Immune thrombocytopenia following vaccination during the COVID-19 pandemic

To date, there have been over 3.2 million doses of ChAdOx1 nCoV-19 (ChAd) COVID-19 vaccine (AstraZeneca) and 1 million doses of BNT162b2 (BNT) COVID-19 vaccine (Pfizer-BioNTech) administered in Australia. Among the numerous safety signals that have been raised, we present our case series of immune thrombocytopenia (ITP) after COVID-19 vaccination.[1-4] ITP following vaccination has been previously described in other settings and after mRNA-based COVID-19 vaccines.[5-8] A Scottish National Registry study examined general practice data and identified a small increased incidence of ITP diagnoses between days 0-27 after vaccination with ChAD.[9] We present the clinical characteristics and treatment outcomes of patients diagnosed with ITP following COVID vaccinations (ChAd or BNT) in Australia.

After obtaining independent ethics committee approval, we contacted hemostasis hematologists across Australia to participate in our comprehensive survey of clinical presentations of vaccine-associated ITP as defined by the temporal relationship of ITP within 42 days following COVID-19 vaccination, without an otherwise apparent alternative cause or thrombosis. Patients with thrombosis or elevated D-dimer levels were investigated and excluded for vaccine-induced immune-mediated thrombotic thrombocytopenia according to international guidelines.[10] Response was defined as per international consensus guidelines as a platelet count ≥30x10^9/L, 2-fold increase over baseline and absence of bleeding. A complete response was defined as a platelet count ≥100x10^9/L and absence of bleeding.[11]

A total of 14 patients were diagnosed with ITP following vaccination. Twelve of these cases followed administration of the ChAd vaccine. Ten cases were *de novo* ITP, presented in Table 1. Four cases were relapses in patients with previously stable chronic ITP, presented in Table 2. None of the 14 patients had concurrent thrombosis. Among the 12 cases of ITP following administration of the ChAd vaccine, an enzyme-linked immunosorbent

Table 1. Demographics and clinical features of patients with newly diagnosed immune thrombocytopenia after COVID-19 vaccination.

Age and gender	Days after vaccination	COVID-19 vaccine	Other antecedent vaccinations (30 days)	Platelets at presentation (and nadir if later) (x10^9/L)	WHO bleeding score	Bleeding	First-line treatment	Second-line treatment	TTR	TTCR	Platelets at day 30 (x10^9/L)	Treatments at day 30	Other relevant history
52M	27	1st ChAd	None	8	1	Petechiae	Pred/IVIg	None	3	4	176	Pred 5 mg daily	None
80F	21	1st ChAd	Influenza	0	4	Life - threatening bleeding	Pred/IVIg	Eltrombopag	18	23	157	Pred 75 mg daily	None
82M	3	1st ChAd	None	22 (1)	1	Petechiae	Pred/IVIg	Eltrombopag	10	37	197	Pred 12.5 mg daily Eltrombopag 50 mg daily	AML in remission (not on chemo)
60F	3	1st ChAd	None	3	1	Petechiae	Dex/IVIg	Pred	2	3	25	None	None
83F	23	1st ChAd	None	10	1	Petechiae, ecchymoses	Dex/IVIg	None	1	3	40	None (Pulse Dex/IVIg repeated day 21)	None
61M	22	1st ChAd	None	17	0	None	Pred/MMF	None	2	10	104	Pred 20 mg daily MMF 500 mg BD	None
82M	9	1st ChAd	None	3	1	Purpura	Dex	Pred	4	47	8	Dex pulse repeated	Influenza vaccination day 17 after presenting with ITP
86M	10	1st ChAd	None	5 (3)	3	Major bleeding requiring hospitalization	Pred/IVIg	None	6	11	259	Pred 25 mg daily	None
46M	2	1st BNT	None	5 (0)	2	Mild blood loss	Pred/IVIg	None	4	7	151	Pred 35 mg daily	None
22M	6	2nd ChAd	1st ChAd given 4 weeks prior	8	1	Petechiae	Pred/IVIg	N/A	2	7	N/A	N/A	AIHA

AIHA: autoimmune hemolytic anemia; AML: acute myeloid leukemia; BD: twice daily; BNT: BNT162b2 (Pfizer); ChAd: ChAdOx1 nCoV-19 (AstraZeneca); COVID-19: coronavirus disease 2019; Dex: dexamethasone; F: female; IVIg: intravenous immunoglobulin; ITP: immune thrombocytopenia; M: male; MMF: mycophenolate mofetil; Pred: prednisone; TTCR: time to complete response; TTR: time to response; WHO: World Health Organization.

