Talactoferrin in Severe Sepsis: Results From the Phase II/III Oral tAlactoferrin in Severe sepsIS Trial

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Objectives: Talactoferrin alfa is a recombinant form of the human glycoprotein lactoferrin, which has been shown to have a wide range of effects on the immune system. This phase II/III clinical trial compared talactoferrin with placebo, in addition to standard of care, in patients with severe sepsis.

Design: Multicenter, randomized, placebo-controlled, phase II/III clinical study.

Setting: Seventy-seven centers in 10 countries.

Patients: Adult (> 18 yr) patients admitted to one of the participating centers with severe sepsis who were receiving antimicrobial therapy and able to take liquid medication by mouth or feeding tube.

Interventions: Patients were randomized to receive either talactoferrin (1.5 g, 15 mL) or placebo three times a day orally or by another enteral route for 28 days or until ICU discharge.

Measures and Main Results: The study was terminated after 305 patients had been enrolled (153 talactoferrin and 152 placebo) because of futility and safety concerns identified by the Data Safety Monitoring Board. There were no significant differences between groups in baseline characteristics including age, sex, site of infection, and severity scores. Twenty-eight-day mortality was higher in talactoferrin-treated patients although this difference was not statistically significant (24.8% vs 17.8% placebo; p = 0.117). The difference was largely the result of differences in patients with shock (talactoferrin, 33/105 [31.4%] vs placebo, 21/104 [20.2%]; p = 0.064); no mortality difference was seen in patients without shock (talactoferrin, 5/48 [10.4%] vs placebo, 6/48 [12.5%]; p = 0.806). In-hospital (43/153 [28.1%] vs 27/152 [17.8%]; p = 0.037) and 3-month (46/153 [30.1%] vs 31/152 [20.4%]; p = 0.036) mortality rates were significantly higher in talactoferrin-treated patients than in patients in the placebo group. The occurrence of treatment-related adverse or serious adverse events was similar between groups.

Conclusions: Administration of oral talactoferrin was not associated with reduced 28-day mortality in patients with severe sepsis and may even be harmful. (Crit Care Med 2015; 43:1832–1838)

Key Words: gut-associated lymphoid tissue; lactoferrin; sepsis; septic shock
Although mortality rates have decreased in recent years (1), sepsis remains the most common cause of death in critically ill patients, with mortality rates reaching 30–50% (1, 2). Despite an improved understanding of the pathogenesis of sepsis and multiple clinical trials of potential immunomodulatory therapies, treatment is still limited to eradication of any underlying infection and organ support (3); there remains an urgent need for effective new therapeutic approaches.

Talactoferrin alfa is a recombinant form of the human glycoprotein, lactoferrin, differing only in the nature of glycosylation (4). Lactoferrin has multiple biological actions including a key role in iron metabolism and important immunomodulatory effects. In a randomized controlled trial in very low-birth-weight neonates, oral bovine lactoferrin supplementation reduced the prevalence of late-onset sepsis (5). Lactoferrin has bacteriostatic and bactericidal effects against certain bacteria and can inhibit the growth of fungi and viruses (6). It is also involved in immune defense with a broad spectrum of activities, including complement activation, stimulation of phagocytosis, and activation of antioxidant and anti-inflammatory mechanisms (6, 7).

Talactoferrin displays similar properties in vitro to those of lactoferrin (8, 9). Talactoferrin has been shown to chemoattract human monocytes in vitro, activate human antigen-presenting cells, including monocytes/macrophages and dendritic cells, and reduce the numbers of human regulatory T lymphocytes in cultured peripheral blood mononuclear cells (8). Oral administration of talactoferrin interacts with gut-associated lymphoid tissue to recruit circulating dendritic cells and stimulate their maturation (9), leading to activation of the innate and adaptive immune systems. Oral talactoferrin protected against indomethacin-induced intestinal damage in healthy volunteers, supporting a potential role in protecting the gut by reducing intestinal permeability (10). Neonatal rats pretreated with oral talactoferrin had less bacteremia and reduced disease severity after intestinal infection with Escherichia coli compared with untreated rats (11). On this preclinical background strongly suggesting immunomodulatory and antimicrobial effects of talactoferrin, a phase II, placebo-controlled study was conducted in 190 patients with severe sepsis. Oral talactoferrin administration (1.5 g, three times a day) was associated with a 12.5% absolute reduction (46.5% relative reduction) in 28-day mortality (12), the primary endpoint, which was sustained during a 6-month follow-up period. The drug was well-tolerated, and there were no differences in adverse events between talactoferrin- and placebo-treated patients. The current phase II/III clinical trial was therefore conducted to evaluate further these initial findings comparing talactoferrin and placebo, in addition to standard of care, in patients with severe sepsis.

