Abstract of the Final Report

Vaccine-induced immune thrombotic thrombocytopenia and thrombosis syndrome (VITT/TTS) after vaccination against SARS-CoV-2

Protocol Number:	EMA/2021/17/TDA
Study type:	Patient registry
Indication:	Vaccine-induced immune thrombotic thrombocytopenia and thrombosis syndrome (VITT/TTS) after vaccination against SARS-CoV-2
Phase:	IV
Sponsor:	Universitätsmedizin Greifswald
Principal/Coordinating Investigator	Prof. Dr. med. Andreas Greinacher
Protocol Version and Date:	Version: 2.0; Date: March 03, 2022

1 ABSTRACT / EXECUTIVE SUMMARY

Background: Rapid diagnosis and treatment improved outcome of patients with Vaccine-induced Immune Thrombotic Thrombocytopenia (VITT). However, after the acute episode many questions on long term management of VITT remained. This prompted the European Medicines Agency to initiate a prospective patient registry to be performed by the Institute for Transfusion Medicine of the Universitätsmedizin Greifswald.

Methods: 71 patients with serologically confirmed VITT in Germany were enrolled into this prospective registry and followed by median 18 months. The course of anti-PF4 antibodies was analyzed by consecutive anti-PF4/heparin IgG enzyme immunoassay (EIA) and PF4-enhanced platelet activation assay. Patients and their treating physicians were regularly contacted by letter, email and telephone to obtain information on new events and changes in health. Informed consent was obtained to perform genome wide analysis to identify potential genetic risk factors to develop VITT.

Findings: Platelet activating anti-PF4-antibodies were transient in 87.3% of patients. In six patients platelet activating anti-PF4-antibodies persisted >18 months. Five of 71 patients (7.0%) showed recurrent episodes of thrombocytopenia and/or thrombosis. In four of them alternative explanations beside VITT were present. After further COVID-19 vaccination with an mRNA vaccine no reactivation of platelet activating anti-PF4-antibodies or new thrombosis was observed. No adverse events occurred in patients with a history of VITT vaccinated against influenza, tick-borne encephalitis, varicella, tetanus, diphtheria, pertussis, and polio. No new thrombosis occurred in 24 patients with a history of VITT developing COVID-19. We further identified the characteristics of anti-PF4 antibodies in VITT patients. There was a strong correlation between antibody reactivity in the PF4/heparin EIA and the probability that these antibodies also activate platelets. Most important, a subset of these antibodies only activates platelets in the confirmatory functional assay, if the serum is further diluted. The explanation for this is that these antibodies form aggregates of PF4 only if the molar ratio between antibodies and PF4 are in an optimal range. Because antibody titers are very high in VITT patients, sensitivity of the confirmatory assay increases if antibodies are diluted. The genetic studies are still ongoing. Analyses up to now did not reveal any candidate gene

polymorphism. As the numbers are limited, we plan to combine the genetic data with the data of similar studies performed in other countries.

Interpretation: Once the acute episode of VITT is over, patients seem to have a low risk for recurrent thrombosis. VITT Patients tolerate further vaccination. The immune response against PF4 is not boosted by a new SARS-CoV2 infection in VITT patients.