Table 2. Demographics and clinical features of patients with relapsed chronic immune thrombocytopenia after COVID-19 vaccination.

Age and gender	Days after vaccination	COVID-19 vaccine	Other antecedent vaccinations	Chronic ITP treatments	Most recent platelets prior to vaccination ($x10^9$/L)	Platelets at presentation ($x10^9$/L)	WHO bleeding score	Bleeding	First-line treatment	Second-line treatment	TTR	TTCR	Platelets at day 30 ($x10^9$/L)	Treatments at day 30	Other relevant history
94F	9	1st BNT	None	Stable on romiplostim	86	12	0	None	No change to ongoing romiplostim	None	5	-	73	None	None
77M	2	1st ChAd	Influenza	Stable off treatment	188	6	1	Petechiae	Pred/IVIg	None	3	8	144	Pred 15 mg daily	None
73F	30	1st ChAd	None	Stable off treatment	255	11	2	Mild blood loss	IVIg	None	3	5	215	None	None
73M	31	1st ChAd	None	Stable off treatment	120	5	1	Petechiae	Pred	None	2	4	234	Pred 10 mg	Positive DAT and ANA

ANA: antinuclear antibodies; BNT: BNT162b2 (Pfizer); ChAd: ChAdOx1 nCoV-19 (AstraZeneca); COVID-19: coronavirus disease 2019; DAT: direct antiglobulin test; Dex: dexamethasone; F: female; IVIg: intravenous immunoglobulin; M: male; Pred: prednisone; TTCR: time to complete response; TTR: time to response; WHO: World Health Organization.

assay for platelet factor 4 (PF4) was performed in six and all of these tested negative.

The median age of the patients was 75 years (range, 22-94), the median time to presentation after vaccination was 10 days (range, 2-31), and the platelet count at presentation was $7x10^9$/L (range, 0-$22x10^9$/L). World Health Organization bleeding scores were mild: ten patients had grade 0 or 1, two patients had grade 2, and one patient each had grades 3 and 4.[12]

Ten cases had no prior history of ITP and all received treatment upfront: seven received prednisone, and three high-dose dexamethasone pulses. Eight patients also received between 1-2 g/kg intravenous immunoglobulins (IVIg) as part of first-line therapy. The median time to response was 3.5 days (range, 1-18). Ten evaluable patients achieved a complete response by a median of 9 days (range, 3-47). Day 30 data were available for nine of these ten patients without a prior history of ITP, as one left Australia: the median platelet count was $151x10^9$/L (range, 8-$259x10^9$/L); eight were still on corticosteroids (median prednisone equivalent 20 mg daily), one was on eltrombopag (commenced as second-line treatment) and another was receiving mycophenolate mofetil that had been commenced in first-line treatment in combination with prednisone.

One 80-year-old female presented with life-threatening bleeding (influenza vaccination 1 day prior and ChAd 21 days prior to presentation) and after no initial response to escalating prednisone doses and IVIg, eltrombopag was commenced on day 15. Platelets began to respond by day 18, and the platelet count rose to $157x10^9$/L by day 30 after presentation while only on prednisone.

One 82-year-old male presented with a platelet count of $3x10^9$/L, and widespread bruising 9 days after his first ChAd vaccination. He was treated with high-dose dexamethasone and platelets responded, reaching $97x10^9$/L by day 16 (Figure 1A). He received influenza vaccination the following day, but his ITP relapsed by day 32. He responded promptly to a second pulse of high-dose dexamethasone with a platelet ount of $65x10^9$/L by day 36. He had never previously developed ITP despite numerous influenza vaccinations in the past.

One 83-year-old female presented with a platelet count of $10x10^9$/L, facial petechiae, and upper chest ecchymoses 23 days after her first ChAd vaccination (Figure 1B). She responded promptly to a dexamethasone pulse 20 mg daily for 4 days and IVIg infusion 0.4 g/kg for 3 days. She relapsed on day 19 with platelets $23x10^9$/L and new lower limb bruising, and was treated with another pulse of dexamethasone and IVIg 0.4 g/kg for 2 days.

