

## The COVID-19 mRNA vaccine Comirnaty induces anaphylactic shock in an anti-PEG hyperimmune large animal model

B.A. Barta<sup>1</sup>, T. Radovits<sup>1</sup>, A.B. Dobos<sup>1</sup>, G.T. Kozma<sup>2</sup>, T. Meszaros<sup>2</sup>, P. Berenyi<sup>2</sup>, R. Facsko<sup>2</sup>, B. Merkely<sup>1</sup>, J. Szebeni<sup>2</sup>

<sup>1</sup>Semmelweis University, Scientific Research Laboratory, Heart and Vascular Center, Budapest, Hungary

<sup>2</sup>Semmelweis University, Nanomedicine Research and Education Center, Department of Translational Medicine, Budapest, Hungary

**Funding Acknowledgements:** Type of funding sources: Public grant(s) – National budget only. Main funding source(s): 2020-1.1.6-JÖVÖ-2021-00013, ÚNKP-22-3-II-SE-30

**Background:** The polyethylene-glycol (PEG)-containing COVID-19 mRNA vaccines can cause hypersensitivity reactions (HSRs), or rarely, life-threatening anaphylaxis in a small fraction of patients. The role of anti-PEG antibodies (Abs) has been proposed, but causality has not yet been proven in an animal model.

**Purpose:** The aim of this study was to provide such evidence using an anti-PEG hyperimmune porcine model wherein the Ab levels are increased by PEGylated liposomes called Doxebo. We also aimed to find evidence for a role of complement activation and thromboxane A2 release in blood.

**Methods:** Experimental pigs (n=6) were immunized with 0.1 mg/kg BW Doxebo i.v., and the rise of anti-PEG Abs were measured with ELISA. 2-3 weeks later the animals were injected with 1/3 human dose of Pfizer's COVID-19 mRNA vaccine Comirnaty i.v., and the hemodynamic, hematological and blood immune mediator changes were measured to assess the severity of hypersensitivity reaction (HSR). The endpoints were PAP, SAP, HR, EtCO<sub>2</sub>, WBC, granulocyte, lymphocyte and platelet counts, C3a and plasma TXB<sub>2</sub>.

**Results:** The level of anti-PEG IgM rose 5-10-thousand-fold in all pigs immunized with Doxebo by day 10. Each of the 6 animals developed an anaphylactic shock to injection of 1/3 human dose of Comirnaty that required cardiopulmonary resuscitation in 4 cases. The reaction, starting within 1 min involved maximal pulmonary hypertension (PAP 13±2 before vs. 37±6mmHg after Comirnaty, median±MAD, P<0.05) and severe systemic hypotension (SAP 63±8 before vs. 42±11mmHg after Comirnaty, median±MAD, P<0.05), tachycardia, granulo- and thrombocytopenia, and skin flushing or rash. These hemodynamic changes were paralleled by C3a and TXB<sub>2</sub> levels in blood.

**Conclusion:** We have established the first relevant large animal model of anaphylactic reaction induced by an mRNA vaccine. Consistent with previous studies, our current data show a causal role of anti-PEG Abs in the anaphylaxis to Comirnaty, which involves complement activation, and, hence, it represents CARPA (complement activation-related pseudo-allergy).