bijwerkingen centrumlareb

Overview of thrombosis with thrombocytopenia syndrome after COVID-19 vaccination

Introduction

To date, the European Medicines Agency (EMA) authorised four COVID-19 vaccines for active immunisation against SARS-CoV-2: BioNTech/Pfizer (Comirnaty®), Moderna, AstraZeneca (Vaxzevria®) and Janssen [1]. BioNTech/Pfizer and Moderna are both mRNA vaccines, encoding the viral spike (S) protein while AstraZeneca and Janssen are using an Adenovirus vector. All COVID-19 vaccines are subject to additional monitoring [2-5].

Table 1: Vaccination numbers in the Netherlands [6,7]

Vaccine	Start date	Population	Number of vaccinations up to June 13th, 2021
BioNTech/Pfizer	January 6th, 2021	Elderly, HCP, high risk groups, general population	8,615,536
Moderna	January 25th, 2021	HCP in primary care and smaller institutions, high risk groups, general population	926,851
AstraZeneca	February 12th, 2021	HCW and people from risk groups aged <65 years (from April 8th only 60-55 years and a few >65 years on demand)	2,318,644
Janssen	April 21st, 2021	HCW, HCP, patients in mental healthcare, general population	247,038

HCP = Healthcare professional, HCW = Healthcare workers

In April 2021, EMA confirmed events of unusual blood clots combined with low blood platelets as new side effect of the vector vaccines AstraZeneca (April 14th) and Janssen (April 22th) [8,9]. Thrombosis with thrombocytopenia syndrome (TTS) is labelled for these vaccines [4,5]. Although reports were also closely reviewed for BioNTech/Pfizer and Moderna [10], for these mRNA vaccines TTS was not labelled [2,3].

Various names were introduced for the new side effect of unusual blood clots with low blood platelets after COVID-19 vaccination: 'thrombosis with thrombocytopenia syndrome (TTS)', 'vaccine-induced immune thrombotic thrombocytopenia (VITT)' or 'vaccine-induced prothrombotic immune thrombocytopenia (VIPIT)' [11]. In literature, there is no clear distinction between these terminologies. On May 18th, the Brighton Collaboration (BC) published an interim case definition of TTS. This case definition includes all patients with acute venous or arterial thrombosis combined with a new onset thrombocytopenia, defined by a platelet count of less than 150,000/µl [12]. For VIPIT/VITT no precise case definition is available and the spectrum of this disease is not crystallised yet. Pharmacovigilance Centre Lareb considered TTS as the name for all cases with thrombosis and combined thrombocytopenia. TTS can have various causes including a vaccine related aetiology. If TTS has a vaccine related aetiology, Lareb used the names VIPIT/ VITT which was defined by a positive diagnostic test result (HIT ELISA and/or heparin induced platelet activation (HIPA) test) or was based on clinical judgement.

This overview presents all received reports that comply to the BC's interim case definition of TTS.

Reports

Till June 17th 2021, Pharmacovigilance Centre Lareb received 44 reports of thrombosis combined with thrombocytopenia after vaccination with a COVID-19 vaccine that adhere to the BC's interim case definition. The reports had at least one thrombo-embolic event combined with a platelet count below 150,000/µl. In six reports, thrombocytopenia was reported without reporting a platelet count. These reports were included since in the Netherlands thrombocytopenia is defined as a platelet count below 150,000/µl. An overview of the reports is shown in Table 2.

Table 2: Characteristics of the TTS reports, categorised by vaccine

		BioNTech/ Pfizer	Moderna	AstraZeneca	Janssen
TTS reports		13	1	29	1
Dose	1	9 (69.2%)	1 (100%)	24 (82.8%)	1 (100%)
	2	3 (23.1%)	-	1 (3.4%)	NA

	Unknown		1 (7.7%)	-	4 (13.8%)	-
Reporter	HCP		13 (100%)	1 (100%)	26 (89.7%)	1 (100%)
	CONS		-	-	3 (10.3%)	-
Sex	Male		8 (61.5%)	1 (100%)	9 (31.0%)	1 (100%)
	Female		5 (38.5%)	-	20 (69%)	-
Age (Years) (median; range)			73 (45 – 88)	56 (NA)	61 (23-67)	53 (NA)
Serious*			13 (100%)	-	29 (100%)	1 (100%)
Fatal outcome			-	-	4 (13.8%)	-
Time to onset (days)	Thrombocytopenia (median, range)		6.5 (0.1-23)	1 (NA)	14 (6-28)	11 (NA)
	Thrombosis (median, range)		8.5 (0.1-26)	1 (NA)	13 (6-28)	11 (NA)
Lowest thrombocyte count (/µl) (median, range)			125 (25-145)	149 (NA)	69 (11-147)	42 (NA)
Recent COVID-19 test?	Yes, positive		1 (7.7%)	-	-	-
	Yes, negative		5 (38.5%)	-	12 (41.4%)	-
	Not performed		2 (15.4%)	-	9 (31%)	1 (100%)
	Unknown		5 (38.5%)	1 (100%)	8 (27.6%)	-
HIT tests	Screening	NEG	-	-	5 (17.2%)	-
		POS	-	-	-	-
	Test unspecified	NEG	3 (23.1%)	-	8 (27.6%)	-
		POS	-	-	4 (13.8%)	-
	HIT aggregation test	NEG	-	-	1 (3.4%)	-
		POS	-	-	-	-
	HIT particle gel immunoassay	NEG	-	-	1 (3.4%)	-
		POS	-	-	-	-
	ELISA	NEG	1 (7.7%)	-	6 (20.7%)	-
		POS	-	-	4 (13.8%)	1 (100%)
	HIPA	NEG	-	-	9 (31%)	-
		POS	1 (7.7%)	-	10 (34.5%)	1 (100%)
	Antibodies against glycoprotein 1B9	NEG	-	-	1 (3.4%)	-
		POS	-	-	-	-
	Performed, test(s) + outcome unknown		2 (15.4%)	-	1 (3.4%)	-
	Not performed		7 (53.8%)	-	3 (10.3%)	-
	No information available		1 (7.7%)	1 (100%)	3 (10.3%)	-