In total, there were four patients with chronic ITP who relapsed following COVID-19 vaccination. Three patients receiving ChAd had stable chronic ITP, and were off ITP-directed therapies at the time of COVID-19 vaccination. They were treated with standard first-line therapies and all responded within 3 days.

IVIg monotherapy alone was successful in one 72-year-old female with chronic ITP who presented with a platelet count of $11x10^9$/L but responded by day 3, achieving a complete response on day 5; her day 30 platelet count was $215x10^9$/L (Figure 1C), and she had no need for steroids at any time despite having had refractory ITP requiring splenectomy in 1994. Her most recent prior platelet count was $255x10^9$/L less than 3 weeks before vaccination. Her most recent prior ITP treatment had been rituximab monotherapy in 2011.

A second chronic ITP patient, a 77-year-old male who received influenza vaccination prior to ChAd vaccination, presented with a platelet count of $2x10^9$/L, achieved a response and complete response by days 3 and 8 respectively, had a day 30 platelet count of $144x10^9$/L, and was on a weaning schedule of prednisone at day 30 after initially being treated with prednisone/IVIg upfront.

The third patient with chronic ITP, a 73-year-old male with a pre-vaccination platelet count of $120x10^9$/L, was thrombocytopenic (platelet count, $5x10^9$/L) 31 days after ChAd vaccination. He was started on prednisone monotherapy and achieved a response within 2 days, a complete response by day 4, and a platelet count of $234x10^9$/L by day 30 while on prednisone 10 mg daily.

The fourth chronic ITP patient in this analysis was a 94-year-old female who received her first dose of BNT 9 days prior to presentation. She had previously enjoyed a stable platelet response on romiplostim for her chronic ITP with a recent platelet count of $86x10^9$/L, falling to $12x10^9$/L without any bleeding; her platelet count returned to baseline within 5 days of presentation. She proceeded to receive her second dose of BNT 21 days

