Talactoferrin alfa reduces mortality in severe sepsis: Results of a Phase 2 randomized, placebo-controlled, double-blind study

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Introduction: Severe sepsis affects approximately 750,000 people in the USA annually, is increasing in incidence, and causes an estimated ICU mortality of 30% (1). Talactoferrin is an orally administered dendritic cell recruiter and activator with gut barrier protection properties as demonstrated by a reduction in indomethacin-mediated gut permeability (2).

Methods: In this multicenter, randomized, placebo-controlled double blind study, patients with severe sepsis (N=190) were randomized to receive talactoferrin 1.5 g or placebo every eight hours for up to 28 days. The primary endpoint was 28 day all cause mortality. A sample size of 95 patients per arm in this exploratory study provided 80% power to detect a ≥43% reduction in 28-day mortality (from 30% to 17%) in the talactoferrin-arm with a 1-sided α of <0.1. Patients were stratified by clinical site and by the presence or absence of cardiovascular dysfunction (hypotension refractory to ≥ 20 ml/kg crystalloid administration). Eligible patients had onset of severe sepsis within 24 hours prior to randomization. All potentially eligible patients were centrally screened prior to randomization. The quality control process during the conduct of the trial identified errors in drug labeling and randomization that altered drug assignment for some patients. Results as to the primary endpoint were therefore analyzed using logistic regression in a modified intent-to-treat (MITT) population using “as treated” instead of “as randomized” for group assignment. The labeling errors were random and did not effect blinding. A sensitivity analysis taking into account the labeling errors was conducted and supported the findings in the MITT analysis.

Results: The baseline characteristics were similar in both groups.

Baseline Characteristics		
Parameter	Talacteroferrin N=96	Placebo N=94
Mean age	58.1	60.9
Sex (females%)	45.8	50
Positive cultures (%)	46.9	52.1
Site of Infection (%) Lung	45.8	52.1

Blood Urine Intra abdominal Skin	38.5 20.8 13.5 14.6	27.7 22.3 14.9 14.9
Cardiovascular dysfunction (%)	60.4	67
Time from first organ dysfunction to randomization (mean hours)	17.6	17.9
Mean APACHE II score	23.1	23.3
Patients with APACHE II >25 (%)	44.2	42.2
Mean SOFA score at baseline	8.7	9.0
Corticosteroid use (%)	57.3	59.6
Drotrecogin alfa activated use (%)	9.4	5.3

28-Day All Cause Mortality

Parameter	Talactoferrin	Placebo	p Value (2-tailed)	p Value (1-tailed)	Odds Ratio
28 day all cause mortality (N=190)	14.6%	26.6%	0.043	0.021	0.47
28 day all cause mortality (N=190) adjusted for cardiovascular dysfunction	14.6%	26.6%	0.057	0.029	0.49
28 day all cause mortality in those without cardiovascular dysfunction (N=69)	2.6%	22.6%	0.031	0.015	0.093
28 day all cause mortality in those with cardiovascular dysfunction (N=121)	22.4%	28.6%	0.44	0.22	0.72

The incidence of grade 3 to 5 adverse events was similar in both groups.

Conclusions: Using a MITT analysis, talactoferrin reduced 28 day mortality in patients with severe sepsis and met the a priori mortality reduction target per protocol. It was very well tolerated. Further study of talactoferrin is warranted in patients with severe sepsis.

References:
1.Bernard GR,Vincent JL,Laterre PF: Efficacy and safety of recombinant human activated protein C for severe sepsis NEJM:2001 344 (10) 699- 709
2.Troost FJ, Saris WH, Brummer RJ. Recombinant human lactoferrin ingestion attenuates indomethacin-induced enteropathy in vivo in healthy volunteers. Eur J Clin Nutr. 2003 Dec; 57(12): 1579-85.

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