A632 - Effects of a non-neutralizing humanized monoclonal anti-adrenomedullin antibody in a porcine two-hit model of hemorrhage and septic shock

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Introduction:
Adrenomedullin (ADM) is a vasoactive peptide improving endothelial barrier function in sepsis, but may cause hypotension and organ failure. Treatment with an ADM monoclonal antibody (mAB) showed improvement in murine sepsis models. Here, we tested effects of the humanized anti-ADM mAB Adrecizumab (AC) in a porcine two hit model of hemorrhagic (HS) and septic shock (SSH).

Methods:
In a randomized, blinded study 12 German Landrace pigs (31 +/- 2 kg) were bled to half of baseline MAP for 45 minutes (HS). SSH was induced using an E.coli clot (7-9x10^11 CFU/kg BW) placed into the abdominal cavity 6 hours after HS. Animals received either 2 mg/kg BW Adrecizumab or vehicle (VH) immediately after SSH induction. After 4 hours, resuscitation was initiated using balanced crystalloids and noradrenalin to maintain a CVP of 8-12 mmHg, a MAP >65 mmHg and a ScvO2 >70% for another 8 hours. Hemodynamics, laboratory parameters and kidney histology were assessed. General linear model, MWU or Chi2 test were used for statistics where appropriate. P<0.05 was considered significant.

Results:
Volume resuscitation was significantly lower in the AC compared to VH group (5300 vs. 6654 ml; p=0.036). Vasopressor therapy was necessary in significantly less animals in the AC group (33 vs. 100%; p=0.014). Horowitz index was higher in the AC group (375 vs 286 mmHg, p=0.055). Kidney histology showed significantly lower granulocytes in both cortex (9.1 vs. 31.1 n/mm^2; p=0.02) and medulla (19.3 vs 53.0 n/mm^2; p=0.004) in AC treated animals. After induction of sepsis, plasma ADM increased immediately in both groups, but increased quicker and more pronounced in the AC group (p=0.003 for time*group effect).

Conclusion:
In this two hit shock model treatment with Adrecizumab overproportionally increased plasma ADM levels. Hemodynamics and pulmonary function were improved and histological kidney damage was reduced. Thus, therapy with Adrecizumab may provide benefit in septic shock, and clinical investigation candidate is warranted.