baseline APACHE II score was 21.8 ± 7.4. The average MAP was 54.8 ± 7.5 mmHg and mean lactate level 4.5 ± 6.9 mmol/L. The "early group" had higher rate of primary outcome achievement (76.2% vs 43.3%; odds ratio 1.96; 95% CI, 1.52 to 2.58; $p < 0.001$). The amount of intravenous fluid given at 6 and 24 hours were similar (2,718.2 ± 1,000.4 vs. 2,834.6 ± 1,097.3 mL; $p = 0.39$ and 5,125.1 ± 1,640.1 vs. 5,084.4 ± 1,686.2 mL; $p = 0.85$). Open label norepinephrine was given in 69.7% of early group and 80% in control group ($p = 0.08$). Also, there were non-significant lower rate of adverse events, namely cardiogenic pulmonary edema (25.6% vs 30.8%; $p = 0.39$) and new onset arrhythmia (12.4% vs. 20.8%; $p = 0.09$).

CONCLUSIONS. Early norepinephrine administration during septic shock resuscitation, when compared with standard therapy, resulted in higher rate of shock reversal at 6 hours.

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0427

Safety, tolerability and pharmacokinetics/-dynamics of the anti-adrenomedullin antibody Adrecizumab: a first in man study

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INTRODUCTION. Adrenomedullin (ADM) is an important regulator of endothelial barrier function and vascular tone during sepsis and septic shock; it therefore may represent a potential novel treatment target. Adrecizumab is a humanized IgG high-affinity antibody against the N-terminus of ADM, which only partially inhibits ADM signalling. Administration of Adrecizumab in septic animals reduced catecholamine requirements and vascular leakage, while improving blood pressure, renal function, and survival.

OBJECTIVES. The aim of this study was to investigate the safety, tolerability and pharmacokinetics/-dynamics of Adrecizumab in a *first-in-man* study.

METHODS. 24 healthy male volunteers (18 to 35 years), were recruited for this randomized, double-blind, placebo-controlled phase I study. Subjects were randomized into four groups (n = 6 each): 0.5, 2, or 8 mg/kg Adrecizumab, or placebo. The study drug was administrated intravenously over 1 hour. Due to the expected long half-life of Adrecizumab, subjects were followed for 90 days. Blood was sampled at various points on the study drug administration day and during the follow-up period. Several clinical safety parameters were monitored, including local tolerability, vital signs and electrocardiographic, biochemical, and haematological parameters. Additionally, pharmacokinetic and -dynamic analyses were performed, including plasma levels of Adrecizumab, ADM and MR-proADM (fragment of the ADM precursor).

RESULTS. Adrecizumab was well tolerated and showed an excellent safety profile. No severe adverse events occurred. Study drug administration did not result in relevant changes in vital signs and electrocardiographic evaluations. Apart from transient laboratory abnormalities, which were deemed not clinically significant, 37 adverse events (AEs) (22 possibly related, 15 unrelated) were reported of which the most common were headaches (n = 9) and symptoms of common cold (n = 11). AEs were evenly distributed across all groups (11 out of 37 AEs were reported in the placebo group), implying no relation to the study drug. All AEs occurred transiently and did not require intervention. PK of Adrecizumab showed proportional increases of the maximum observed plasma concentration (Cmax; 9.7 ± 0.9, 44.1 ± 4.5 and 179 ± 21.1 µg/ml for 0.5, 2 and 8 mg/kg Adrecizumab, respectively), a small volume of distribution (~100 ml/kg), a low clearance rate (~0.2 ml/h/kg) and a terminal $T_{1/2}$ of approx. 14 days. Adrecizumab administration elicited a pronounced increase of plasma ADM levels, while levels of MR-proADM remained unchanged (Fig. 149), indicating that de novo synthesis of ADM is not influenced.

CONCLUSIONS. Administration of Adrecizumab is safe and well-tolerated in humans. These findings pave the way for further investigation of Adrecizumab during systemic inflammation using the human endotoxemia model, and in an upcoming phase II clinical trial in sepsis patients.

GRANT ACKNOWLEDGMENT

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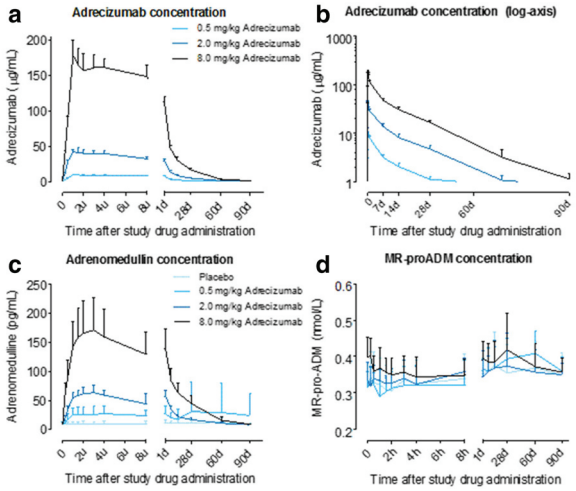

Fig. 149 (Abstract 0427). Plasma concentrations of Adrecizumab (A,B), Adrenomedullin (C) and MR- proADM (D) after sinlge i.v. administration of placabo oe Adrecizumab (0.5, 2 or 8 mg/kg) in healty male volunteers (n = 6 per group). Data are expressed as mean + SD.

0428

Acetylsalicylic acid partially reverses *in vivo* endotoxin tolerance in humans

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INTRODUCTION. Sepsis is a major health care burden with increasing incidence and high mortality rates. A severely suppressed state of the immune system called immunoparalysis is increasingly recognized as the overriding immune dysfunction in septic patients. Experimental studies have demonstrated that ASA exerts pro-inflammatory effects and epidemiologic data show that prehospital use of low dose acetylsalicylic acid (ASA) is associated with improved outcome of patients with sepsis. However, it remains to be determined whether ASA can reverse immunoparalysis.

OBJECTIVE. We investigated whether ASA prophylaxis or treatment prevents or reverses *in vivo* endotoxin tolerance induced by experimental human endotoxemia (a model for sepsis-induced immunoparalysis).

METHODS. We performed a double-blind placebo-controlled randomized study in 30 healthy male volunteers (age 18–35 years) who were intravenously challenged with bacterial endotoxin (LPS) twice (each challenge consisting of a bolus of 1 ng/kg followed by continuous administration of 1 ng/kg/hr during 3 hours). The two LPS