challenges were separated by a week. Subjects were randomized into three groups, a prophylaxis group (80mg ASA daily for a 14-day period starting 7 days before the first LPS challenge), a treatment group (80mg ASA daily for the 7-day period in-between both LPS challenges), and a placebo group that was challenged with LPS twice but received no ASA. We measured plasma cytokine levels (TNFα, IL-6, IL-8, IL-10, MIP-1α, MIP-1β and MCP-1) and changes in vital parameters such as temperature and heart rate.

RESULTS. The first LPS challenge resulted in a profound increase of plasma cytokine levels ($p < 0.0001$ for all cytokines), temperature (+2.9°C, $p < 0.001$) and heart rate (+68%, $p < 0.001$) in all groups. Prophylactic use of ASA enhanced plasma concentrations of TNFα by 50% compared with the placebo group ($p < 0.001$, Fig. 150a). The development of endotoxin tolerance was illustrated by a severely blunted plasma cytokine response upon the second LPS challenge in the placebo group (reduction of TNFα: 58%, $p < 0.001$; IL-6: 73%, $p = 0.004$; IL-8: 65%, $p = 0.003$; IL-10: 56%, $p = 0.003$; MIP-1α: 42%, $p = 0.002$; MIP-1β: 55%, $p = 0.01$; MCP-1: 38%, $p < 0.01$). ASA prophylaxis did not result in different cytokine levels during the second LPS challenge compared with the placebo group. ASA treatment resulted in enhanced plasma levels of TNFα (+53%, $p = 0.02$, Fig. 150b), IL-6 (+91%, $p = 0.03$) and IL-8 (+42%, $p = 0.02$) upon the second LPS challenge compared with the placebo group, whereas the plasma level of the key anti-inflammatory cytokine IL-10 was lower compared with the placebo group (−40%, $p = 0.003$).

CONCLUSION. Low dose ASA partially reverses the development of *in vivo* endotoxin tolerance in humans. These findings may partly explain the beneficial effect of ASA in sepsis patients observed in epidemiological studies and might provide rationale for use of ASA in this group of patients.

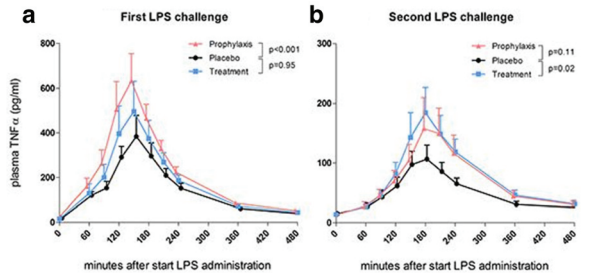

Fig. 150 (Abstract 0428). Plasma TNFα concentration during the first LPS challenge (A) and the second LPS challenge (B)

0429

Effects of the humanized anti-Adrenomedullin antibody Adrecizumab on vascular barrier function and survival during systemic inflammation and sepsis

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INTRODUCTION. Adrenomedullin (ADM) is an important regulator of endothelial barrier function during sepsis and septic shock. Previously, administration of a murine antibody targeted against the N-terminus of ADM resulted in improved outcome in models of murine sepsis.

OBJECTIVES. To determine the effects of Adrecizumab on vascular barrier dysfunction and survival in rodent models of systemic inflammation and sepsis.

METHODS. Male Wistar rats (n = 48) received Adrecizumab (0.02, 0.1, 0.5 or 2.5 mg/kg) or placebo, directly followed by lipopolysaccharide (LPS; 5 mg/kg). Evans Blue dye was administered 24 hours later and vascular leakage was assessed in kidney tissue. In subsequent experiments, C57BL/6 mice (n = 24) received Adrecizumab or placebo, immediately followed by CLP-surgery. Eighteen hours later, kidneys were harvested for immunohistochemical analysis of albumin, vascular endothelial growth factor (VEGF) and angiopoietin-1 (Ang-1). Finally, survival was assessed in a CLP model using C57BL/6 mice (n = 60) that received single (2 mg/kg) or repeated dosages (4 mg/kg followed by 2 mg/kg after 24 and 48 hours) of Adrecizumab or placebo.

RESULTS. In rats, LPS administration resulted in a 3.5-fold increase in renal albumin leakage compared with saline-treated controls, which was significantly attenuated by Adrecizumab at dosages of 0.1 and 2.5 mg/kg (71% and 40% attenuation, respectively), whereas a trend towards decreased renal albumin leakage was observed for the 0.5 mg/kg dose (33% attenuation). Adrecizumab administration resulted in significantly attenuated albumin (79%, 75% and 78% attenuation for 0.1, 2.0 and 20 mg/kg Adrecizumab, respectively) and VEGF concentrations (55%, 45% and 59% attenuation) in the kidneys of septic mice, whereas concentrations of the protective protein Ang-1 were augmented (387%, 474% and 379% augmentation, respectively). Both single and repeated administration of Adrecizumab resulted in improved survival during murine sepsis (single dose: from 10% to 50%; repeated dose: from 0% to 40%; Fig. 151).

CONCLUSIONS. Pre-treatment with the humanized anti-ADM antibody Adrecizumab improves vascular barrier function and survival in rodent models of systemic inflammation and sepsis. These results pave the way for clinical development of this antibody. A phase I study is in its final stages and a phase II study in septic patients is planned.

GRANT ACKNOWLEDGEMENT

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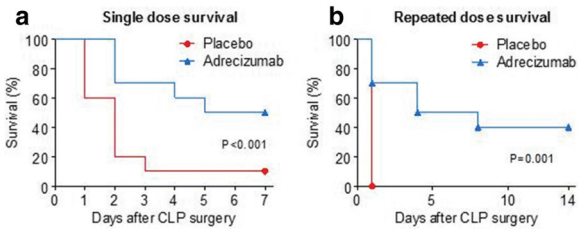

Fig. 151 (abstract 0429). Survival after CLP-surgery in mice, comparing sinlge (A) or repeated do ses (B) of either placebo or Adrecizumab (n = 10 per group). Kaplan-Meier curves are depicted and p-values were calculated using log-rank tests

Non-mortality outcomes after critical illness

0430

Psychiatric symptoms in unselected ICU survivors one year after the ICU discharge

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