Review 3: "Anti-PF4 levels of patients with VITT do not reduce 4 months following AZD1222 vaccination"

Pier Meroni¹, Maria Orietta Borghi¹

¹Fondazione Istituto Auxologico Italiano

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RR:C19 Evidence Scale rating by reviewer:

- **Reliable.** The main study claims are generally justified by its methods and data. The results and conclusions are likely to be similar to the hypothetical ideal study. There are some minor caveats or limitations, but they would/do not change the major claims of the study. The study provides sufficient strength of evidence on its own that its main claims should be considered actionable, with some room for future revision.

Review:

The paper reported a novel study on the clinical and laboratory follow-up of seven patients with VITT and were followed up for 82-145 days. In one refractory case, all the patients improved after hospital admission and treatment that included nonheparin anticoagulation, glucocorticoids, IVIg, plasmapheresis, and rituximab. High titers of anti-PF4 antibodies (by the commercial solid-phase assay detecting IgM, IgG & IgA) were found in all of the cases, which is in line with recently published reports. Despite the clinical improvement and the normalization of other circulating biomarkers described in VITT (e.g., D-dimers, fibrinogen, and platelet count), PF4 antibody titers remained high in all 7 patients (but reduced in one patient treated with rituximab) at 80-100 days after the diagnosis. However, sera collected during the follow-up were much weaker in activating normal platelets in the presence of PF4 compared to the samples collected at the time of the diagnosis of VITT. Since anti-PF4 IgG is thought to be pivotal in causing VITT thrombosis/thrombocytopenia by engaging platelet FcγRIIa, the authors investigated whether or not platelets from patients at follow-up displayed abnormal FcγRIIa expression and/or aggregation by standard agonists (e.g., thrombin and collagen related-peptide). This was not the case suggesting that another - not yet identified - factor(s) is needed for triggering VITT manifestations in addition to the anti-PF4 antibodies.

The information is new and important from a biological and clinical point of view since it can offer information on how long the patients should be considered at risk for recurrences and anticoagulation.

Since the anti-PF4 IgG only are apparently responsible for platelet aggregation, the solid-phase assay (LIFE CODES PF4 enhanced assay; Immucor GTI Diagnostics) detects all Ig isotypes. It would be useful to know whether the positivities found in the

follow-up sera were due to non-IgG antibodies. This could explain the discrepancy between the antibody detection assay and the functional platelet test.

The occurrence of antibodies against PF4 in the absence of any effect on in vitro platelet activation has been reported in patients with HIT and other disorders (e.g., SLE, APS). Although the levels of these antibodies are usually lower than those reported in the present study, this aspect could be discussed.

Finally, a brief report showing the decline of anti-PF4 IgG antibodies in VITT patients has been recently published and should be quoted/discussed (DOI: 10.1056/NEJMc2112760).