Acute immune thrombocytopenic purpura post first dose of COVID-19 vaccination

The rapid pace of COVID-19 vaccine development and the uncertainty of potential adverse effects have led to concerns about safety and some hesitancy in vaccine uptake. In the UK, four COVID-19 vaccines —ChAdOx1-S (Oxford–AstraZeneca, hereafter ChAdOx1), mRNA BNT162b2 (Pfizer–BioNTech), mRNA-1273 (Moderna) and Janssen—have been authorised for use in the national vaccination programme. Reports of extremely rare adverse events of concurrent thrombosis and thrombocytopenia following vaccination with ChAdOx1 have been well documented and have led to several countries suspending or restricting its use.[1] To address ongoing public, professional and regulatory concerns, evidence on the safety of COVID-19 vaccines relating to potential haematological adverse events is required, especially given the relative paucity of population-based data. Here we present two cases of acute immune thrombocytopenia purpura (ITP) following administration of ChAdOx1 treated in our department.

Patient 1 was an 86-year-old man presenting with gingival bleeding, tongue blisters and widespread ecchymoses 2 days after receiving one dose of ChAdOx1. He had no personal or family history of bleeding disorders. Initial blood showed a profound thrombocytopenia with a platelet count of 4×10^9/L. Haemoglobin (Hb) concentration, white cell count (WCC) and coagulation studies were within normal range. Peripheral blood film was normal apart from severe thrombocytopenia. Autoimmune, viral serology and haematinics were unremarkable. He was commenced on treatment for ITP with high-dose dexamethasone 20 mg for 4 days. A CT of the head was requested for new mild confusion. This revealed an 8 mm left parietal haemorrhage, therefore intravenous immunoglobulin (IVIG) 1 g/kg and platelet transfusion support were also initiated. After 3 days, his platelet count was 48×10^9/L. Repeat CT showed stable appearances. Despite a further 10 days of treatment, the platelet count remained low at 42×10^9/L. He was commenced on weekly rituximab infusions at a dose of 375 mg/m^2 due to persistent moderate thrombocytopenia. His inpatient COVID-19 swabs two times per week were negative. He was discharged under close outpatient monitoring and completed his rituximab course. His platelet counts have since normalised.

Patient 2 was a fit 38-year-old woman presenting with widespread petechiae and purpura 10 days following one dose of ChAdOx1. She had no personal or family history of bleeding disorders or autoimmune conditions. Admission bloods showed severe thrombocytopenia (platelet count 3×10^9/L), and normal Hb, WCC and clotting studies. Peripheral blood film was normal, apart from severe thrombocytopenia. Viral, autoimmune screens and haematinics were unremarkable. A clinical diagnosis of ITP was made, and she was commenced on prednisolone 1 mg/kg. On the following day, she exhibited buccal bleeding and her platelet count was 2×10^9/L. She was commenced on IVIG at 1 g/kg for 2 days with close outpatient monitoring. At day 4 of treatment, the platelet count was 44×10^9/L; this steadily improved to 430×10^9/L at day 8. She had a weaning course of prednisolone with regular teleclinic appointments and blood counts. Her purpura resolved, and her platelet count remained stable.

Both patients presented with profound thrombocytopenia with no other apparent cause for a low platelet count. Previous studies have demonstrated a causal association between vaccinations and ITP, thought to be most likely due to virally induced molecular mimicry: the binding of pathogenic antibodies to platelet and megakaryocytes can cause thrombocytopenia by various methods, including opsonisation, direct activation of complement and apoptotic pathways.[2] A case of ITP following a dose of BNT162b2 mRNA in the USA was published.[3] The *New York Times* recounted 36 reports of ITP following doses of BNT162b2 mRNA and ChAdOx1, which were submitted to the US government's Vaccine Adverse Event Reporting System.[4] More recently, a Scottish prospective cohort study found an association between ChAdOx1 and ITP, but not with BNT162b2 mRNA.[5] Simpson *et al* estimated an incidence of 1.13 ITP cases per 100 000 doses. Of note, there were no reported cases of ITP in the 11 636 participants analysed in the earlier AstraZeneca trial.[6] Viral infections, including COVID-19 infection, can also cause acute ITP or worsen stable chronic ITP.[7] Thus, it is essential to rule out COVID-19 infection as a trigger even in those who are asymptomatic.

ITP is an immune-mediated condition in which antibody-coated or immune complex-coated platelets are destroyed prematurely by the reticuloendothelial system, leading to peripheral thrombocytopenia. Diagnosing ITP can be challenging, with no single 'gold standard' test to reliably prove the diagnosis and an extensive list of differential diagnoses. The presumptive diagnosis can be made when other causes of thrombocytopenia have been excluded. Serial platelet monitoring after commencing therapy serves dual purposes of assessing response to treatment and providing additional evidence to support the diagnosis. Most cases are mild to severe but are highly responsive to IVIG.

Treatment recommendations have also changed in the setting of the COVID-19 pandemic. Previously, first-line treatment was with steroids and IVIG.[8] The current guidelines from NHS England promote the use of thrombopoietin receptor agonists (TPO-RAs) as first-line therapy for new or relapsed acute ITP in adults and children aged over 1 year.[9] These should be commenced under the guidance of haematologists. However, patients hospitalised with COVID-19 infection requiring steroids for immunosuppression may not be suitable candidates for TPO-RAs. Another therapeutic agent is rituximab, an anti-CD20 monoclonal antibody that binds to the CD20 antigen on the B-cell surface, activating complement-dependent B-cell cytotoxicity. The B-cell depleting effect of rituximab results in a diminished humoral immune response to vaccinations.[10] Thus, rituximab should be avoided or delayed for those patients who have not yet been vaccinated. This is a challenge for those patients already on rituximab immunosuppression for treatment of rheumatic disease, non-Hodgkin's lymphoma, chronic lymphocytic leukaemia and vasculitis.

Although existing COVID-19 vaccines are associated with a small risk of developing ITP, recent evidence suggest that the overall benefits of vaccination greatly outweigh ITP-associated risks.[5] We suggest that patients with pre-existing ITP have a baseline platelet count recorded prior to vaccination and successive counts depending on their clinical history. It is important that clinicians are made aware of the potential to develop ITP secondary to the COVID-19 vaccines and to seek early input from clinical haematologists if patients become thrombocytopenic or exhibit clinical features suggestive of this.

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