METHODS

This was a multicenter, randomized, placebo-controlled, double-blind phase II/III clinical study (ClinicalTrials.gov identifier NCT01273779) in patients with severe sepsis. The protocol was approved by the institutional review board of each participating center, and written informed consent was obtained from either the patient or their next-of-kin.

All adult (> 18 yr) patients admitted to one of the participating centers who were receiving antimicrobial therapy were able to take liquid medication by mouth or feeding tube and had an onset of severe sepsis within the previous 24 hours as defined by meeting all the following criteria were considered for inclusion (for full details of inclusion and exclusion criteria, see Appendix 1, Supplemental Digital Content 1, http://links.lww.com/CCM/B301):

1. Objective evidence of confirmed or suspected infection
2. The presence of at least three components of the systemic inflammatory response syndrome (13).
3. Acute dysfunction of at least one organ system.

Exclusion criteria included lack of consent; pregnancy; severe congestive heart failure (New York Heart Association class IV); end-stage liver disease; inclusion in another investigational clinical trial within 4 weeks of randomization; recent 3rd degree burns involving more than 20% of the body surface area; imminent death; known HIV infection with CD4 count less than 200 cells/mm³ or illnesses associated with end-stage AIDS; or immunosuppressant therapy. Inclusion and exclusion criteria were reviewed with a clinical coordinating center prior to approval for randomization.

Patients were centrally randomized in a 1:1 ratio to the talactoferrin or placebo arm by a permuted block method stratified by septic shock (presence of septic shock limited to 60% of enrolled patients), urinary tract as primary site of infection (limited to 15% of enrolled patients), and geographical region, to receive either talactoferrin (1.5 g, 15 mL) or placebo (with the same phosphate-based buffer used as the diluent for the talactoferrin solution and identical in appearance to talactoferrin, 15 mL) three times daily (every 8 ± 2 hr) orally or by another enteral route, until ICU discharge or for 28 days, whichever came first. The study drug was administered at least 60 minutes after meals or 30 minutes before meals. If the patient required continuous enteral feeding, the feed was interrupted for 60 minutes prior to administration of study drug and not restarted until 30 minutes after administration of study drug.

Initial patient assessment at inclusion included a complete medical and medication history and physical examination. Blood samples were taken for hematology and serum chemistry, international normalized ratio, serum lactate, liver function tests, and serum albumin. Acute Physiology and Chronic Health Evaluation (APACHE) II (14) and Sequential Organ Failure Assessment (SOFA) (15) scores were calculated. After the first dose of study drug, blood samples were taken daily for hematology, serum chemistry, including bilirubin and serum lactate, until day 14 and then weekly. SOFA scores were calculated daily. Fluid balance, vasopressor use, dialysis use, ventilator use, occurrence of new infections (defined as infections occurring at a different site than the sepsis-initiating infection, but not including spread of the original sepsis-initiating infection to a new body site), and concomitant medication were recorded daily.

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All adverse events were recorded prospectively. A serious adverse event (SAE) was defined as any adverse event that resulted in death; was life-threatening (i.e., immediate risk of death); required inpatient hospitalization or prolongation of existing hospitalization; resulted in persistent or significant disability/incapacity; or required intervention to prevent any one of the other outcomes listed above.

**Study Endpoints**

The primary endpoint was 28-day all-cause mortality. Secondary efficacy endpoints included all-cause mortality at 3, 6, and 12 months; number of ICU-free, shock-free, ventilator-free, dialysis-free, organ dysfunction–free days during the 28-day period; occurrence and severity of additional organ dysfunction; occurrence of new infections; and time to initial ICU/hospital discharge after first dose of study drug. Safety endpoints included number of treatment-emergent and study-agent-related adverse events; number of SAEs; number of study drug discontinuations due to adverse events; and anti-talactoferrin antibodies.

**Statistical Analysis**

The study was carried out in two parts (Fig. 1): initially, a phase II component with planned enrollment of 350 patients was conducted (because a previous phase II study of 190 patients had suggested a positive treatment effect without safety issues but study drug allocation issues were identified). A sample size of 350 patients (175 per arm) would have 80% power to detect a 28-day all-cause mortality rate reduction from 30% in the placebo group to 18.1% in the talactoferrin arm using a two-sided Fisher exact test at a significance level of 0.1.

