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CONNECTIVE TISSUE DISEASES

A new therapeutic approach for APS?

Prevention of the vascular thrombosis and pregnancy morbidity associated with antiphopholipid syndrome (APS) remains an unmet clinical need, as a substantial proportion of patients with the condition are unresponsive to or experience serious adverse effects from standard anticoagulant and antiplatelet therapy. A new study published in *Blood* suggests that a novel approach, which uses a non-complement-fixing monoclonal antibody against β2-glycoprotein I (β2GPI), could be a useful tool in the treatment of APS.

β2GPI has previously been identified as a potential target antigen of pathogenic antiphospholipid antibodies (aPL) and the present work, led by Francesco Tedesco and Pier Luigi Meroni, shows that a human antibody that binds to the D1 domain of β2GPI with high affinity is indeed pathogenic in animal models.

Injection of the anti-β2GPI D1 antibody into lipopolysaccharide (LPS)-primed rats caused thrombus formation, and in pregnant mice caused fetal loss and low fetal weight, mimicking the clinical effects of aPL.

> “...the CH2-deleted anti-β2GPI D1 antibody could offer an innovative way to prevent aPL-induced fetal loss...”

However, these effects of the anti-β2GPI D1 antibody were not observed in complement-deficient or complement-depleted animals. Furthermore, injection of a variant of the antibody engineered to lack the CH2 domain (which is required for C1q binding and complement activation) did not affect pregnancy outcomes or coagulation *in vivo*. Together, these findings confirm a critical role for complement activation in the pathogenic mechanisms of aPL.

Antibody-binding assays demonstrated that the CH2-deleted variant bound to β2GPI equally as well as the parent antibody, but was unable to activate complement. On ELISA, the CH2-deleted variant was able to displace IgG from patients with APS bound to β2GPI on ELISA, owing to its higher affinity.

Demonstrating the potential clinical benefits of this displacement, administration of the CH2-deleted variant to pregnant mice and LPS-primed rats abrogated the pathogenic effects of IgG from patients with APS. The authors contend that the CH2-deleted anti-β2GPI D1 antibody could offer an innovative way to prevent aPL-induced fetal loss and thrombosis in patients refractory to standard therapy.

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Original article Agostini, C. *et al.* A non complement-fixing antibody to beta-2 glycoprotein I as a novel therapy to control abortions and thrombosis in antiphospholipid syndrome. *Blood* doi:10.1182/blood-2013-11-537704