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Immune thrombocytopenia following immunisation with Vaxzevria ChadOx1-S (AstraZeneca) vaccine, Victoria, Australia

Sally F. Gordon a, c, Hazel J. Clothier a, c, Hannah Morgan a, Jim P. Buttery a, b, Linny K. Phuong a, Paul Monagle h, i, Sanjeev Chunilalg, Erica M. Wood f, g, Huyen Tran f, g, 1, Jeff Szer d, e, i, 1, Nigel W. Crawford a, c, 1, on behalf of the SAEFVIC and VicSIS investigators j, 2

a Surveillance of Adverse Events Following Vaccination In the Community (SAEFVIC), Murdoch Children’s Research Institute, 50 Flemington Rd, Parkville, Vic 3052, Australia
b Centre for Health Analytics, Melbourne Children’s Campus, 50 Flemington Rd, Parkville, Vic 3052, Australia
c Victorian Department of Health, 50 Lonsdale St, Melbourne, Vic 3000, Australia
d Peter MacCallum Cancer Centre, 305 Grattan St, Melbourne, Vic 3000, Australia
e The Royal Melbourne Hospital, 300 Grattan St, Parkville, Vic 3050, Australia
f Alfred Health, 55 Commercial Rd, Melbourne, Vic 3004, Australia
g Monash Health, 246 Clayton Rd, Clayton, Vic 3168, Australia
h Sydney Children’s Hospital, High St, Randwick, NSW 2031, Australia
i The University of Melbourne, Parkville, Vic 3010, Australia
j Monash University, Wellington Rd, Clayton, Vic 3800, Australia
k Monash University is School of Public Health and Preventive Medicine, Monash University, 553 St Kilda Road, Melbourne 3004, Australia

A R T I C L E   I N F O

Article history:
Received 26 September 2021
Received in revised form 13 October 2021
Accepted 14 October 2021
Available online 30 October 2021

Keywords:
Immune thrombocytopenia
Vaccination
Vaccine
COVID-19

A B S T R A C T

Emerging evidence suggest a possible association between immune thrombocytopenia (ITP) and some formulations of COVID-19 vaccine. We conducted a retrospective case series of ITP following vaccination with Vaxzevria ChadOx1-S (AstraZeneca) and mRNA Comirnaty BNT162b2 COVID-19 (Pfizer-BioNTech) vaccines and compare the incidence to expected background rates for Victoria during the first six months of the Australian COVID-19 vaccination roll-out in 2021. Cases were identified by reports to the Victorian state vaccine safety service, SAEFVIC, of individuals aged 18 years or older presenting with thrombocytopenia following COVID-19 vaccination without evidence of thrombosis. Twenty-one confirmed or probable cases of ITP were identified following receipt of AstraZeneca (n = 17) or Pfizer-BioNTech (n = 4) vaccines. This translates to an observed incidence of 8 per million doses for AstraZeneca vaccine, twice the expected background rate of 4.1 per million. The observed rate for Pfizer-BioNTech was consistent with the expected background rate. The median time to onset for the cases post AstraZeneca vaccination was 10 days (range 1–78) and median platelet nadir 5 × 10^9/L (range 0–67 × 10^9/L). Hospital presentations or admissions for management of symptoms such as bleeding occurred in 18 (86%) of the cases. The majority of cases (n = 11) required intervention with at least 2 therapy modalities. In conclusion, we observed a substantially higher than expected rate of ITP following AstraZeneca vaccination. ITP is the second haematological adverse event, distinct from that of thrombosis with thrombocytopenia syndrome (TTS), observed following AstraZeneca vaccination.

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1. Introduction

With the emergence of SARS-CoV-2 variants, such as the B.1.617.2 Delta variant, high vaccine uptake is an even more crucial component of the global pathway out of the Coronavirus disease (COVID-19) pandemic, including in Australia. The Vaxzevria ChadOx1-S (AstraZeneca) and mRNA Comirnaty BNT162b2 (Pfizer-BioNTech) COVID-19 vaccines are both integral parts of the current Australian vaccine strategy [1], and are generally well tolerated with mild, common, and expected adverse effects such as fever, fatigue, headache and myalgia [2]. However, recent studies identified Thrombosis with Thrombocytopenia Syndrome (TTS) as a rare but serious condition associated with AstraZeneca vaccine [3,4]. Early research suggests that TTS is likely an auto-immune phenomenon.

https://doi.org/10.1016/j.vaccine.2021.10.030
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and may have similar pathophysiology to heparin-induced thrombocytopenia (HIT) [3].

