Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Thrombosis Update 5 (2021) 100086

Contents lists available at ScienceDirect

Thrombosis Update

journal homepage: www.sciencedirect.com/journal/thrombosis-update

Vaccine-induced thrombosis and thrombocytopenia (VITT) in Ireland: A review of cases and current practices

D. Swan [a,*], H. Enright [b], R. Desmond [b], G. Le [b], E. El Hassadi [c], B. Hennessy [c], F. Lynott [c], D. O'Keeffe [d], M. Crowley [e], L. Smyth [f], K. Perera [g], C. Jennings [g], F. Ni Ainle [h], J. Coll [h], K. Ryan [a], J. O'Donnell [a], M. Lavin [a], N. O'Connell [a]

[a] National Coagulation Centre, St James' Hospital, Dublin, Ireland
[b] Tallaght University Hospital, Dublin, Ireland
[c] Waterford University Hospital, Waterford, Ireland
[d] University Hospital Limerick, Limerick, Ireland
[e] Cork University Hospital, Cork, Ireland
[f] St Vincent's University Hospital, Dublin, Ireland
[g] Midland Regional Hospital Tullamore, Tullamore, Ireland
[h] Mater Misericordiae University Hospital, Dublin, Ireland

ARTICLE INFO

Keywords:
Thrombosis
Thrombocytopenia
VITT
COVID-19

ABSTRACT

Since the beginning of the Severe Acute Respiratory Syndrome Coronavirus-2 (SARS CoV-2) virus pandemic, several highly effective and safe vaccines have been produced at remarkable speed. Following global implementation of vaccination programmes, cases of thrombosis with thrombocytopenia following administration of adenoviral vector-based vaccines started being reported.

In this review we discuss the known pathogenesis and epidemiology of so-called vaccine induced thrombocytopenia and thrombosis (VITT). We consider the available guidelines, diagnostic laboratory tests and management options for these patients. Finally, we discuss important unanswered questions and areas for future research in this novel pathoclinical entity.

1. Introduction

The Severe Acute Respiratory Syndrome Coronavirus-2 (SARS CoV-2) virus pandemic has caused high levels of mortality and morbidity, leading to approximately 4.5 millions deaths world-wide [1]. Several vaccines have been developed with unprecedented speed, with four vaccines approved by early 2021. These vaccines are highly effective at reducing disease incidence and severity, with one vaccine dose reducing risk of hospitalization and death by over 80% [2].

In March 2021, three groups in Norway, Germany and the United Kingdom, reported the occurrence of thrombotic complications with thrombocytopenia in previously healthy patients who had recently received the AstraZeneca (AZ) ChAdOx1 nCoV-19 vaccine [3–5], with further reports in the following weeks and months [6,7]. A high proportion of cases had thrombosis at unusual sites, in particular, cerebral venous sinus thrombosis (CVST) and splanchnic vein thrombosis (SVC). Cases associated with the Johnson & Johnson (J&J) vaccine (AD26.COV2.S) have since been published [8]. This syndrome, termed vaccine induced thrombocytopenia and thrombosis (VITT), vaccine-induced prothombotic immune thrombocytopenia (VIPIT) or thrombosis with thrombocytopenia syndrome (TTS), is a rare complication of vaccination, limited to the replication-defective adenoviral vector-based SARS CoV-2 vaccines. The AZ vaccine uses a chimpanzee adenoviral vector encoding a modified membrane-bound SARS CoV-2 spike protein that does not shed, and the J&J vaccine uses a recombinant human adenoviral vector that encodes an unmodified spike glycoprotein. Cases of VITT are almost exclusively seen following adenoviral vector-based vaccines with only rare reports in association with mRNA-based vaccines [9].

This review summarises the current understanding of the pathogenesis and epidemiology of VITT and compares the initial published cases to more recent reports including experience from a cohort of Irish patients. The available guidelines, laboratory testing and management options for VITT are discussed and future areas of research are

* Corresponding author.
E-mail address: dswan@stjames.ie (D. Swan).

https://doi.org/10.1016/j.tru.2021.100086
Received 28 September 2021; Received in revised form 26 October 2021; Accepted 27 October 2021
Available online 10 November 2021

highlighted.

2. Pathogenesis

The similarities in clinical presentation between initial patients with VITT and with heparin-induced thrombocytopenia (HIT) led to the recognition that the pathogenesis of both conditions might be similar. The groups who first reported this phenomenon independently identified that affected patients had high circulating levels of immunoglobulin G (IgG) antibodies against platelet factor 4 (PF4), detected by enzyme linked immunosorbent assay (ELISA) [3–5]. HIT is characterized by thrombosis and thrombocytopenia secondary to antibodies directed against PF4-heparin complexes, which crosslink FcγIIa receptors (FcγRIIa) on platelets, causing platelet activation, degranulation and aggregation. FcγRIIa is also present on monocytes, endothelial cells and neutrophils. Anti-PF4 binding leads to enhanced tissue factor expression, thrombin generation and formation of neutrophil extracellular traps (NETs), generating a hypercoagulable state [10]. Atypical HIT is a rare form of HIT, occurring in the absence of prior heparin exposure, in which the anti-PF4 antibodies are heparin-independent [11]. Similarly, anti-PF4 antibodies in patients with VITT are able to bind to platelets and other cells via FcγRIIa receptors, leading to platelet activation, consumption and thrombosis, in the absence of heparin [3].

The pathogenesis of HIT relies upon the differential electric charges between PF4 and heparin. PF4 is a positively charged cation stored in platelet alpha-granules. PF4 binds to heparin, which is strongly anionic (termed a polyanion), producing a conformational change and exposing a new epitope, thus stimulating autoantibody formation [12]. In patients with VITT, it is hypothesized that anionic surfaces present in adenoviral vector-based vaccines are performing a similar role to heparin in HIT. One group has shown that VITT anti-PF4 antibodies consistently bind within the heparin-binding site of PF4, whereas HIT anti-PF4 antibodies may bind to other sites within PF4. This may partly explain the mechanism by which VITT antibodies mimic the effect of heparin, by binding a similar site on PF4, enabling PF4 tetramers to cluster and form immune complexes, leading to FcγRIIa-dependent platelet activation [13].