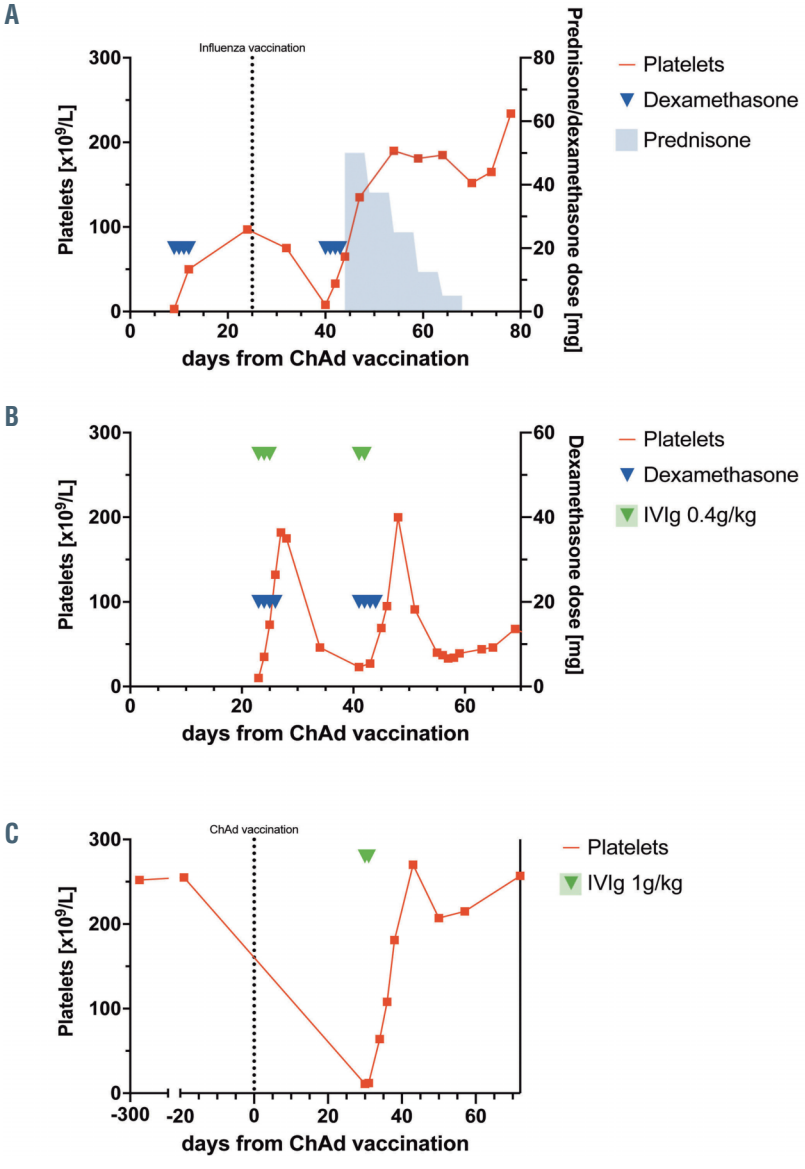

Figure 1. Clinical course of three separate cases of immune thrombocytopenia following COVID-19 vaccination. (A) An 82-year-old male with newly diagnosed immune thomrbocytopenia (ITP) was treated with dexamethasone an initially responded, received influenza vaccination, relapsed, and responded again to another pulse of dexamethasone and weaning prednisone taper. (B) An 83-year-old female with newly diagnosed ITP was treated with two pulses of dexamethasone/IVIg. (C) A 73-year-old female had a relapse of chronic ITP after receiving ChAd vaccination, received IVIg 2 g/kg over 2 days as monotherapy. ChAd: ChAdOx1 nCoV-19 (AstraZeneca); IVIg: intravenous immunoglobulin.

after the first, relapsing again on day 15 with a platelet count of 14x10^9/L before returning to her stable baseline within a further 7 days.

Our case series of vaccine-associated ITP comprises more cases of ITP following administration of the ChAd vaccine than after the BNT vaccine (12 from 3.2 million ChAd vaccinations *vs.* 2 from 1 million BNT), although there may be an ascertainment bias due to greater scrutiny of patients following ChAd vaccination, as suggested in a recent Scottish study even though this paper also concluded that there was an increased rate of ITP diagnoses of 1.13 per 100,000 doses.[9] In contrast, a Scandinavian epidemiological study was unable to identify an increased rate of ITP diagnoses although rates of "unspecified thrombocytopenia" and bleeding events were increased significantly.[13] Our study was not designed to address the questions of frequency or causality. Our designation of these cases as "vaccine-associated" ITP as opposed to co-incident ITP is based on the clinical diagnosis of ITP as one of exclusion. As vaccine association cannot be excluded, we cannot conclude that these patients have primary ITP, conceding that future outcomes may eventually justify revision of our diagnosis, which is common in ITP.[14]

Two of 14 cases are confounded at presentation by the recent administration of influenza vaccination, and another patient received influenza vaccination shortly after initial recovery from ITP before relapsing. However, these limitations reflect an unavoidable real-world dilemma as public health imperatives to protect populations at risk during a pandemic will likely outweigh the considerably smaller numerical risk of uncertain outcomes and vaccination side effects when immunization programs overlap.

Most cases responded rapidly to first-line therapy although the majority remained on corticosteroids for at least 30 days (median prednisone equivalent dose 13.75 mg daily for all cases, 20 mg daily for those with newly diagnosed ITP). Patients whose chronic ITP relapsed after vaccination responded rapidly to first-line therapies, consistent with other observations,[8] and reassuringly for those with underlying ITP who are at present hesitant to receive COVID-19 vaccination. So far, in three patients, a single pulse of high-dose dexamethasone was insufficient to maintain remission in this cohort, but repeat courses have been successful and well tolerated. Additional

strategies used successfully include eltrombopag and mycophenolate mofetil. Further data will be needed to understand the durability of these responses.

We anticipate that there may be cases along a spectrum of clinical presentations between vaccine-induced immune-mediated thrombotic thrombocytopenia and vaccine-associated ITP, as have already been noted elsewhere.[15] In our cohort, overlapping characteristics have not yet been identified, and all six patients with samples tested were negative for anti-PF4 antibodies.

Both local and international registries are currently collecting data that will be useful for investigating treatment strategies and clinical outcomes for patients developing ITP following COVID-19 vaccination.

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