Intensive Care Medicine Experimental 2018, **6**(Suppl 1):32
https://doi.org/10.1186/s40635-018-0196-z

Intensive Care Medicine Experimental

MEETING ABSTRACTS Open Access

Sepsis 2018

Bangkok, Thailand. 1-3 October 2018

Published: 1 October 2018

P1

Safety and pharmacodynamic activity of a novel TREM-1 pathway inhibitory peptide in septic shock patients: phase IIa clinical trial results

Bruno François[1], Xavier Wittebole[2], Ricard Ferrer[3], Jean-Paul Mira[4], Thierry Dugernier[5], Sébastien Gibot[6,7], Marc Derive[8], Peter Pickkers[9], Jean-Jacques Garaud[8], Miguel Sanchez[10], Margarita Salcedo-Magguilli[8], Pierre-François Laterre[2]

[1]Medical-Surgical ICU department and Inserm CIC1435, CHU Limoges, France; [2]Department of Critical Care Medicine, St Luc University Hospital, Université Catholique de Louvain, Brussels, Belgium; [3]ICU department, Vall d'Hebron University Hospital, Barcelona, Spain; [4]Medical ICU, Cochin Hotel-Dieu, AP-HP, Paris, France; [5]ICU department, Clinique St. Pierre, Ottignies, Belgium; [6]Medical ICU department, Hospital Central, CHU Nancy, France; [7]Inserm U1116, Nancy Medical Faculty, Lorraine University, France; [8]Inotrem SA, Paris, France; [9]ICU department, Radboudumc Hospital, Nijmegen, The Netherlands; [10]ICU department, Hospital Clínico San Carlos, Madrid, Spain

Correspondence: Bruno Francois (Bruno.Francois@chu-limoges.fr)

Intensive Care Medicine Experimental 2018, **6(Suppl 1):**P1

Background

Nangibotide (LR12) peptide is a specific TREM-1 inhibitor. In preclinical septic shock models, nangibotide was able to restore appropriate inflammatory response, vascular function, and improved survival. In phase I, nangibotide was found to be safe and well tolerated up to the highest dose (6 mg/kg/h).

Materials and methods

International, multi-center phase IIa randomized, double-blind, two-stage, placebo-controlled study (NCT03158948). Main inclusion criteria were septic shock according to Sepsis 3 definition and nangibotide to be initiated within 24 hours of shock onset. Patients were randomized to receive either placebo, 0.3, 1 or 3 mg/kg/h of nangibotide. Stage-1 investigated ascending doses. In stage-2 patients were randomized to complete 12 patients in each group. Study drug was infused until end of vasopressors + 12h or up to 5 days. Safety data were reviewed by an independent Data Safety Monitoring Board (DSMB). Primary endpoint was safety and tolerability. Patient follow-up period was 90 days.

Results

50 patients were randomized and 49 treated (1 patient died before dosing). All groups were well balanced in terms of baseline characteristics, except for APACHE II score which tend to be non-significantly lower in placebo group. Primary infection source was 40% abdominal, 50% pulmonary and 10% urinary.

Nangibotide was safe and well tolerated in all groups. During the trial, the DSMB did not raise any safety concern. The number of SAEs/AEs and the number of patients with SAEs/AEs was comparable between all groups (Table 1). Most frequent AEs were atrial fibrillation, anemia, pleural effusion and thrombocytopenia.

Ventilator and vasopressors free days alive were similar in all groups (Table 2). All-cause mortality at day-28 was 14% (5/37) in pooled nangibotide groups and 25% (3/12) in placebo group. In the subgroup with sTREM-1 levels above median, the day-5 mortality was calculated as 40% (2/5) and 20% (4/20) in placebo and nangibotide groups respectively. A trend toward a decrease in circulating levels of endothelium injury markers was observed in nangibotide-treated patients.

Conclusion

Nangibotide was shown to be safe and well tolerated in septic shock patients. Although this small exploratory study was not powered to conclude on efficacy, a signal with non significant lower mortality was observed in the nangibotide group. These results support the need of a larger study to demonstrate the role of nangibotide in the treatment of septic shock.

Table 1 (abstract P1). Treatment emergent adverse event and serious adverse event

Patients with at least one	PlaceboN=12	0.3N=13	1.0N=12	3.0N=12	TotalN=49
TEAE	10 (83.3%)	12 (92.3%)	12 (100.0%)	11 (91.7%)	45 (91.8%)
Severe TEAE	8 (66.7%)	6 (46.2%)	5 (41.7%)	4 (33.3%)	23 (46.9%)
TEAE related to the study drug	2 (16.7%)	-	2 (16.7%)	-	4 (8.2%)
Serious AE incl. death	7 (58.3%)	4 (30.8%)	2 (16.7%)	4 (33.3%)	17 (34.7%)

Table 2 (abstract P1). Vasopressors and ventilator free days

Days alive and free of	PlaceboN=12	0.3N=13	1.0N=12	3.0N=12	TotalN=49
Vasopressors median (min/max)	25.5 (0/35)	25.0 (0/33)	25.5 (0/31)	23.0 (0/28)	24.0 (0/35)
IMV median (min/max)	24.0 (0/36)	22.0 (0/35)	25.5 (0/30)	24.0 (0/36)	23.0 (0/36)