Greinacher et al. have recently published important results suggesting a two-step mechanism for thrombosis in VITT [14]. In the first step, vaccine components including adenovirus hexon protein, bind to PF4, induce a conformational change and expose a neoantigen. Proinflammatory responses to vaccination amplify antibody production. The AZ vaccine contains EDTA (Ethylenediaminetetraacetic acid), which increases vascular permeability, a hallmark of inflammation [15]. In addition, around 50% of proteins within the AZ vaccine are derived from the T-Rex HEK293 human embryonic kidney-derived production cell line. The immunogenicity of these proteins and impact on inflammation has yet to be established [16]. In the second step, five to 20 days after vaccination, anti-PF4 VITT antibodies have been produced in sufficient quantities to activate platelets and other cellular lineages via FcγRIIa receptors.

Thrombi are composed of fibrin, erythrocytes and platelet aggregates. Historically, arterial thrombi were considered to be 'white' clots, comprised mainly of platelets and thus treated with antiplatelet agents, whereas venous thrombi were 'red' clots, made predominantly of fibrin and red cells requiring anticoagulation [17]. VITT is characterized by thrombocytopenia alongside decreased fibrinogen and increased D-Dimers, suggesting involvement of both platelets and the coagulation system. Postmortem analysis of two patients who died as a consequence of extensive thrombosis and intracranial haemorrhage revealed increased complement components on vascular endothelial surfaces, the presence of platelet aggregates lining small and medium sized vessel walls and inflammatory cells, particularly monocytes. These findings indicate further involvement by both the innate immune system and complement activation in the aetiology of thrombosis in VITT [18]. Greinacher et al. showed that incubation of human neutrophils with VITT patient serum induced NETosis in a platelet dependent fashion. Immunohistochemical analysis of samples from CVST in two VITT patients showed abundant activated neutrophils and evidence of enhanced NETosis compared with similar material from a patient with CVST not caused by VITT [14]. The precise interplay between platelet activation, inflammation, the complement system and the coagulation cascade in the pathogenesis of VITT has yet to be elucidated and may be key to optimizing management of these cases in future.

3. Epidemiology

As of April 4, 2021, 169 cases of CVST and 53 of SVT had been reported to the European Drug Safety Database, Eudravigilence. Updated guidance concerning the AZ vaccine released in June 2021 proposes a risk of thrombosis with thrombocytopenia of up to 1/10,000 [19]. The initial estimated incidence of VITT based on the primary case reports was approximately 1/100,000 exposures [20]. As of September 22, 2021, the UK MHRA (Medicines and Healthcare products regulatory agency) has received 419 reports of cases of thrombosis and thrombocytopenia following approximately 48.8 million doses of the AZ Covid-19 vaccine, which remains relatively consistent with this initial estimate [21]. 89% of reported cases in the UK occurred after the first vaccine dose. Rates associated with the J&J vaccine are possibly slightly lower, with 47 cases out of 14.8 million doses administered in the United States reported to the CDC (Centres for disease control and prevention) by September 22, 2021 [22]. The MHRA has also received reports of 18 cases of thrombosis and thrombocytopenia following the Pfizer mRNA vaccine and two after the Moderna vaccine. Whether these represent true cases of VITT is not certain from the information available [21].

4. Published case series and cases within Ireland: changing demographics and outcomes

A summary of reported case series is presented in Table 1 [3–6,8,23]. Considering five initial case reports, concerning patients identified in March and April 2021, 52 patients are described, 51 of whom received the AZ vaccine and 1 the J&J vaccine [3–6,8]. There was a strong female predominance in these first initial reports, ranging from 61% to 100% of cases. The average time between vaccination and symptom onset was between approximately 8-12 days and up to 24 days. CVST was the most frequently observed thrombotic complication followed by SVT. A mean platelet nadir of 30-40 x 10^9/l was seen across the reports, D-dimers were consistently extremely elevated, at levels higher than usually seen in acute VTE, and hypofibrinogenaemia was found in around half of patients. Mortality ranged from 25 to 60%, predominantly as a consequence of intracranial haemorrhage in patients with CVST. PF4 ELISA results were positive in nearly all cases, usually with higher optical density (OD) readings than seen in patients with HIT. Several functional assays were used in a subset of patients. Modified heparin induced platelet aggregation (HIPA) and PF4-induced platelet aggregation (PIPA) assays were positive in the majority of cases, whereas only 1 in 10 patients reported by See et al. tested positive using the serotonin release assay (SRA) [6].

From March to August 2021, the National Coagulation Centre in Ireland has identified 10 probable cases of VITT [24]. Nine patients received AZ and one received J&J. 50% were female and the mean age was 42 years (range 21–63). Four patients were over the age of 50 years. Mean time from vaccination to hospital presentation was 17.7 days (median 14 days). Two patients had no confirmed thrombotic event and eight patients had venous thrombosis of which some had multiple events: PE [5], CVST [3], DVT [3] or SVT [2]. One patient presented initially with a central venous catheter-associated thrombosis and a normal platelet count and was treated with therapeutic low molecular weight heparin. Later, this patient developed thrombocytopenia and recurrent acute lower limb arterial thrombosis requiring emergency embolectomy and fasciotomies. As the patient had recently received an adenoviral vector vaccination, both HIT and VITT were considered

Table 1
Demographics and outcomes of published cases of VITT.

Paper	Cases (n)	Age (years)	Female (%)	Vaccine[a]	Days to symptom onset (range)	Thrombosis	Platelet nadir x 10^9/l (range)	Fibrinogen	D-dimer	PF4 ELISA	Functional assay	Treatment	Mortality (%)
Schultz et al.	5	Mean 41 (32–54)	80	AZ	8 (7–10)	5 CVST 1 SVT	27 (10–70)	Reduced in 60%	Highly elevated in 100%	OD range 2.9–3.8	Positive in 4 of 5	IVIg and steroids in 4 patients	60
Greinacher et al.	11	Mean 30 (22–49)	82	AZ	8 (5–16)	9 CVST 3 SVT 3 PE 4 other	35 (8–107)	Reduced in 3 of 7	Elevated in all tested (n=7). Mean 35 mg/l (1.8–142)	Positive in all tested (n=9). Mean OD 2.71. OD >2 in 8 of 9	Positive in all tested (n=9)	Not reported	55
Scully et al.	23	Mean 46 (21–77)	61	AZ	12 (6–24)	13 CVST 4 PE 2 portal vein 2 ischaemic strokes 1 DVT	44 (7–113)	Reduced in 57%	Highly elevated in all tested (n=20). Mean 31,301 mcg/l (5000–80,000)	21 positive, 1 negative, 1 equivocal	Positive in 5 of 7 tested	Not reported	30
Muir et al.	1	48	100	J&J	14	1 CVST 1 SVT	13	Reduced	117.5 mg/l	OD 2.55	ND	Argatroban and IVIg	Critically ill at time of writing
See et al.	12	18- <60	100	AZ	9 (6–15)	12 CVST 8 non-CVST	46 (9–127)	Reduced in 58%	Elevated in 100%. 1.1–112 mg/l	Positive in all tested (n=11). OD >2 in 8 of 11	SRA positive in 1 of 10 tested	Non-heparin anticoagulation in 10 (6 initially received heparin), IVIg in 7, IVIg and steroids in 3, platelet transfusions in 4 patients	25
Pavord et al.	220 (170 definite, 50 probable)	Median 48 (18–79)	55	AZ	Median 14 (5–48)	110 CVST (50%) 43 DVT 63 PE 21 DVT/PE 41 SVT 47 arterial events	47 (6–344)	Median 2.2 g/l (range 0.3–4.4)	Median 24,000 mcg/l (range 5000–80,000)	Positive in 198 of 220 patients tested	Not reported	Non-heparin anticoagulation 68%, IVIg 1 dose 72%, 2 doses 11%, corticosteroids 26%	22

