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Suggested treatment of serious complications to COVID-19 vaccination with IdeS, a bacterial antibody-cleaving enzyme

Several recent reports have independently described a rare thrombosis with thrombocytopenia syndrome (TTS) post-vaccination with ChAdOx1 nCoV-19. In *J. Thromb. Haemost*., Blauenfeldt et al.[1] described the clinical presentation of a case of fatal acute ischemic stroke associated with profound thrombocytopenia. The pathogenesis behind this case may involve mechanisms similar to autoimmune heparin-induced thrombocytopenia (HIT) because anti-platelet factor 4 (PF-4) antibodies were detected in the patient plasma. A recent study by Greinacher et al. in *N. Eng. J. Med*.[2] reported several cases with combined thrombosis and thrombocytopenia post-vaccination with ChAdOx1 nCoV-19, where anti-PF4 antibodies were detected in serum from affected patients. The authors also demonstrated that platelet activation through the FcγRII-receptor was an underlying mechanism because activation could be blocked *ex vivo* using monoclonal antibodies targeting the receptor. Functional tests for HIT diagnosis differ between laboratories, therefore in *J. Thromb. Haemost*. Platton et al.[3] described recommendations for standardization of investigation of TTS post-vaccination.

We have previously described IgGFc-mediated platelet activation by immune complexes containing IgG antibodies and fibrinogen generated in response to M1-protein, a bacterial virulence factor. The induced platelet activation was critically dependent on engagement of the FcγRII receptor by IgG in the complexes.[4] Analogous to the work presented by Greinacher et al.,[2] activation in our *ex vivo* model could be blocked using monoclonal antibodies targeting FcγRII. In addition, we successfully and specifically abolished the immune complex-mediated platelet activation by treatment of blood with IdeS (Immunoglobulin G-degrading enzyme of *Streptococcus pyogenes*).

IdeS is a secreted bacterial cysteine proteinase that cleaves IgG with a unique degree of specificity; no other substrate has been identified.[5] The enzyme cleaves human IgG (all four human subclasses are cleaved) in the lower hinge region generating one $F(ab')_2$ fragment and two Fc halves. Before cleavage can occur, IdeS has to bind to the Fc region, and the extreme specificity is explained by the requirement for this initial protein--protein interaction. In many autoimmune conditions and in transplant rejection IgG antibodies play a pathogenic role. The specific cleavage of IgG by IdeS indicated that the proteinase could potentially be used to disarm pathogenic IgG antibodies *in vivo*, and several studies demonstrated the ability of IdeS to abolish IgG-mediated diseases in animal models of autoimmune conditions. In this context it is important to highlight that IgG antibodies contained in immune complexes are fully available for IdeS cleavage.[4] In relation to the theme of this letter, it is interesting that in a mouse model of IgG-mediated thrombocytopenia IdeS treatment rescued 100% of the mice from lethal disease,[6] and that the enzyme has been successfully used to treat HIT in a mouse model.[7] In humans a single intravenous dose of IdeS within minutes cleaves the entire extracellular IgG-pool inactivating IgGFc-mediated effector function.[8] This is important because rapid interventions are required to counteract the complicated pathogenic mechanisms underlying TTS. A therapeutic combination including intravenous immunoglobulin (IVIG) was recently presented in this journal by Thaler et al.[9] IVIG is already indicated as a treatment for several autoimmune diseases including HIT; however, the exact mode of action is not clarified.

IdeS (Idefirix®) is approved within the European Union for desensitization treatment of highly sensitized transplant patients with positive crossmatch against an available donor.[10] Compared to other measures to counteract detrimental IgG, for example, plasmapheresis and IVIG, IdeS is efficient (one IdeS molecule cleaves more than 2000 IgG antibodies) and has a very rapid onset. Given the ominous prognosis, the IgG-driven pathogenesis, and the unique specificity, safety (no significant adverse effects have been recorded and IgG levels are back to normal after 2–3 weeks), and efficiency of IdeS, we propose that an off-label compassionate use of IdeS may be considered in patients with life-threatening TTS with positive anti-PF4 antibodies following vaccination against COVID-19 with adenoviral vaccine vectors. We believe that this information is important to share with colleagues treating this rare but very serious syndrome. If such an IdeS treatment is put into practice, it is noteworthy that *Streptococcus pyogenes*, one of the most significant bacterial pathogens in humans, has evolved an enzyme to protect the bacteria against phagocytic killing, which now could be utilized to treat complications to vaccination against a pandemic virus.

CONFLICTS OF INTEREST

Dr Kahn and Prof Björck have stock ownership in Hansa Biopharma. Prof Björck is listed as inventor on two patents for IdeS owned by Hansa Biopharma AB. Prof Björck has received grants from Hansa Biopharma until the end of 2020.

AUTHOR CONTRIBUTIONS

The authors have drafted and written the manuscript together.

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