Argatroban /AZD-1222/fondaparinux-sodium

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Vaccine-induced immune thrombosis with thrombocytopenia and recurrent and fatal intracranial haemorrhage: case report

A 54-year-old man developed vaccine-induced immune thrombosis with thrombocytopenia (VITT) during treatment with AZD-1222 and recurrent and fatal intracranial haemorrhage (ICH) with argatroban, and fondaparinux-sodium as anticoagulation therapy [*not all dosages, routes and durations of treatments to reaction onsets not sated*].

The man presented with new onset of severe headache 12 days after first vaccination with AZD-1222 [ChAdOx1 nCoV-19]. His medical history was unremarkable. On admission, he had thrombocytopenia and signs of disseminated intravascular coagulation. PCR from nasopharyngeal swab ruled out SARS-CoV-2 infection. Serology revealed a normal SARS-CoV-2-spike IgG titer with no signal to nucleocapsid in chemiluminescent immunoassay (CLIA) and immunoblot testing compatible with a vaccine-induced, but not SARS-CoV-2-infection related immunological response (on day 18 after vaccination). Cranial MRI revealed an extensive superior sagittal sinus vein thrombosis with frontal haemorrhagic infarction. Thoracic, abdominal, and pelvic CT showed bilateral adrenal haemorrhages. Follow-up cranial CT showed cerebral sinus and venous thrombosis (CVST) with intracranial haemorrhage (ICH) progression to both frontal lobes, which required hemicraniectomy within 24h after admission.

The man started receiving immune-globulin and anticoagulation therapy with argatroban *[initial dosege not stated*]. His platelet count was increased to 282×10^9/L until day 5. However, three more courses of immune-globulin were needed to resolve recurrent, almost weekly occurring episodes of thrombocytopenia. His anticoagulant therapy was changed from argatroban 2 µg/kg/min to tinzaparine to SC fondaparinux-sodium [fondaparinux] 7.5 mg per day to argatroban, to danaparoid, and finally to fondaparinux-sodium. Anticoagulation therapy was changed four times due to pharmacological considerations (liver toxicity, half-life, possibility of antagonisation) without affecting the platelet count. After ruling out cross-reactivity of VITT antibodies with PF4/heparin complexes, he was initiated on heparin, which was tolerated well. Because of recurrent episodes of thrombocytopenia, prednisolone was initiated. From thereon, platelets remained $>150 \times 10^9$/L, but still reduced from 581 to 182×10^9/L after three months, which could not be explained by changes in medication or other new co-morbidities. During ICU treatment, he suffered recurrent epileptic seizures and pneumonia for which he required unspecified antiepileptic and antibacterial [antibiotic] treatment, respectively. Otherwise, his clinical condition stabilised. Fourty days after admission, he was transferred to a neurological rehabilitation center and he returned to hospital after 6 weeks for therapeutic and diagnostic re-evaluation. Subsequently, he was diagnosed with minor recurrent ICH. At 90 days, he was sent to another rehabilitation center for further neurological rehabilitation. On day 103, he developed new clinical signs for increased intracranial pressure with vomiting, decreased level of consciousness, pupillary abnormalities, and clinical swelling at the site of hemicraniectomy as a sign of herniation. Four months after onset of VITT, he developed a new space-occupying intracerebral haemorrhage as a secondary complication to previous CVST/ICH and anticoagulation therapy. According to his and family's wish, ICU treatment goal was changed to a comfort care approach. Eventually, four days later, he died. On autopsy, a residual thrombus in the left sinus transversus without evidence for other thromboembolic pathology in the brain or other solid organs was found. The brain showed signs of severe oedema. Several hemorrhages were detectable predominantly in the left hemisphere. Microscopy revealed large haeamorrhages, as well as perivascular haemorrhages and extensive neuronal death together with brain oedema. Also, a florid bronchopneumonia and a small liver haemangioma were seen. Autopsy determined an intracerebral haemorrhage as cause of death.

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