If the phase II results suggested beneficial effects in terms of primary endpoint, safety, and tolerability, it was then planned to enroll 930 patients into a phase III component of the study. This would provide approximately 87% power to detect a more than 9% absolute reduction in 28-day mortality (from 30% to 21% mortality) in the talactoferrin arm with a two-sided p = 0.0497. Three Data Safety Monitoring Board (DSMB) meetings were planned for each phase, the first after 100 patients had been enrolled. For the phase III part of the study, an α allocation of 0.0001 was allocated for each review meeting. There were no predefined stopping rules.

The primary statistical analysis was conducted on an intent-to-treat (ITT) basis. The per protocol population included all randomized patients who received at least six doses of study drug and had no major protocol violations. The safety population included all patients who received at least one dose of study drug, and safety evaluations were performed based on the actual treatment the patient received.

Analysis of the primary endpoint was conducted using a Cochran-Mantel-Haenszel (CMH) test with groups stratified according to the presence or absence of septic shock, the presence or absence of urinary tract as primary site of infection, and geographic region (North America, Europe group 1 [Belgium, Denmark, Germany, The Netherlands], and Europe group 2 [France, Israel, Spain, United Kingdom]). The rationale for the stratification groups was based on published mortality rates for patients with severe sepsis in these countries at the time of the study: Group 1 countries had published ICU mortality rates up to 15%, and group 2 countries had published ICU mortality rates at least 19% (2). Kaplan-Meier curves were constructed and compared using the stratified log-rank test.

The mean/median SOFA score; the number of ICU, shock-free, ventilator-free, dialysis-free, organ-dysfunction-free days; and duration of hospitalization were compared across treatment groups using an analysis of variance or Wilcoxon rank-sum tests. The occurrence of additional organ dysfunction, new infection, and ICU discharge were compared across treatment groups using the CMH method. The following subgroup analyses were defined a priori: age (≤ 60 vs > 60 yr); sex (male vs female); race (white vs nonwhite); presence of cardiovascular dysfunction (yes vs no); presence of urinary tract infection as primary site (yes vs no); region (North America vs European group 1 vs European group 2); APACHE II score (< 25 vs ≥ 25); number of organ dysfunctions (single vs multiple); site of infection (lung, abdomen, urinary tract, and other); type of organ dysfunctions (cardiovascular, respiratory, hematologic, renal, and metabolic).

All statistical analyses were performed using SAS version 8.2 (SAS Institute, Cary, NC). Data are expressed as mean ± SD unless otherwise indicated. Statistical significance was defined as a p value of less than 0.05.

**RESULTS**

The trial was terminated on the recommendation of the DSMB for futility and safety concerns after 305 patients had been randomized (153 talactoferrin

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**Figure 1.** Phase II/III study design plan. PD = pharmacodynamics, PK = pharmacokinetics, TLF = talactoferrin.
and 152 placebo) (Fig. 2). There were no significant differences between the groups in baseline characteristics, including age, sex, site of infection, and severity scores (Table 1).

Efficacy
Twenty-eight-day mortality was higher in talactoferrin-treated patients than in the placebo group although this difference was not statistically significant (38/153 [24.8%] vs 27/152 [17.8%]; p = 0.117) (Fig. 3). The difference was largely the result of differences in patients with shock (talactoferrin, 33/105 [31.4%] vs placebo, 21/104 [20.2%]; p = 0.064); no mortality difference was seen in patients without shock (talactoferrin, 5/48 [10.4%] vs placebo, 6/48 [12.5%]; p = 0.806). In preplanned subgroup analyses, there was a significant difference in mortality rates between talactoferrin- and placebo-treated patients aged older than 65 years (39% vs 24%; p = 0.04). There were no differences in any of the other planned subgroup analyses.

There were no differences between groups in ICU-free, shock-free, ventilator-free, or organ-dysfunction-free days (Table S1, Supplemental Digital Content 1, http://links.lww.com/CCM/B301). In-hospital mortality rates (43/153 [28.1%] vs 27/152 [17.8%]; p = 0.037) and 3-month mortality rates (46/153 [30.1%] vs 31/152 [20.4%]; p = 0.036) were significantly higher in talactoferrin-treated patients than in patients in the placebo group.

Safety
There were no significant differences between groups in the occurrence of treatment-related adverse or SAEs (Table 2). The most common SAEs were multiple organ failure, new sepsis, respiratory failure, cardiac arrest, and pulmonary embolism. The occurrence of new infections was similar in the two groups (40 [26%] for talactoferrin and 32 [21%] for placebo).