CVST (cerebral venous sinus thrombosis), DVT (deep vein thrombosis), IVIg (intravenous immunoglobulin), OD (optical density), PE (pulmonary embolism), SRA (serotonin release assay), SVT (splanchnic vein thrombosis).

[a] AZ (AztraZeneca); J&J (Johnson and Johnson).

possible, but it was noted that HIPA was negative and PIPA was positive. After diagnosis with VITT, all patients were therapeutically anticoagulated with a direct oral anticoagulant (DOAC), two receiving the direct thrombin inhibitor argatroban, and six received intravenous immunoglobulin infusions. There have been no deaths.

The mean platelet count on presentation was 106 x 10^9/l (range 24-258 x 10^9/l), with a nadir of 89 x 10^9/l (range 24-230 x 10^9/l). Mean fibrinogen was 2.6 g/l (median 2.3 g/l), with hypofibrinogenaemia identified in three cases. D-dimers were highly elevated in nine of 10 cases, with an average of >10 mg/l (normal <0.5 mg/l). Particle gel immunoassay screening was poorly sensitive, with only 1 positive result in 5 cases tested, in keeping with other case-series and published data [25]. PF4 IgG ELISA (Immucor) was strongly positive in all 10 cases. The mean OD was 2.3 (upper limit of normal 0.352 OD), with nine of 10 cases having an OD > 2, and all samples showing strong inhibition by heparin (mean 99%). The HIPA was positive in three out of 10 cases, whereas the PIPA was positive in 9 of 10 cases (1 negative sample was subsequently positive on retesting following optimisation of the assay, the patient was treated as presumed VITT prior to confirmation of a positive PIPA).

In comparison with the first case series published, our cohort have a higher platelet count, an equal sex distribution, fewer CVSTs and no mortality. A recent, larger publication of 220 definite or probable VITT cases from the UK reported a slight female excess of 55%, median age of 48 years and a median platelet count of 47 x 10^9/l. CVST occurred in 50% and D-dimers were markedly elevated. Mortality was 22% overall and 73% in patients with a baseline platelet count of <30 x 10^9/l with concomitant intracranial haemorrhage (ICH) [23]. Data from the MHRA have also reported no clear sex predominance, with 51% of 417 cases being female, and a rate of CVST of 36%, similar to our findings. Average age was 46 years for those with CVST and 54 years for other cases, however patients were affected up to the age of 93 years [21]. Mortality in the 417 cases was 17%, far lower than rates initially reported.

It has been suggested that the over-representation of female cases in initial reports may reflect differences in national rollout schedules. Norway and Germany concentrated on early vaccination of healthcare workers, who are disproportionately female [26]. Discrepant mortality rates may reflect variable rates of CVST within studies, and the now heightened awareness and prompt treatment of this condition. Pavord et al. showed that mortality was associated with CVST and worsening coagulopathy. Hazard ratios (HR) for mortality were increased in the presence of certain clinical features including CVST (HR 2.7, 95% confidence interval [CI] 1.4–5.2), every 50% decrease in platelet count (HR 1.7, 95% CI 1.3–2.3), every 10,000 mcg/l increase in D-Dimer (HR 1.2, 95% CI 1.0–1.3) and every 50% decrease in baseline fibrinogen level (HR 1.7, 95% CI, 1.1–2.5) [23]. Initial cases were very advanced before VITT was recognized, leading to a higher proportion of patients with severe disease manifestations such as marked thrombocytopenia, coagulopathy and ICH, which may account for the higher mortality rates seen initially in comparison to recent publications and the experience in Ireland.

5. Approach to the patient with suspected VITT

5.1. Published guidelines

Following the identification of VITT, several bodies have rapidly formulated and released guidelines regarding diagnosis and management. Perhaps unsurprisingly, given the limited available information on which to form these recommendations, significant differences exist between documents, and a number of recommendations have been amended since initial release [27–33]. A summary of the available guidelines is presented in Table 2.

The interval to presentation post-vaccination for consideration of VITT varies significantly from up to 16 days–42 days. The International Society on Thrombosis and Haemostasis (ISTH), Thrombosis Canada guidelines and those from the National Institute for Health and Care Excellence (NICE) do not require either a positive ELISA or functional assay, the German guidelines stipulate both, and the American Society of Haematology (ASH) and the UK Expert Haematology Panel (EHP) require a positive PF4 ELISA only. The German guidelines are the only which do not mandate thrombocytopenia at diagnosis. The ISTH and ASH recommendations specify a D-Dimer of >4 times the upper limit of normal and the UK EHP merely states that D-Dimers should be elevated.

Given the lack of consensus regarding diagnostic criteria in this newly discovered condition and the fact that early detection and management of less advanced disease may profoundly impact outcomes, clinician awareness and input from senior clinical decision makers are of

Table 2
Summary of published guidelines regarding diagnosis of VITT.