While TTS is a new idiosyncratic adverse event of special interest (AESI), with low platelets and associated thrombosis, another haematological condition, immune thrombocytopenia (ITP) has been closely monitored as an AESI [5], given its similar autoimmune basis, and known occurrence following the Measles-Mumps-rubella (MMR) vaccine [6,7]. This is considered biologically plausible because ITP has also been associated with SARS-CoV-2 infection [8]. Emerging evidence suggests a causal link between ITP and COVID-19 vaccines, particularly AstraZeneca vaccine [9,10]. Other studies have investigated ITP following mRNA vaccines and to date found no association [11–13]. In our analysis, we examine a series of reported cases of ITP following vaccination with AstraZeneca and Pfizer-BioNTech vaccines and compare these to expected background rates in Victoria, Australia.

2. Methods

In the Australian jurisdiction of Victoria [population ~ 6.6 million] [14], adverse events following immunisation (AEFI) are spontaneously reported by patients or health-care providers to SAEFVIC, the state-wide vaccine safety service [15]. SAEFVIC comprises a central reporting enhanced passive and active surveillance system integrated with clinical services. Vaccine providers and recipients are encouraged to report AEFI following COVID-19 vaccination, regardless of vaccine brand. SAEFVIC is responsible for the follow-up of AEFI, including referral to the Victorian Specialist Immunisation Services (VicSIS), a network of COVID-19 specialist immunisation clinics, for further management as required [16]. All AEFI are also forwarded to the national regulator, the Therapeutic Goods Administration (TGA), which is responsible for pharmacovigilance and national collation of spontaneous (passive) adverse event reports [17,18].

Identified reports of thrombocytopenia submitted to SAEFVIC within the first six months of the Australian COVID-19 vaccination roll-out, between 22 February and 20 August 2021, were assessed. Of the forty-seven cases of thrombocytopenia identified, 6 were excluded due to evidence suggestive of TTS and a further 15 because they either had pseudo-thrombocytopenia (defined as platelet < 150 × 10⁹/L with clumping on specimen) or had a clear alternate diagnosis (e.g. sepsis, malignancy). Patient demographics were described by vaccine brand and dose, with clinical review undertaken of platelet nadir, time to onset, existing history of ITP and possible alternate causes, associated symptoms/signs, severity, and response to treatment for the 26 remaining cases (Fig. 1). Additional information was collated from treating clinicians and hospital sites.

Thrombocytopenia was defined as platelets < 150 × 10⁹/L and Brighton Collaboration criteria utilised to allocate level of diagnostic certainty [19]. Platelet nadir was based on the lowest platelet count documented as serial full blood counts were not performed on all cases. The remaining 26 cases were classified as possible, probable or confirmed ITP by at least one independent haematologist, after considering clinical history, comorbidities, investigations, and response to treatment. The World Health Organization (WHO) bleeding score was used to grade severity [20]. Similarly, for comparison, cases of TTS were identified by reports submitted to SAEFVIC, as well as direct reports from VicSIS clinicians and haematology colleagues. TTS cases were classified locally by at least one independent haematologist as either likely, unlikely or

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**Fig. 1.** Consort diagram.
Table 1

| AstraZeneca | Pfizer-BioNTech | Total |
|-------------|-----------------|-------|
| **Cases and rates** | **Cases and rates** | **Cases and rates** |
| **Observed Total** | **Dose 1** | **Dose 2** |
| 17 | 16 | 1 | 4 | 21 |
| | 2 | 1 | 1 | 4 |
| | 1 | 1 | 1 | 3 |
| | 1 | 1 | 1 | 3 |
| | 1 | 1 | 1 | 3 |
| **Doses** | **Dose 1** | **Dose 2** |
| 2,009,966 | 2,101,880 | 2,131,946 |
| 1,433,925 | 1,315,009 | 1,748,934 |
| 639,041 | 476,938 | 1,115,979 |
| 2,009,966 | 1,433,925 | 639,041 |
| **Rate per 100,000** | **Rate per 100,000** | **Rate per 100,000** |
| 0.8 (0.54–1.27) | 0.2 (0.04–0.64) | 0.6 (0.39–0.84) |
| 1.0 (0.64–1.61) | 0.3 (0.06–1.00) | 0.7 (0.45–1.06) |
| 0.3 (0.06–1.1) | 0.3 (0.06–1.00) | 0.3 (0.11–0.76) |
| 0.87 (5) | 0.26 (1) | 0.18 (1) |

