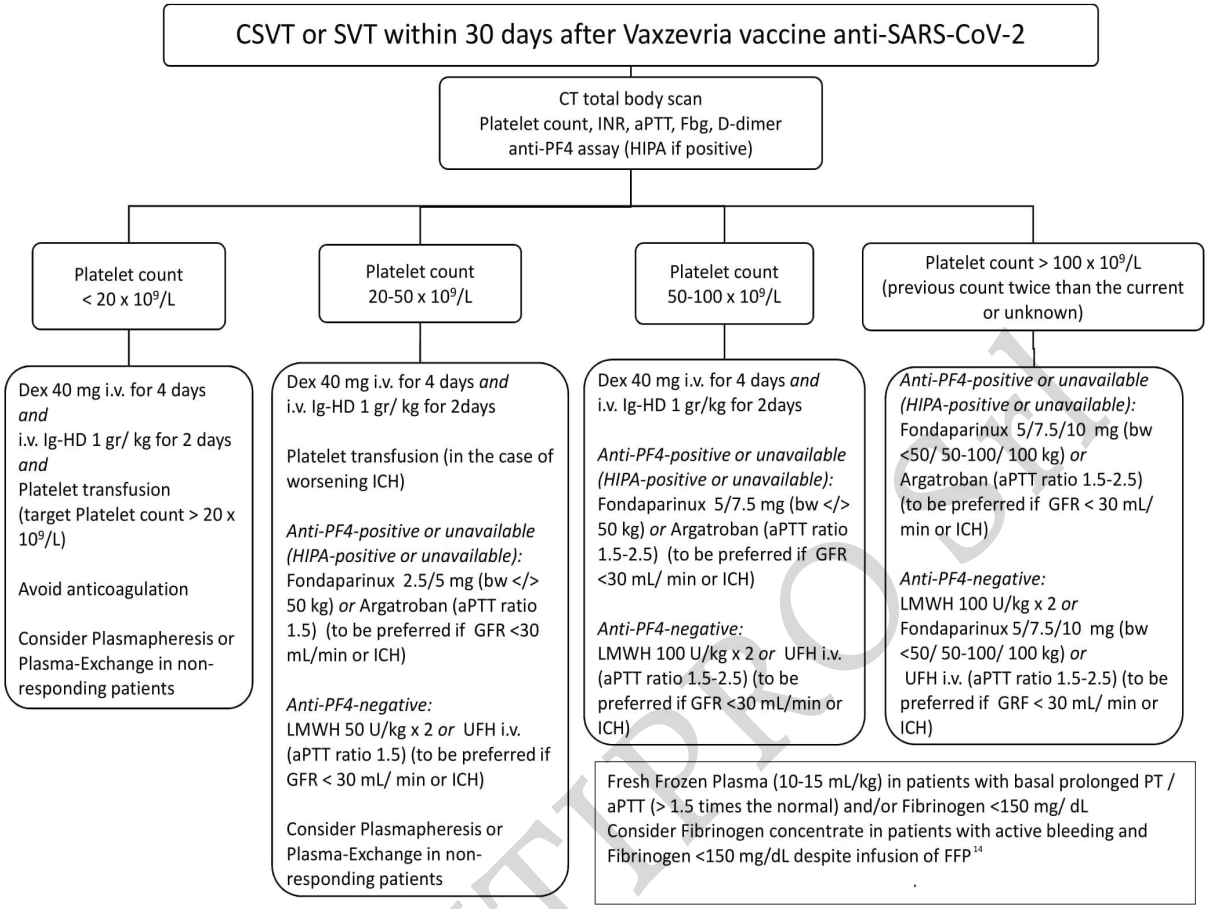

Figure 1 - Proposed flow-chart for the management of cerebral sinus or splanchnic vein thrombosis occurring after Vaxzevria vaccine within a timeframe suggesting a causal relationship
aPTT: activated partial thromboplastin time; CSVT: cerebral sinus venous thrombosis; Dex: dexamethasone; FFP: fresh frozen plasma; GFR: glomerular filtration rate; HIPA: heparin-induced platelet aggregation; ICH: intracranial haemorrhage; Ig-HD: high doses of immunoglobulins; INR: international normalised ratio; i.v.: intravenous; LMWH: low-molecular-weight heparin; SVT: splanchnic vein thrombosis; UFH: unfractionated heparin.

of the pathogenic mechanisms involved, the Italian Society for the Study of Haemostasis and Thrombosis (SISET) aims to provide some recommendations based on expert consensus for the management of cerebral and splanchnic vein thrombotic events associated with thrombocytopenia occurring in subjects vaccinated in the previous 30 days with the Vaxzevria vaccine. The syndrome, here provisionally named Vaxzevria-associated thrombocytopenia thrombotic syndrome (VATTS), calls for the following actions:

- any new event should be immediately reported to the National Pharmacovigilance Authority specifying the exact localisation of the thrombotic event and the degree and temporal evolution of the thrombocytopenia;
- these patients should be hospitalised in high-intensity intensive care units and undergo rapid assessment for the presence of thrombosis at sites other than that leading to hospitalisation (e.g. by total body angio-computed tomography scan);
- haemostatic screening for DIC should be performed immediately along with a complete blood count and monitored thereafter; PF4 antibodies should be assessed. However, consideration must be given to the fact that positivity by standard enzyme immunoassay (EIA) may be unspecific; pathogenicity of antibodies should only be considered when a functional test (HIPA) is positive.

Based on the limited experience so far, the following therapeutic options should be considered (**Figure 1**):

- anticoagulant therapy is generally not advisable in patients with platelets <20×10⁹/L and this should be evaluated on a case by case basis;
- i.v. Ig (1 g/kg/day for 2 days) and dexamethasone (40 mg/day for 4 days) should be started for patients with thrombocytopenia (<50×10⁹/L)[13];
- in the most severe cases (e.g. active intracranial haemorrhage, ICH) platelet transfusions may be considered; similarly, platelet transfusions should be considered in cases in which severe persistent thrombocytopenia prevents anti-thrombotic therapy;
- in severe cases, when thrombocytopenia is resistant to the above measures, plasmapheresis or plasma-exchange may be considered;
- it is advisable to use fresh frozen plasma (10-15 mL/kg/every 12-24 hours) in case of severe consumption coagulopathy, according to the ISTH guidelines[14].

As soon as the platelet count allows (>20×10⁹/L), the following anti-thrombotic options should be considered:

- i.v. unfractionated heparin or s.c. low-molecular weight heparin, whenever positivity for anti-PF4 has been excluded. Dosage should be adjusted according to platelet count and degree of coagulopathy (see **Figure 1**). Full drug dosage can be considered when platelets reach 50×10⁹/L in the absence of active bleeding. If an anti-PF4 assay is not available, heparin should be avoided. Similarly, in the case of anti-PF4 positivity, heparin should be avoided both if HIPA is positive or if HIPA is not available;
- s.c. Fondaparinux, with dosage adjusted as indicated in **Figure 1**;
- i.v. Argatroban, with dosage adjusted as indicated in **Figure 1**;
- direct oral anticoagulants are not advised for limited prescription for this indication in some countries, for difficult dosage management and problems of administration in subjects who are not conscious.

It must be remembered, however, that COVID-19 itself has a strong impact on haemostasis and that a relevant fraction of infected subjects undergo thrombotic complications[15]. Therefore, vaccination of the largest proportion of the population in the shortest possible time, with careful vigilance of side effects, remains an absolute priority.

The Authors declare no conclicts of interest.

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