Guideline	Definite	Suspected	Unlikely
UK EHP	D+5 to +30 (or +42 if isolated DVT or PE) Acute thrombosis Plts <150 × 10^9/l Positive anti-PF4 ELISA D-Dimer >4000 mcg/l	D-Dimer >4000 mcg/l but one criterion not fulfilled (timing, thrombosis, thrombocytopenia, anti-PF4 ELISA) OR D-Dimer unknown or 2000–4000 mcg/l with all other criteria present	Plts <150 × 10^9/l without thrombosis with D-Dimer <2000 mcg/l OR thrombosis with Plts >150 × 10^9/l and D-Dimer <2000 mcg/l, regardless of anti-PF4 ELISA result AND/OR alternative diagnosis more likely
NICE Guideline		D+5 to +30 Thrombosis Plts <150 × 10^9/l D-Dimer >4000 mcg/l Normal or low (<2 g/l) fibrinogen OR Thrombosis Plts <150 × 10^9/l D-Dimer >2000 mcg/l Normal or low (<2 g/l) fibrinogen Strong clinical suspicion	No thrombocytopenia OR Thrombocytopenia without thrombosis Near normal D-Dimer Normal fibrinogen OR Thrombosis without thrombocytopenia D-Dimer <2000 mcg/l Normal fibrinogen
Thrombosis Canada		D+4 to +20 Acute thrombosis Plts <150 × 10^9/l Normal blood film Elevated D-Dimer	If following criteria met: Presenting at D+1–3 or after D+20 or plts >150 × 10^9/l or D-Dimer normal or No thrombosis
ISTH	D+4 to +28 Acute thrombosis Plts <150 × 10^9/l Positive anti-PF4 ELISA OR D-Dimer >4x ULN if anti-PF4 ELISA unavailable	D+4 to +28 Acute thrombosis Plts <150 × 10^9/l	Outside D+4 to +28 or no signs of thrombosis or no thrombosis on imaging AND Plts >150 × 10^9/l
GTH	D+4 to +16 Thrombosis and/or thrombocytopenia Positive anti-PF4 ELISA Positive modified HIPA assay	D+4 to +16 Thrombosis and/or thrombocytopenia	
ASH	D+4 to +42 Acute thrombosis Plts <150 × 10^9/l Raised D-Dimer >4x ULN Positive anti-PF4 ELISA	D+4 to +42 Confirmed thrombosis AND at least one of the following: Plts <150 × 10^9/l AND/OR markedly elevated D-Dimer	

paramount importance in the investigation and management of VITT.

5.2. Laboratory testing

Patients who warrant further investigation should have samples sent for confirmatory lab testing. There are several tests used to confirm the presence of clinically relevant HIT antibodies. These differ in various technical aspects including the source of PF4 and polyanion used, which alter their ability to reliably detect VITT antibodies. Serum samples from 12 patients with confirmed VITT by functional testing were used to assess the utility of three ELISA tests (Immucor, Hyphen and Stago), a particle gel immunoassay (PaGIA), a chemiluminescence immunoassay (CLIA) and lateral flow immunoassay (LFA). The PF4 ELISAs performed well, with calculated sensitivities of 100%, 92% and 91% for the respective assays. PaGIA, CLIA and LFA had sensitivities of <1% and should not be used to screen suspected VITT [25]. A functional test is subsequently required to confirm that the VITT antibodies detected lead to platelet aggregation *in vitro*. Available tests include a modified HIPA test with the addition of PF4 (PIPA) [3], heparin-induced multiple electrode aggregometry (HIMEA) [4] and SRA, which had poor specificity in the report by See et al. but has been used successfully elsewhere [6]. There are also flow cytometry-based tests, such as the PF4-induced flow cytometry-based platelet activation assay (PIFPA) [34] and the 'procoagulant platelets' test, which uses annexin V as a flow cytometric marker of donor platelet activation following exposure to patient serum [35]. These tests vary in their requirement for washed platelet or whole blood, serum or plasma, and volume of sample (summarized in Table 3). They are highly specialized and should only be performed by experienced centres, with choice of test dependent on available expertise.

5.3. Management of suspected or confirmed VITT

Patients with suspected or confirmed VITT should be treated without delay. We next discuss the therapies recommended or suggested by the published guidelines, and the relevant supporting evidence. The mainstay of treatment comprises intravenous immunoglobulins and non-heparin anticoagulation.

Table 3
Functional Laboratory Tests in the diagnosis of VITT.

Functional Assay				
	Patient Sample	Platelet donor material	Advantages	Disadvantages
Modified HIPA	Serum	Washed platelets	Activation may be graded as weak, intermediate or strong Rapid turnaround time	Requires washed platelets-technically challenging
HIMEA	Serum or plasma	Whole blood	Easy to perform Rapid turnaround time	Large volume patient sample required No PF4 activation step
SRA	Serum	Washed platelets	Considered 'gold standard' in HIT	Requires washed platelets-technically challenging Requires radioelements Time-consuming
PIFPA	Serum or plasma	Whole blood	Does not require washed platelets Small sample required	Performance highly dependent on donor platelets
Procoagulant Platelet	Serum	Washed platelets	Small sample required	Requires washed platelets-technically challenging

HIPA (heparin induced platelet aggregation), HIMEA (heparin-induced multiple electrode aggregometry), SRA (serotonin release assay), PIFPA (PF4-induced flow cytometry-based platelet activation assay).

5.4. Intravenous immunoglobulins (IVIg)

Greinacher et al. demonstrated that PF4-dependent platelet activation in VITT is mediated by binding to FcγRIIa. Platelet activation was inhibited by both the anti-FcγRIIa monoclonal antibody IV.3, and by the addition of IVIg (Privigen) [3]. Three VITT patients with predominantly arterial thrombosis received IVIg with consistent platelet increments in platelet count seen in two, and an initial response in the third. IVIg treatment did not significantly impact ELISA OD results, indicating lack of inhibition of VITT antibody binding to PF4. IVIg did however lead to reduced reactivity by SRA in the presence of PF4, demonstrating a reduction in the functional ability of VITT antibodies to induce platelet aggregation following IVIg treatment [36]. Based on current evidence, IVIg is the treatment most likely to modify disease course. The majority of guidelines recommend 2 doses of 1 g/kg (NICE suggests 1 dose with clinical review). The EHP advise IVIg irrespective of degree of thrombocytopenia [30], Thrombosis Canada have advised its use in severe or life-threatening thrombosis [28], and the ISTH recommend in cases with a platelet count of $<50 \times 10^9$/l [27].

