Brain-kidney interplay during sepsis-associated AKI: results from the RACERS study

M.Fiorentino[1], M.T.Cimmarusti[1], A.Stasi[1], R.Franzin[1], S.Carparelli[1], M.Campioni[1], R.Losapio[1], G.Caggiano[1], P.Pontrelli[1], C.Keyserling-Peyrottes[2], C.Tupin[2], L.Gesualdo[1]

1. Nephrology Unit, Department of Precision and Regenerative Medicine and Ionian Area (DiMEPRE-J), Università degli Studi di Bari "Aldo Moro", Bari, ITALY. 2. Abionyx Pharma, Toulouse, France

BACKGROUND

Recent studies revealed the strong association between low levels of high-density lipoprotein (HDL) and dysregulation of the kynurenine pathway (KP) in sepsis responsible for cognitive impairment. Preclinical model demonstrated that treatment with a new engineered HDL (CER-001) significantly downregulated Indolamine-2,3-dioxygenase 1 (IDO1) enzyme, a crucial mediator of KP, by reducing kynurenine/tryptophan ratio (KYN/Trp) and quinolinic acid (QA) levels.

OBJECTIVE

The aim of the present study was to analyze the effects of CER-001 in mitigating brain dysfunction in a Phase 2a clinical trial (RACERS study).

METHODS AND MATERIAL

A randomized, Phase 2a study including patients with Gram negative sepsis, admitted at the ICUs and the Nephrology Unit at A.O.U. Policlinico, Bari, Italy. 20 patients were randomized to receive CER-001 twice a day on Days 1, 2, 3 and 6 at three different dosages (5, 10 or 20 mg/kg) or standard of care (SOC) only. Clinical and laboratory parameters were collected at treatment start, at days 3, 6, 9 and 30 (the end of the study).

CONTACT INFORMATION: marco.fiorentino@uniba.it

SUMMARY OR RESULTS

We analyzed the activity of KP between patients treated with CER-001 and SOC group, by reporting changes from baseline values of specific neuroactive metabolites. A profound alteration in the KP was reported in sepsis patients; KYN and KYN/Trp ratio values correlated with the severity of organ dysfunction and mortality risk, as calculated with SOFA (r^2 0.250, p=0.02) and SAPS II score (r^2 0.293, p=0.01) (**Figure 1**). Patients presenting with AKI at enrollment presented a tendence to higher values of KYN/Trp ratio (0.22, IQR 0.12-0.46) compared to patients without any stage of AKI at enrollment (0.12, IQR 0.07-0.28). Treatment with CER-001 reduced QA, KYN values and KYN/Trp ratio, suggesting that IDO-1 was significant downregulated after treatment, thus reducing the production of potential neurotoxic metabolites (**Figure 2**). We showed increased levels of tryptophan during treatment course, as well as the increased levels of the neuroprotective KYNA and a slight increase in serotonin, supporting the hypothesis of different regulation of tryptophan metabolism leading to neuroprotection.

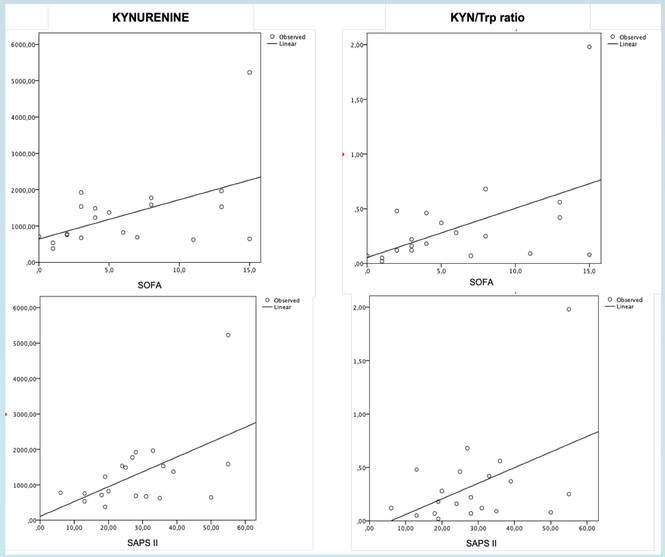

Figure 1. Correlation of SOFA and SAPS II score with markers of brain dysfunction

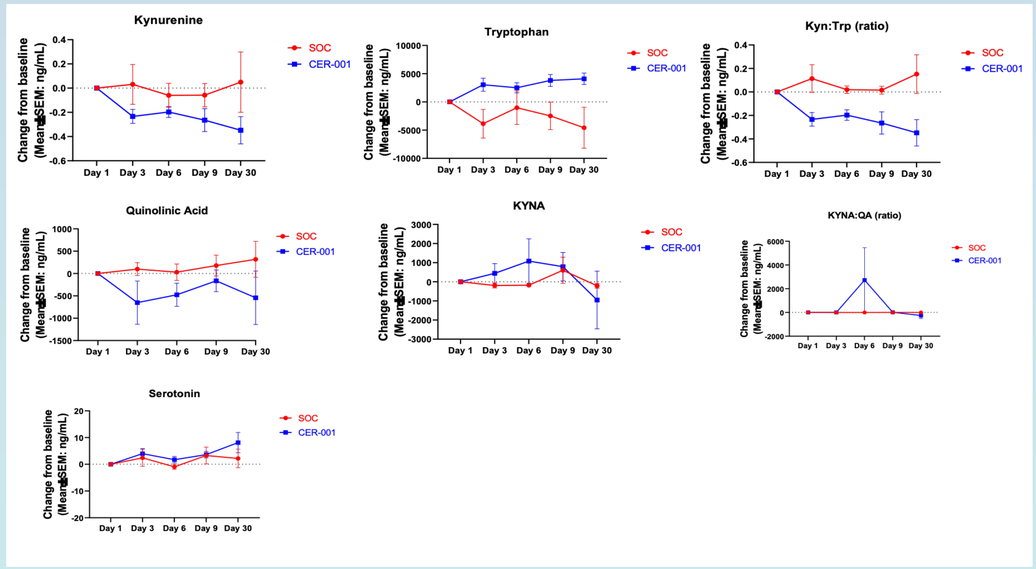

Figure 2. Effect of a recombinant HDL on the kynurenine pathway in the pilot study RACERS

CONCLUSIONS

CER-001 treatment attenuated systemic inflammation, downregulated IDO1, thereby reducing neuroactive metabolites and waste accumulation.