*According to one of the CIOMS criteria: life threatening, hospitalisation, disabling/incapacitating, death or other medically important condition

In April 15th 2021, a national clinical guideline was published for the management of suspected VIPIT/VITT patients. According to this guideline, the approach to confirm the diagnosis VIPIT/VITT is to screen for heparin induced thrombocytopenia (HIT) and confirm this test with HIT ELISA (against autoantibodies to platelet factor 4 complexes) and/or HIPA [13].

In 29 reports (65.9%) one or more HIT tests were performed (BioNTech/Pfizer n=5, AstraZeneca n=23, Janssen n=1). In twelve reports, the patient had a positive ELISA and/or HIPA confirming VIPIT/VITT [13]. Ten of these patients were vaccinated with AstraZeneca (first dose n=9, vaccination moment unknown n=1). One of them was treated with dalteparin during hospitalisation for an appendectomy, seven weeks before vaccination. One patient was vaccinated with Janssen and another patient had his second administration of BioNTech/Pfizer. However, since this patient had been treated with heparin during an endovascular aortic aneurysm repair twelve days after vaccination, it could not be determined whether this was HIT or VIPIT/VITT caused by the COVID-19 vaccine BioNTech/Pfizer.

The eleven confirmed VIPIT/VITT cases associated with AstraZeneca and Janssen concerned five men and six women. Their median age was 63 years (range 27-67 years). Reported thrombotic events were cerebral venous thrombosis (n=2), cerebral arterial thrombosis (n=1), cerebral infarction (n=1), splanchnic vein thrombosis (n=4), disseminated intravascular coagulation (n=1), pulmonary embolism (n=4), thrombophlebitis (n=1) and deep vein thrombosis (n=2). The time to onset varied between six and nineteen days. Four patient had not recovered at time of reporting, four were recovering and of

one patient the outcome is unknown. Moreover, two patients died. The patients with fatal outcome are described separately.

Another five AstraZeneca reports were strongly suggestive for VIPIT/VITT based on clinical judgement (first administration n=3, vaccination moment unknown n=2). In these reports, diagnostic tests were not supportive or test results were missing. These patients concerned four women and one men with a median age of 39 years (range 31-62 years). The thrombotic events included splanchnic thrombosis (n=10), aortic thrombosis (n=1), peripheral artery thrombosis (n=1) and pulmonary embolism (n=1). It should be noted that for one patient multiple types of thrombosis could be reported. Symptoms started between nine and twenty days after vaccination. At time of reporting, three patients were recovering and two had not recovered.

In ten reports (22.7%) no HIT test was performed. Three of these reports were reported before the national clinical guideline was published. In another five reports, no information about HIT diagnostics was obtained.

Treatment
Most reports (n=41; 93.2%) included information about the medical treatment of the patients. In a report several medications could be reported. Treatment with a direct oral anticoagulants (rivaroxaban n=13, apixaban n=6, edoxaban n=2, dabigatran n=1, unspecified n=1), IVIG (n=15), fondaparinux (n=8) and/or argatroban (n=3) was mostly reported. Danaparoid, acenocoumarol and clopidogrel were all mentioned once and in five reports the type of anticoagulant was not specified. Two patients received nadroparin and one patient was treated with dalteparin. Other treatments included steroids (n=3), alteplase (n=2), thrombolysis (agent not specified) (n=1), tranexamic acid (n=2), fresh frozen plasma (n=1), prothrombin complex (n=1), fibrinogen (n=1), transfusion with thrombocytes (n=1), erythrocytes (n=1), plasmapheresis (n=1) and adrenalin (n=1).

Reports with fatal outcome
Out of the 44 reports concerning TTS, four patients (9.1%) died. All patients were vaccinated with AstraZeneca (first dose n=3, vaccination moment unknown n=1). The patients were three women and one men with an age between 40 and 65 years. Reported thrombosis were pulmonary embolism (n=3) and cerebral arterial thrombosis (n=1). For two patients classical risk factors for thrombo-embolism were described: smoking, oral contraceptive and obesity. In two patients the diagnosis VIPIT/VITT was confirmed with a positive HIT ELSISA and/or HIPA test result.