5.5. Anticoagulation

The available guidelines are consistent in recommending the use of non-heparin anticoagulants in patients with thrombosis. Whether heparin adversely affects outcomes in VITT is not definitively known. An early publication described worsened thrombosis in one patient receiving heparin [5]. A review of 70 patients with VITT and CVST reported reduced death or dependency in patients who received non-heparin anticoagulants (36% of 50 patients) compared with those who did not (75% of 20 patients) [37]. Conversely, the recent larger UK dataset reported a mortality rate of 20% in patients treated with heparin, versus 16% in those who received alternate anticoagulants. The authors of this review concluded that heparin did not appear harmful [23]. However, the sample size in these publications is small, and until it is conclusively known whether heparin is safe in patients with VITT, its use is not recommended. Suitable alternatives, which have proven safe and effective in HIT include parenteral direct thrombin inhibitors argatroban and bivalirudin, direct oral anticoagulants without a heparin lead-in phase (apixaban and rivaroxaban), fondaparinux or danaparoid [38]. Therapeutic dose anticoagulation is safe in patients with a platelet count of 50×10^9/l or higher [39].

Whether therapeutic anticoagulation is required in patients with VITT without documented thrombosis, similar to patients with HIT, is not certain. The NICE guidelines and EHP suggest consideration of non-heparin VTE prophylaxis in patients with VITT without confirmed thrombosis, but with thrombocytopenia and D-Dimers >4000 mcg/l [30,33]. The other guidelines do not discuss VTE prophylaxis in suspected VITT patients.

5.6. Blood product support

Historically, HIT was thought to be a prothrombotic condition in which bleeding was a rare manifestation. Although this belief has been challenged in recent years [40], the rate of haemorrhagic complications in VITT patients seems to be higher than seen previously in the setting of HIT. This is particularly true of those with CVST, in which ICH may be seen in up to 80% of cases, with high associated morbidity and mortality [3–6]. Blood product support to manage coagulopathy may therefore be more important in this novel disease entity.

Fibrinogen levels should be maintained at 1.5 g/l or higher using fibrinogen concentrate or cryoprecipitate depending on national and

local policy. Platelet transfusions have been associated with increased thrombosis and mortality rates in HIT, although this remains an area of debate [41,42]. At the time of writing, it is unclear whether platelet transfusions will exacerbate the pathogenesis of VITT. As such, they are not recommended routinely, but may be considered in thrombocytopenic patients requiring neurosurgery and in the context of active bleeding [31]. Reduced 'critical care' dosing of argatroban is an option in patients with a platelet count $<50 \times 10^9$/l as an alternative to transfusing platelets in order to facilitate full therapeutic dose anticoagulation [30].

5.7. Other treatments

5.7.1. Corticosteroids

Whether corticosteroids are beneficial in VITT is unknown. There are case reports showing benefit in patients with HIT [43,44], and the combination of IVIg with methylprednisolone raises platelet counts faster in childhood ITP, another autoantibody-mediated condition, than IVIg alone [45]. NICE recommends corticosteroids if IVIg treatment is insufficient, the ISTH advocates their use in patients with a platelet count $<50 \times 10^9$/l, and the EHP guidelines suggest upfront corticosteroids in patients with CVST due to high mortality rates amongst this cohort [27,30,33].

5.7.2. Plasma exchange

Plasma exchange may be of benefit. A 90% survival rate was reported following use of plasma exchange in 17 patients with CVST and/or extensive thrombosis, using solvent detergent plasma (Octaplas). The two deaths were both in patients with intracranial haemorrhage at presentation [23]. Successful use of plasma exchange was also reported in three cases of persistent thrombocytopenia and progressive thrombosis despite IVIg [46]. The UK EHP recommends early plasma exchange in those with extensive thrombosis and a platelet count $<30 \times 10^9$/l [30]. The ISTH recommendations are for patients with refractory thrombocytopenia (platelets $<30 \times 10^9$/l) after IVIg and steroids [27].

5.7.3. Rituximab

There is no evidence that the anti-CD20 monoclonal antibody Rituximab improves outcomes in VITT, with anecdotal use in HIT only [47]. The UK guidelines both suggest consideration of rituximab in patients refractory to IVIg and plasma exchange, although there is no evidence to support this approach at the current time [30,33].

5.7.4. Eculizumab

Activation of complement in VITT has been demonstrated in post-mortem findings [18]. Eculizumab, a monoclonal antibody directed against complement C5, prevents terminal complement activation. A case report describes its use in two cases of VITT, one with thrombotic microangiopathy and renal failure, and the other with a severe thromboembolic event following IVIg administration [48]. The ASH guidelines include eculizumab as a treatment option, however supportive evidence is lacking [31].

6. Future directions

The astute observation of acute thrombosis and thrombocytopenia after vaccination with adenoviral vector-based SARS CoV-2 virus vaccines, and the subsequent description and characterization of VITT happened with great rapidity. At the time of writing, much remains unknown, including the pathogenesis of the antibody response against PF4, the varying prevalence of VITT following vaccination with the AZ versus J&J vaccine, the reason for disproportionate numbers of CVST and SVT in cases of VITT, and the risk associated with revaccination. The majority of cases have occurred following the first vaccine dose (89% in the MHRA report [21]). Data is awaited on outcomes for these patients after a second vaccine dose with an mRNA-based vaccine.

VITT is a rare complication following receipt of an adenoviral-vector derived SARS CoV-2 vaccine. No risk factors, other than a younger age, have been consistently associated with development of VITT, and there currently are no means of predicting which individuals might be at greater risk. A population-based study reported a prevalence of anti-PF4 antibodies of 1.2% in nearly 500 AZ-treated patients [49]. Low-titre anti-PF4 antibodies have been demonstrated in similar proportions of individuals receiving the adenoviral vector-based AZ and the mRNA-based Pfizer vaccines (8% and 6.8% respectively), with antibodies also present in a number of patients prior to vaccination. OD readings were generally less than 1 and none of these antibodies activated platelets in the presence of PF4 [50,51]. These antibodies are likely induced by the mild systemic inflammation which accompanies all vaccinations against Covid-19 and do not herald development of VITT. This is perhaps not surprising, given that similar antibodies are detected in 25–50% of patients post-cardiac surgery, whereas the rate of HIT is far lower [20,52].

