CER-001, an Engineered High-Density Lipoprotein, shows beneficial pleiotropic effects in patients with sepsis in RACERS: a Phase 2a randomized clinical trial

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Background

Sepsis is characterized by a dysregulated immune response and metabolic alterations, including decreased High-Density Lipoprotein cholesterol (HDL-C) levels. Our recent research highlighted the diverse properties of HDL, including LPS scavenging, anti-inflammatory effects, and preservation of endothelial integrity in an LPS-induced AKI swine model treated with CER-001, an engineered HDL mimetic (**Figure 1**).

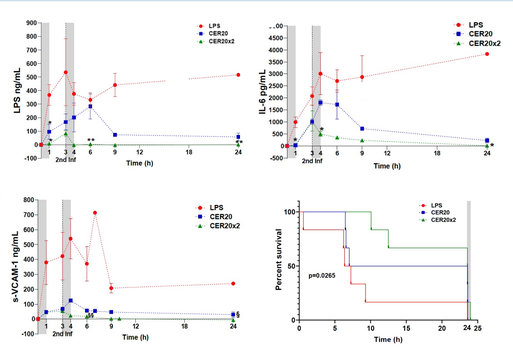

Figure 1. *Decrease of systemic pro-inflammatory response and endothelial dysfunction and improved survival in a swine model of LPS-induced AKI.*

All animals received an infusion of LPS 300 ug/kg (T0) without (control group) or with infusion of CER-001 at 20 mg/kg (CER20 group) followed for half of this group by a second infusion at 3 h of 20 mg/kg of CER-001 (CER20x2 group).

Objective

We investigated the effects of CER-001 in a Phase 2a clinical trial, aiming to better understand its molecular basis in systemic inflammation and renal function.

Methods and Material

Open-label, randomized, dose-ranging (Phase 2a) study including 20 patients with sepsis due to intra-abdominal cavity infection or urosepsis, admitted at the Intensive Care Units (ICUs) and the Sub-intensive Nephrology Unit at A.O.U. Policlinico, Bari, Italy (N° EUDRACT 2020-004202-60, Protocol CER-001-SEP_AKI_01)(**Figure 2**).

Main Inclusion criteria

1) Sepsis sustained by Gram-negative bacteria receiving antibiotic treatment;
2) Met Sepsis 3 criteria;
3) Signed and dated informed consent provided by the patient or by a legal representative.

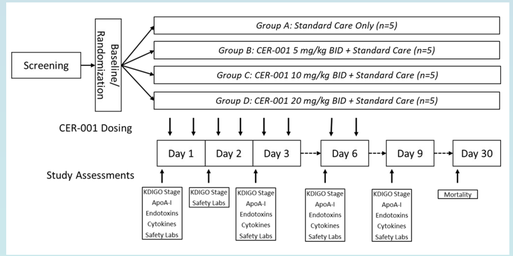

Figure 2. *Treatment allocation and study interventions*

Study Objectives

- Determine an optimal dose of CER-001 in combination with standard of care in septic patients based on safety.
- Effects on AKI onset and severity
- Changes from baseline for endotoxin and IL-6 levels, and other key inflammatory and endothelial dysfunction markers.

Results

Rapid normalization of apoA-I levels with CER-001 was associated with significant and sustained LPS removal ($p<0.05$ on days 3, 6 and 9) and subsequent immunomodulation. CER-001 treatment led to rapid and significant decreases in pro-inflammatory cytokines (e.g., IL-6, IL-8, TNF-α, MCP-1), endothelial dysfunction markers (sVCAM, sICAM) and mortality biomarker (sTREM-1)(**Figure 3**).

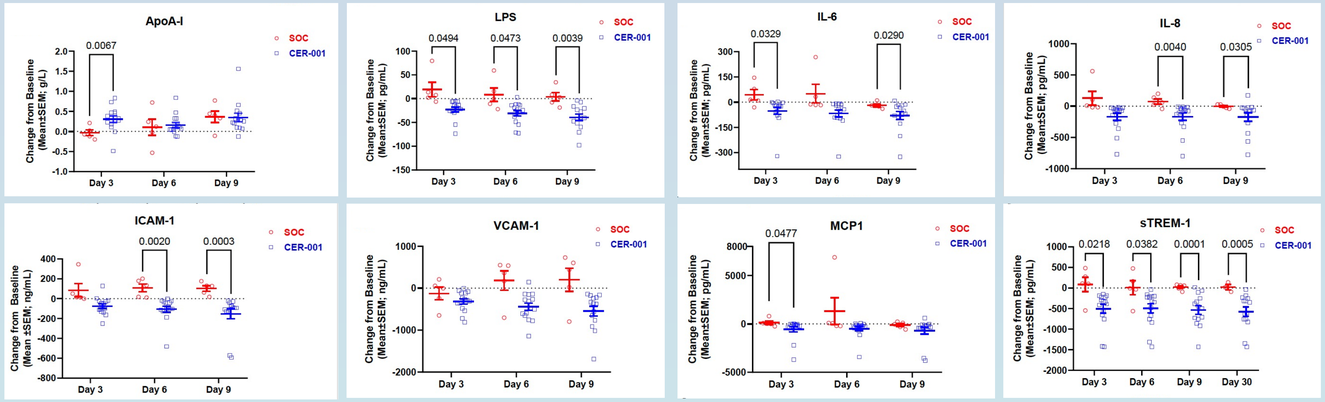

Figure 3*. Effect of CER-001 on ApoA-I level, LPS removal and inflammatory response in the pilot study RACERS*

CER-001-treated patients had a reduced risk of developing or progressing to severe AKI and a trend for improved survival. In a subset of critically ill patients, a shorter ICU stay with decreased need for organ support was observed with CER-001 (**Figure 4**).

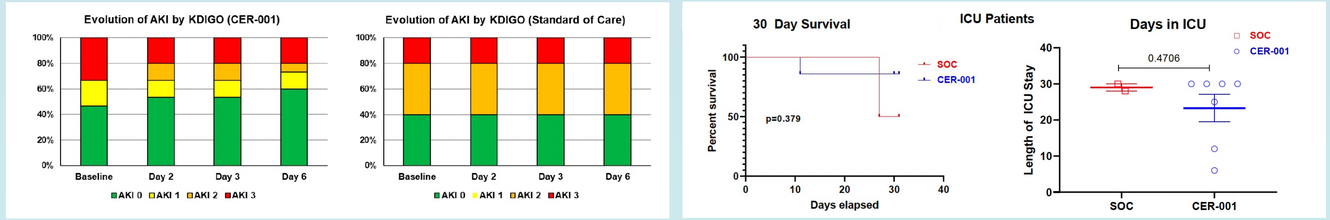

Figure 4. *Effect of CER-001 on AKI risk and progression, length of stay and need for organ support in ICU patients*

Conclusions

CER-001 represents a promising therapeutic strategy for sepsis management, improving outcomes and mitigating the cytokine storm and associated organ damage often observed in our patients.

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