Received: 27 June 2021 | Accepted: 2 July 2021
DOI: 10.1111/jth.15465

Reply to the letter entitled "Suggested treatment of serious complications to Covid-19 vaccination with IdeS, a bacterial antibody-cleaving enzyme"

Dear Editor,

We have read with interest the letter written by Dr. Kahn and colleagues,[1] who suggest that IdeS (imlifidase), a bacterial protease that cleaves IgG and strongly inhibits the interaction of pathogenic IgG antibodies with FcγRIIa receptors and the resulting clinical consequences, could be used to treat patients severely affected by vaccine-induced thrombotic thrombocytopenia (VITT).

This interesting proposal is actually not original, as we published a short report a few weeks ago in the *New England Journal of Medicine* (not cited in the Kahn et al. letter) demonstrating that rapid tests used for the diagnosis of heparin-induced thrombocytopenia (HIT) were ineffective in detecting anti-platelet factor 4 (PF4) antibodies in patients with VITT.[2] More importantly, using a serotonin release assay sensitized with PF4, we also showed that IdeS completely inhibited the strong platelet activation induced by several VITT samples. Because intravenous immunoglobulins may be inappropriate to treat severe cerebral venous thrombosis with intracranial hypertension, we therefore emphasized that IdeS may be an effective alternative treatment in VITT but should be evaluated in this particularly severe condition.

This effectiveness of IdeS in suppressing the pathogenic effect of VITT antibodies *in vitro* was not surprising to us, as we had previously shown that IdeS cleavage of anti-PF4/H IgG associated with HIT also completely abolished heparin-dependent cellular activation.[3] Furthermore, IdeS prevents anti-PF4/heparin HIT antibody-induced thrombocytopenia and hypercoagulability in transgenic mice expressing human PF4 and FcγRIIA receptors. Therefore, we also proposed that IdeS injection could be a potential treatment for patients with severe HIT.

In VITT and HIT, IdeS should be effective within minutes of intravenous injection, but almost all IgG will also be cleaved and non-functional, which could expose treated patients at increased risk for bacterial infections. Therefore, an infusion of polyclonal IgG will be required early on to restore normal IgG levels in all IdeS-treated patients. Importantly, this protease does not appear to affect blood coagulation, with no impact on thrombin generation, as assessed in our mouse model, and should not increase thrombotic risk, which is particularly high in VITT patients.

In conclusion, our data obtained with pathogenic anti-PF4 antibodies strongly support the proposal that IdeS can be used as an emergency treatment in the most severely affected VITT patients.

Manuscript handled by: David Lillicrap

CONFLICTS OF INTEREST

The authors have no conflicts of interest to disclose.

AUTHOR CONTRIBUTIONS

All authors contributed to the writing of this text.

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