Although VITT is thought to be primarily mediated by platelet activation, anti-platelet agents are not recommended by the available guidelines due to concerns regarding increased bleeding risk and unclear evidence of potential benefit [27–31,33]. One group assessed the ability of serum from four confirmed VITT cases to induce platelet aggregation in the presence of the COX inhibitor indomethacin and the P2Y12 inhibitor ticagrelor. Both these agents, as well as heat inactivation of sera, impaired aggregation, which the authors hypothesized might reflect a contribution from complement [53]. Aspirin has been shown to only partly inhibit platelet aggregation induced by anti-PF4 antibodies in serum from patients with HIT [54], and is not recommended as part of the treatment of either HIT or VITT [55]. One hypothesis considers the structure of clots, whereby a core of highly activated platelets is surrounded by a looser shell of less activated platelets. Thrombin activity and fibrin formation are found mainly in the densely packed core, where close proximity means fibrinogen is better able to bind to platelet glycoprotein (GP) IIb/IIIa [56]. It has been postulated that perhaps platelet activation is so robust in VITT that dense clots are formed within circulatory beds, consuming platelets and fibrinogen via GPIIb/IIIa, producing the picture of thrombosis and coagulopathy observed [57]. Addition of the GPIIb/IIIa inhibitor eptifibatide to donor platelets treated with VITT serum inhibits aggregation [53], however use of such potent antiplatelet agents in clinical practice would likely be associated with an unacceptable bleeding risk. At the current time, the value of antiplatelet therapy in management of VITT is unproven.

The effects of inhibitors of FcγRIIa and its downstream signaling pathways on platelet aggregation in VITT were also analysed. Platelet activation was abolished by the monoclonal antibody IV.3 as seen previously [3], but also by the Src (sarcoma genes tyrosine kinases) inhibitor dasatinib, the Syk (spleen tyrosine kinase) inhibitor entosplentinib and the Btk (bruton tyrosine kinase) inhibitors ibrutinib and rilzabrutinib [53]. Further consideration of the cellular pathways involved in this condition may shed light on how to optimize future treatment strategies.

Another important question concerns duration of anticoagulation. VTE in patients with HIT is considered to be provoked by a transient reversible risk factor, warranting 3 months of therapeutic anticoagulation [55]. Consensus regarding duration of anticoagulation in patients with HIT without thrombosis has not been reached, with recommendations ranging from until resolution of thrombocytopenia to 4–6 weeks [58]. It seems reasonable to treat patients with VITT and proven thrombosis for a minimum of 3 months. However whether it is safe to discontinue anticoagulation after this period in cases with persistent evidence of anti-PF4 antibodies by functional assays is unknown. Greinacher et al. recently reported results from a study of 35 confirmed cases of VITT. After a median follow-up of 11 weeks, 66% had a negative PIPA. In 14 of the 15 patients with follow-up of over three months duration, the PIPA became negative within a median of 12 weeks. Five of these cases received a second vaccine dose with an

mRNA-based vaccine. Based on these results, the authors have suggested that second vaccination may be considered once functional antibody assays are negative, or after 12 weeks where these are not available [59]. In the Irish patient cohort, one case had evidence of a reduction in OD over time in serial PF4 ELISAs (OD 1.84 at 5 weeks and 0.86 at 14 weeks with a negative PIPA). Conversely, another two cases still have strongly positive OD >2 after 13 weeks, with no reduction in intensity over time, and a positive PIPA. The time at which anticoagulation can be safely discontinued, especially in patients with confirmed thrombosis and ongoing laboratory evidence of detectable, functional antibodies remains uncertain, and an important area of ongoing investigation.

Governance

This clinical audit has been approved by the local institutional research and innovation office.

Author contributions

DS analysed the data and wrote the manuscript. HE, RD, GL, EE, BH, FL, DOK, MC, LS, KP, CJ, FNA, JC provided patient information. JOD, KR, ML and NOC provided critical appraisal of the manuscript.

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.