Demographics

| Age range | Median | male | female |
|-----------|--------|------|--------|
| 50–97 (72) | 85 | 8 | 77 |
| 20–49 (47) | 1,476 | 14 | 1,462 |
| 20–97 (68) | 14 | 3 | 11 |

Clinical results

| Days to plt nadir (median) | Brightons Collaboration level |
|---------------------------|-----------------------------|
| 1–78 (10) | 1 |
| 2–21 (9) | 2 |
| 1–24 (10) | 1 |

3. Results

A total of 21 patients were classified as confirmed (15 cases) or probable (6 cases) ITP (Table 1). Seventeen of these were following AstraZeneca vaccine (15 following dose 1 and 2 following dose 2). There were also 5 possible cases of ITP in which other concurrent medical issues may have also contributed to thrombocytopenia and so these were excluded from the analysis.

The observed rate of confirmed or probable ITP following Pfizer-BioNTech was 2 per million, similar to the expected background rate of 1.9 per million (20–49 years of age) within 28 days of vaccination. The observed rate following AstraZeneca was 8 per million, and as high as 10 per million following dose 1, which is more than twice the expected background rate of 4.1 per million among persons aged ≥ 50 years of age within 28 days of vaccination.

Of the seventeen cases following AstraZeneca vaccination, following expert haematology review, sixteen were de novo ITP, while one is thought to have chronic ITP. Two had some bruising noted prior to vaccination. Eleven of the cases (65%) had bleeding, with a WHO bleeding score of 2 or 3. As expected, the most common signs reported were mucocutaneous bleeding (53%). One case had ocular bleeding and subdural haematoma, and there was one fatality in, secondary to myocardial infarction 7 weeks after the vaccine and was deemed as unrelated to the diagnosis of ITP.

Cases reported following AstraZeneca (n = 17) had onset within 28 days of vaccination, except for one case that presented late on day 78. Platelet nadir was extremely low in these confirmed and probable cases, with a median nadir of 5 × 10^9/L (range 0–67) (Table 1). The median platelet nadir for ITP cases was markedly lower when compared to the median platelet nadir of 80 × 10^9/L for 36 confirmed and probable cases of TTS reported to date in Victoria (Fig. 2).
Sixteen (94%) received treatment with corticosteroids. Eight patients also received between 1 and 2 g/kg intravenous immunoglobulin (IVIG) as part of first-line therapy. Three patients were significantly refractory to treatment requiring the addition of a thrombopoietin receptor agonist. Four cases (24%) recovered (defined as platelets > 100 × 10^9/L) without ongoing anti-platelet treatment (e.g. corticosteroids and/or IVIG), and 5 (29%) had platelet recovery with ongoing treatment with corticosteroids and/or thrombopoietin receptor agonists. Seven (41%) remained thrombocytopenic (platelets < 100 × 10^9/L) at the time of the review, four of which were despite ongoing anti-platelet treatment, one which was mild and never received treatment. The final case was the fatality in our series, and the individual remained thrombocytopenic at time of death (platelets 76 × 10^9/L).

Of the four cases following Pfizer-BioNTech vaccine, two were de novo ITP, while 2 are thought to have chronic ITP. Of the de novo cases, both presented with only skin petechiae and/or bruising. Of the 2 cases of exacerbation of chronic ITP, one presented with severe menorrhagia and the second with haematuria (although investigations as to the cause of the haematuria are ongoing). Two cases required no treatment and two required treatment with corticosteroids, one of whom was also treated with IVIG as part of first-line therapy. None of the Pfizer-BioNTech cases were refractory to treatment.

4. Discussion

We describe twenty-one cases of ITP following vaccination with either AstraZeneca or Pfizer-BioNTech vaccines, with the majority (n = 17) associated with AstraZeneca vaccine. For Pfizer-BioNTech vaccine, based on the number of vaccines administered in the study period we would have expected 3 cases, comparable with the 4 cases observed, indicating the robustness of case ascertainment in this series.