Discussion

Case definition
TTS includes all cases with the co-occurrence of thrombosis and thrombocytopenia. TTS can be vaccine related. However, it should be kept in mind that TTS can have other causes. The background incidence for various forms of thrombosis in combination with thrombocytopenia is estimated from 1.0 to 1.5 per 100,000 person-years for deep vein thrombosis up to 0.2 to 4.4 per 100,000 person-years for stroke [14]. Others found a low thrombocyte count in 10.9% of the patients with a venous thromboembolism at time of diagnosis [15]. In massive thrombotic events many thrombocytes are being used causing a relatively low blood platelet count. Furthermore, some (COVID-19) vaccines are associated with a transient decrease of platelet count or with Immune Thrombocytopenia (ITP) which theoretically could occur simultaneously in recently vaccinated persons who develop thrombosis.

In contrast to TTS, to date there is no definitive case definition for VIPIT/VITT. According to the Dutch clinical guideline, a positive ELISA and/or HIPA confirms VIPIT/VITT [13]. However, negative test results seems not to exclude this diagnosis. Among the received reports, some patients (repeatedly) tested negative, but clinical characteristics were very suggestive for VIPIT/VITT. Possibly the sampling moment, e.g. during or after treatment IVIG, could influence the test results. Furthermore, more investigation concerning the sensitivity of these tests is needed.

Reports
Currently, TTS is only labelled for the Adenovector vaccines AstraZeneca and Janssen. Although most reports in this overview were related to AstraZeneca (n=29) and one case concerned Janssen, fourteen cases concerned a mRNA vaccine (BioNTech/Pfizer n=13, Moderna n=1). Nearly all reports (97.7%) were considered serious, reflecting the severe characteristics of this syndrome. This is further underlined by the four reports with a fatal outcome.

The Summary of Product Characteristics (SmPC) of AstraZeneca and Janssen describes that the majority of TTS cases occurred in women under the age of 60 years [4,5]. However, our overview includes nineteen reports (43.2%) concerning men and overall patients had a median age of 63 years (range 23-88 years). It should be noted that since April 8th only patients between 60 years and 65 years are vaccinated with the COVID-19 vaccine AstraZeneca.

In most cases the reported time to onset (median 11 days; range 0.1- 28 days) was plausible and reported types of thrombosis included both classical venous and arterial thrombosis as well unusual locations (e.g. splanchnic vein thrombosis, cerebral venous thrombosis). These findings are consistent with the described characteristics in the literature [4,5,11].

According to the Dutch clinical guideline, the performance of a HIT screening and ELISA and HIPA are recommended [13]. In seven (15.9%) reports, all these three tests were described. Furthermore, in 29 reports (65.9%) at least one or more HIT tests was performed. No HIT diagnostic test was done in ten (22.7%) of the reports. The most described treatments in the reports (rivaroxaban, apixaban, IVIG, fondaparinux, argatroban) are in line with this guideline. However, three patients received a low molecular weight heparin which is contra-indicated in suspected VIPIT/VITT cases [13]. Although, it is uncertain if low molecular weight heparins truly aggravate this reaction. Furthermore, it should be kept in mind that some reports predate the publication date of the clinical guideline. Besides, the treating physician could intentionally deviate from this guideline based on for us unknown information.

In sixteen TTS cases the causality with the COVID-19 vaccine was confirmed by positive HIT tests or strongly suggestive based on clinical judgement and therefore named VIPIT/VITT. All sixteen reports were related to an Adenovector vaccine (AstraZeneca n=15, Janssen n=1) of which thirteen reports concerned the first administration. In three cases the vaccination moment was unknown. Based on the current available information, the reported TTS cases on BioNTech/Pfizer and Moderna are less suspicious for VIPIT/VITT, considering the clinical characteristics and known laboratory tests. However, so far a causal relation could not be excluded either.

Conclusion

In this overview we presented 44 cases of thrombosis with thrombocytopenia syndrome (TTS) after vaccination with a COVID-19 vaccine. Lareb used the interim case definition of the Brighton Collaboration (BC) for the inclusion of the TTS reports.

Although TTS is only labelled as new side effect for the vector vaccines AstraZeneca and Janssen, a third of the included cases concerned a mRNA vaccine. In sixteen reports, a relation with one of the Adenovector vaccines was confirmed or highly suggestive. Based on the current available information, none of the TTS cases related to BioNTech/Pfizer or Moderna was highly suspected for VIPIT/VITT.

To date, many aspects about TTS and VIPIT/VITT are still unknown. Consequently, new insights can possibly lead to adjustments of the case finding. Therefore, it is important to keep monitor all potential cases of TTS, using a broad case definition like the BC's case definition, regardless of the reported vaccine type, gender, age, vaccination moment, etc. Further awareness of this association is warranted.

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This signal has been raised on July 7, 2021. It is possible that in the meantime other information became available. For the latest information, including the official SmPC's, please refer to website of the MEB www.cbg-meb.nl