References

[1] https://covid19.who.int.WHO, 2021.
[2] J. Lopez Bernal, N. Andrews, C. Gower, C. Robertson, J. Stowe, E. Tessier, et al., Effectiveness of the Pfizer-BioNTech and Oxford-AstraZeneca vaccines on covid-19 related symptoms, hospital admissions, and mortality in older adults in England: test negative case-control study, BMJ 373 (2021) n1088.
[3] A. Greinacher, T. Thiele, T.E. Warkentin, K. Weisser, P.A. Kyrle, S. Eichinger, Thrombotic thrombocytopenia after ChAdOx1 nCov-19 vaccination, N. Engl. J. Med. 384 (22) (2021) 2092–2101.
[4] N.H. Schultz, I.H. Sørvoll, A.E. Michelsen, L.A. Munthe, F. Lund-Johansen, M. T. Ahlen, et al., Thrombosis and thrombocytopenia after ChAdOx1 nCoV-19 vaccination, N. Engl. J. Med. 384 (22) (2021) 2124–2130.
[5] M. Scully, D. Singh, R. Lown, A. Poles, T. Solomon, M. Levi, et al., Pathologic antibodies to platelet factor 4 after ChAdOx1 nCoV-19 vaccination, N. Engl. J. Med. 384 (23) (2021) 2202–2211.
[6] I. See, J.R. Su, A. Lale, E.J. Woo, A.Y. Guh, T.T. Shimabukuro, et al., US case reports of cerebral venous sinus thrombosis with thrombocytopenia after Ad26. COV2.S vaccination 325 (24) (March 2 to April 21, 2021) 2448–2456. Jama. 2021.
[7] J. Thaler, C. Ay, K.V. Gleixner, A.W. Hauswirth, F. Cacioppo, J. Grafeneder, et al., Successful treatment of vaccine-induced prothrombotic immune thrombocytopenia (VIPIT), J. Thromb. Haemostasis 19 (7) (2021) 1819–1822.
[8] K.-L. Muir, A. Kallam, S.A. Koepsell, K. Gundabolu, Thrombotic thrombocytopenia after Ad26.COV2.S vaccination, N. Engl. J. Med. 384 (20) (2021) 1964–1965.
[9] S. Sangli, A. Virani, N. Cheronis, B. Vannatter, C. Minich, S. Noronha, et al., Thrombosis with thrombocytopenia after the messenger RNA–1273 vaccine, Ann. Intern. Med. (2021).
[10] G.M. Arepally, A. Padmanabhan, Heparin-induced thrombocytopenia: a focus on thrombosis, Arterioscler. Thromb. Vasc. Biol. 41 (1) (2021) 141–152.
[11] A. Greinacher, K. Selleng, T.E. Warkentin, Autoimmune heparin-induced thrombocytopenia, J. Thromb. Haemostasis 15 (11) (2017) 2099–2114.
[12] M. Hogan, J.S. Berger, Heparin-induced thrombocytopenia (HIT): review of incidence, diagnosis, and management, Vasc. Med. 25 (2) (2020) 160–173.
[13] A. Huynh, J.G. Kelton, D.M. Arnold, M. Daka, I. Nazy, Antibody epitopes in vaccine-induced immune thrombotic thrombocytopaenia, Nature 596 (7873) (2021) 565–569.
[14] A. Greinacher, K. Selleng, R. Palankar, J. Wesche, S. Handtke, M. Wolff, et al., Insights in ChAdOx1 nCov-19 vaccine-induced immune thrombotic thrombocytopenia (VITT), Blood (2021).
[15] X. Gao, P. Kouklis, N. Xu, R.D. Minshall, R. Sandoval, S.M. Vogel, et al., Reversibility of increased microvessel permeability in response to VE-cadherin disassembly, Am. J. Physiol. Lung Cell Mol. Physiol. 279 (6) (2000) L1218–L1225.
[16] A.A. Stepanenko, V.V. Dmitrenko, HEK293 in cell biology and cancer research: phenotype, karyotype, tumorigenicity, and stress-induced genome-phenotype evolution, Gene 569 (2) (2015) 182–190.
[17] G. Lippi, Favaloro EJ. Venous, Arterial Thromboses, Two sides of the same coin? Semin. Thromb. Hemost. 44 (3) (2018) 239–248.
[18] C. Pomara, F. Sessa, M. Ciaccio, F. Dieli, M. Esposito, S.F. Garozzo, et al., Post-mortem findings in vaccine-induced thrombotic thombocytopenia, Haematologica 106 (8) (2021) 2291–2293.
[19] Agency EM, Vaxzevria (previously COVID-19 vaccine AstraZeneca). https://www.ema.europa.eu/en/medicines/human/EPAR/vaxzevria-previously-covid-19-vaccine-astrazeneca. (Accessed 28 August 2021).
[20] D.B. Cines, J.B. Bussel, SARS-CoV-2 vaccine–induced immune thrombotic thrombocytopenia, N. Engl. J. Med. 384 (23) (2021) 2254–2256.
[21] Kingdom GotU, Coronavirus vaccine- weekly summary of Yellow Card reporting. https://wwwgovuk/government/publications/coronavirus-covid-19-vaccine-adverse-reactions/coronavirus-vaccine-summary-of-yellow-card-reporting#annex-1-vaccine-analysis-print. (Accessed 4 October 2021).
[22] Response CfDCaPEPa. https://www.cdc.gov/coronavirus/2019-ncov/vaccines/safety/adverse-events.html. (Accessed 4 October 2021).
[23] S. Pavord, M. Scully, B.J. Hunt, W. Lester, C. Bagot, B. Craven, et al., Clinical features of vaccine-induced immune thrombocytopenia and thrombosis. New England journal of medicine, 2021.
[24] M. Lavin, P.T. Elder, D. O'Keeffe, H. Enright, E. Ryan, A. Kelly, et al., Vaccine-induced immune thrombotic thrombocytopenia (VITT) – a novel clinico-pathological entity with heterogeneous clinical presentations, Br. J. Haematol. (2021) n/a(n/a).
[25] U.J. Sachs, N. Cooper, A. Czwalinna, J. Müller, B. Pötzsch, A. Tiede, et al., PF4-Dependent immunoassays in patients with vaccine-induced immune thrombotic thrombocytopenia: results of an interlaboratory comparison, Thromb. Haemostasis (2021).
[26] M. Makris, S. Pavord, W. Lester, M. Scully, B. Hunt, Vaccine-induced immune thrombocytopenia and thrombosis (VITT), Res. Pract. Thrombosis Haemostasis 5 (5) (2021), e12529.
[27] (ISTH) ISoTaH, International society on thrombosis and haemostasis (ISTH). ISTH guidance on vaccine-induced immune thrombotic thrombocytopenia, 2021. https://cdnymawscom/wwwisthorg/resource/resmgr/news/ISTH_VITT_Flow_Chart_Finalpdf.
[28] Canada T. VACCINE-INDUCED PROTHROMBOTIC IMMUNE THROMBOCYTOPENIA (VIPIT). https://thrombosiscanadaca/wp-uploads/uploads/2021/04/51-Vaccine-induced-prothrobotic-immune-thrombcytopenia_02April2021pdf, 2021.
[29] J. Oldenburg, R. Klamroth, F. Langer, M. Albisetti, C. von Auer, C. Ay, et al., Diagnosis and management of vaccine-related thrombosis following AstraZeneca COVID-19 vaccination: guidance statement from the GTH, Hämostaseologie 41 (3) (2021) 184–189.
[30] Panel) EEH, Guidance from the expert Haematology Panel (EHP) on covid-19 vaccine-induced immune thrombocytopenia and thrombosis (VITT). https://b-s-horguk/media/19718/guidance-v20-20210528-002pdf, 2021 version 2.0.
[31] Haematology ASo, Thrombosis with thrombocytopenia syndrome (also termed vaccine-induced thrombosis and thrombocytopenia). https://www.hematology.org/covid-19/vaccine-induced-immune-thrombotic-thrombocytopenia. (Accessed 28 August 2021).
[32] I. Nazy, U.J. Sachs, D.M. Arnold, S.E. McKenzie, P. Choi, K. Althaus, et al., Recommendations for the clinical and laboratory diagnosis of VITT against COVID-19: communication from the ISTH SSC subcommittee on platelet immunology, J. Thromb. Haemostasis 19 (6) (2021) 1585–1588.
[33] (NICE) NIoCE, COVID-19 rapid guideline: vaccine-induced immune thrombocytopenia and thrombosis (VITT). www.nice.org.uk/guidance/ng200, published 29 july 2021.
[34] S. Handtke, M. Wolff, C. Zaninetti, J. Wesche, L. Schönborn, K. Aurich, et al., A flow cytometric assay to detect platelet-activating antibodies in VITT after ChAdOx1 nCov-19 vaccination, Blood 137 (26) (2021) 3656–3659.
[35] K. Althaus, P. Möller, G. Uzun, A. Singh, A. Beck, M. Bettag, et al., Antibody-mediated procoagulant platelets in SARS-CoV-2-vaccination associated immune thrombotic thrombocytopenia, Haematologica 106 (8) (2021) 2170–2179.
[36] A. Bourguignon, D.M. Arnold, T.E. Warkentin, J.W. Smith, T. Pannu, J.M. Shrum, et al., Adjunct immune globulin for vaccine-induced immune thrombotic thrombocytopenia, N. Engl. J. Med. 385 (8) (2021) 720–728.
[37] R.J. Perry, A. Tamborska, B. Singh, B. Craven, R. Marigold, P. Arthur-Farraj, et al., Cerebral venous thrombosis after vaccination against COVID-19 in the UK: a multicentre cohort study. Lancet, 2021.
[38] T.E. Warkentin, M. Pai, L.A. Linkins, Direct oral anticoagulants for treatment of HIT: update of Hamilton experience and literature review, Blood 130 (9) (2017) 1104–1113.
[39] M. Napolitano, G. Saccullo, M. Marietta, M. Carpenedo, G. Castaman, E. Cerchiara, et al., Platelet cut-off for anticoagulant therapy in thrombocytopenic patients with blood cancer and venous thromboembolism: an expert consensus, Blood Transfus 17 (3) (2019) 171–180.
[40] A.M. Pishko, D.S. Lefler, P. Gimotty, K. Paydary, S. Fardin, G.M. Arepally, et al., The risk of major bleeding in patients with suspected heparin-induced thrombocytopenia, J. Thromb. Haemostasis 17 (11) (2019) 1956–1965.
[41] R. Goel, P.M. Ness, C.M. Takemoto, L. Krishnamurti, K.E. King, A.A. Tobian, Platelet transfusions in platelet consumptive disorders are associated with arterial thrombosis and in-hospital mortality, Blood 125 (9) (2015) 1470–1476.
[42] M.A. Refaai, C. Chuang, M. Menegus, N. Blumberg, C.W. Francis, Outcomes after platelet transfusion in patients with heparin-induced thrombocytopenia, J. Thromb. Haemostasis 8 (6) (2010) 1419–1421.
[43] K. Doucette, C.B. DeStefano, N.A. Jain, A.L. Cruz, V. Malkovska, K. Fitzpatrick, Treatment of refractory delayed onset heparin-induced thrombocytopenia after thoracic endovascular aortic repair with intravenous immunoglobulin (IVIG), Res. Pract. Thrombosis Haemostasis 1 (1) (2017) 134–137.