The observed rate of ITP following the adenoviral vector vaccine AstraZeneca was 8 per million and as high as 10 per million following dose 1, which was substantially higher than the expected rate of 4.1 per million. This finding is important, because the Therapeutic Goods Administration (TGA) convened an external Vaccine Safety Investigation Group (VSIG) of clinical experts which concluded that a fatal case ITP case in a 61 year old woman from Western Australia was likely linked to the AstraZeneca vaccine[18]. A formal signal investigation into ITP as an AESI in Australia is ongoing.

Our analysis is in keeping with a nested incident-matched case control study in Scotland, which found an association between AstraZeneca vaccine and ITP, with an estimated incidence of 1.13 cases per 100,000 doses [9]. In this study, increased risk was first found at 7–13 days after vaccination. The finding of increased risk of ITP following AstraZeneca vaccine and the window of increased risk was supported by a case control study in the United Kingdom (UK)[10]. The Scottish and UK self-controlled case series both used an adjusted risk ratio to demonstrate increased risk of ITP first occurring within 7–13 and 8–14 days, respectively. Although the methodology within these case series is different, the adjusted risk ratios are consistent with the median time to onset seen in our series [9,10]. Only two of our confirmed or probable ITP cases underwent testing with Human PF-4 solid-phase sandwich ELISA (enzyme-linked immunosorbent assay) to investigate TTS, both of which were negative, and suggesting that presentation of these cases is different to TTS. These two cases also underwent independent haematology review for other factors, including
Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

Department of Health - Emma Roney, Anita Ona, Anna Power, Thiruverni Ananthanathan, Ngaree Blow, Elise Virah Sawmy, Eleanor Duckworth, Michelle Wolthusien, Naveen Tennyti.

VicsIC clinic sites.

Michelle Giles (Alfred Health), Sarah Bullen (Alfred Health), Danielle Kennedy (Alfred Health), Kayleigh Malone (Alfred Health), Ciara Burke (Alfred Health), Brian Price (Alfred Health), Joseph de Luca (Austin Health), Jason Trubiano (Austin Health), Kerryn McInnes (Austin Health), Jamie Rotin (Austin Health), Callum Maggs (Barwon Health), Elyse Stevens (Barwon Health), Julie Carlisle (Barwon Health), Loretta Mitchen (Barwon Health), Katrina Bellamy (Barwon Health), Caroline Poynder (Barwon Health), Susan Cirillo (Barwon Health), Katherine Gibney (Melbourne Health), Charlotte Slade (Melbourne Health), Elise Wang (Melbourne Health), Tony Korman (Monash Health), Sara Barnes (Monash Health), Karen Bellamy (Monash Health), Jo Hickman (Monash Health), Elizabeth Leahy (Monash Health), Sara Pitts (Monash Health), Craig Abolitins (Northern Health), Jenna Paterson (Northern Health), Hayley Gray (Northern Health), Jade Mertens (Northern Health), Lunnise Gashi (Northern Health), Ben The (Peter MacCallum Cancer Centre), Cindy Yuen (Peter MacCallum Cancer Centre), Marion Kainer (Western Health), Katherine Langan (Western Health), Claire Sanguinetti (Western Health), Kayleen Kral (Western Health).

All other medical, nursing and administrative staff that support the VicsIC clinics.

SAEFVIC.

Josh O'Connell, Daryl Cheng, Priya Shenton, Mel Addison, Louise Dempsey, Adele Harris, Georgie Lewis, Bianca Penak, Laura Voss, Jaimee Craft, Victoria Scott, Lois Tham.

All other hospital sites and clinicians involved in providing information on cases.

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In conclusion, we identified an increased rate of ITP following receipt of AstraZeneca vaccine. This is a second haematological AESI identified following the AstraZeneca vaccine in Australia and is distinct from TTS. This case series highlights the benefit of all cases of thrombocytopenia temporally associated with vaccination being further evaluated by a haematologist. Future studies are required to confirm causality. Further evaluate the possible immuno-pathogenic mechanisms, as well as document the outcomes with subsequent COVID19 vaccine doses to provide important information in support of the COVID-19 vaccine programs both in Australia and globally.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.
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