[44] M. Gonzales, A. Pipalia, A. Weil, Refractory heparin-induced thrombocytopenia with cerebral venous sinus thrombosis treated with IVIg, steroids, and a combination of anticoagulants: a case report, J Investig Med High Impact Case Rep 7 (2019), 2324709619832324.
[45] M. Carcao, M. Silva, M. David, R.J. Klaassen, M. Steele, V. Price, et al., IVMP+IVIG raises platelet counts faster than IVIG alone: results of a randomized, blinded trial in childhood ITP, Blood Adv 4 (7) (2020) 1492–1500.
[46] C.J. Patriquin, V. Laroche, R. Selby, J. Pendergrast, D. Barth, B. Côté, et al., Therapeutic plasma exchange in vaccine-induced immune thrombotic thrombocytopenia, N. Engl. J. Med. 385 (9) (2021) 857–859.
[47] A.M. Schell, M. Petras, Z.M. Szczepiorkowski, D.L. Ornstein, Refractory heparin induced thrombocytopenia with thrombosis (HITT) treated with therapeutic plasma exchange and rituximab as adjuvant therapy, Transfus. Apher. Sci. 49 (2) (2013) 185–188.
[48] A. Tiede, U.J. Sachs, A. Czwalinna, S. Werwitzke, R. Bikker, J.K. Krauss, et al., Prothrombotic immune thrombocytopenia after COVID-19 vaccination, Blood 138 (4) (2021) 350–353.
[49] I.H. Sørvoll, K.D. Horvei, S.L. Ernstsen, I.J. Laegreid, S. Lund, R.H. Grønli, et al., An observational study to identify the prevalence of thrombocytopenia and anti-PF4/polyanion antibodies in Norwegian health care workers after COVID-19 vaccination, J. Thromb. Haemostasis 19 (7) (2021) 1813–1818.
[50] L. Rauova, M. Poncz, Understanding VITT(ual) reality, Blood 138 (4) (2021) 285–286.
[51] T. Thiele, L. Ulm, S. Holtfreter, L. Schönborn, S.O. Kuhn, C. Scheer, et al., Frequency of positive anti-PF4/polyanion antibody tests after COVID-19 vaccination with ChAdOx1 nCoV-19 and BNT162b2, Blood 138 (4) (2021) 299–303.
[52] I.J. Welsby, E.F. Krakow, J.A. Heit, E.C. Williams, G.M. Arepally, S. Bar-Yosef, et al., The association of anti-platelet factor 4/heparin antibodies with early and delayed thromboembolism after cardiac surgery. Journal of thrombosis and haemostasis : JTH 15 (1) (2017) 57–65.
[53] C.W. Smith, C. Kardeby, Y. Di, G.C. Lowe, W.A. Lester, S.P. Watson, et al., Platelet activation by vaccine-induced immune thrombotic thrombocytopenia (VITT) patient serum is blocked by COX, $P2Y_{12}$ and kinase inhibitors, medRxiv 2021 (2021), 04.24.21255655.
[54] B.H. Chong, P.A. Castaldi, Heparin-induced thrombocytopenia: further studies of the effects of heparin-dependent antibodies on platelets, Br. J. Haematol. 64 (2) (1986) 347–354.
[55] H. Watson, S. Davidson, D. Keeling, Guidelines on the diagnosis and management of heparin-induced thrombocytopenia, Br. J. Haematol. 159 (5) (2012) 528–540, second ed.
[56] T.J. Stalker, E.A. Traxler, J. Wu, K.M. Wannemacher, S.L. Cermignano, R. Voronov, et al., Hierarchical organization in the hemostatic response and its relationship to the platelet-signaling network, Blood 121 (10) (2013) 1875–1885.
[57] J. Thachil, COVID-19 vaccine-induced immune thrombosis with thrombocytopenia (VITT) and the shades of grey in thrombus formation, Semin. Thromb. Hemost. (2021), https://doi.org/10.1055/s-0041-1735453.
[58] A. Cuker, G.M. Arepally, B.H. Chong, D.B. Cines, A. Greinacher, Y. Gruel, et al., American Society of Hematology 2018 guidelines for management of venous thromboembolism: heparin-induced thrombocytopenia, Blood Adv 2 (22) (2018) 3360–3392.
[59] L. Schönborn, T. Thiele, L. Kaderali, A. Greinacher, Decline in pathogenic antibodies over time in VITT, N. Engl. J. Med. (2021).