DISCUSSION
In this phase II/III study, enteral administration of talactoferrin alfa was associated with increased in-hospital and 3-month mortality in patients with severe sepsis, although 28-day mortality rates were not significantly different. These results are in contrast to those reported in the earlier phase II randomized controlled trial (12), in which 28-day mortality was 14.4% in the talactoferrin group and 26.9% in the placebo group (two-sided p = 0.052), representing a 12.5% absolute and a 46.5% relative reduction in mortality.

There are several possible reasons for the different results of the present study compared with those of the earlier phase II trial (12). First, the results of the first study may simply have been the effects of random chance, and the drug was indeed not effective. Although preclinical data strongly suggest immunomodulatory and antibacterial effects and clinical use, largely in patients with various solid tumors (16, 17), has not demonstrated specific safety issues, there are no published data to support a biological effect of talactoferrin in patients with sepsis. Second, the patient populations in the two studies may have differed, although severity of illness, as assessed by SOFA and APACHE II scores, site of infection, and age were similar. Third, unknown improvements in patient management that led to a reduced placebo mortality rate may have made it more difficult to demonstrate a difference in mortality compared to the earlier study. Indeed, the required sample size in the present study was calculated based on a placebo mortality rate of 30%, but the actual rate was just 18%. A
similar association between a lower placebo mortality rate and an apparent loss of clinical efficacy was seen in the PROWESS-Shock study of drotrecogin alfa in septic shock (18).

It is unclear why patients with septic shock fared worse with talactoferrin compared with those treated with placebo. In the earlier phase II study (12), patients with septic shock also benefitted less from talactoferrin (28-d mortality, 22.4% talactoferrin vs 28.6% placebo; \( p = 0.439 \)) than patients without shock (28-d mortality, 2.6% vs 23.3%; \( p = 0.026 \)). These data suggest that patients with shock may not be an appropriate target population for treatment with talactoferrin. Interestingly, mortality differences were not significant at the widely used and Food and Drug Administration mandated 28-day cutoff, but they were significant at the longer time period of 3 months, as also reported in other recent trials (19–21), raising the possibility that prolonged outcome data should be mandatory when reporting results of clinical trials.

These results add to the long list of studies in similar populations of patients with sepsis that have culminated in negative findings despite promising preclinical and early clinical studies, most notably

<table>
<thead>
<tr>
<th>Variable</th>
<th>Talactoferrin ((n = 153))</th>
<th>Placebo ((n = 152))</th>
<th>( p )</th>
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<tbody>
<tr>
<td>Age, yr, mean (sd)</td>
<td>62.9 (16.5)</td>
<td>61.6 (16.2)</td>
<td>0.488</td>
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<tr>
<td>Sex (male), ( n ) (%)</td>
<td>82 (53.6)</td>
<td>97 (63.8)</td>
<td>0.081</td>
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<td>Diabetes, ( n ) (%)</td>
<td>46 (30.1)</td>
<td>66 (43.4)</td>
<td>0.017</td>
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<tr>
<td>Steroid use (any), ( n ) (%)</td>
<td>94 (61.4)</td>
<td>85 (55.9)</td>
<td>0.353</td>
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<td>Site of infection, ( n ) (%)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Lung</td>
<td>71 (46.4)</td>
<td>62 (40.8)</td>
<td>0.356</td>
</tr>
<tr>
<td>Urine</td>
<td>26 (17.0)</td>
<td>27 (17.8)</td>
<td>0.881</td>
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<tr>
<td>Abdomen</td>
<td>17 (11.1)</td>
<td>31 (20.4)</td>
<td>0.028</td>
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<tr>
<td>Skin</td>
<td>14 (9.2)</td>
<td>15 (9.9)</td>
<td>0.848</td>
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<td>Acute Physiology and Chronic Health Evaluation II score, mean (sd)</td>
<td>25.8 (7.0)</td>
<td>25.5 (6.7)</td>
<td>0.703</td>
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<tr>
<td>Sequential Organ Failure Assessment score, mean (sd)</td>
<td>9.3 (3.2)</td>
<td>8.9 (3.1)</td>
<td>0.266</td>
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<tr>
<td>No. of organ dysfunctions, mean (sd)</td>
<td>2 (1)</td>
<td>2 (1)</td>
<td>0.998</td>
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<tr>
<td>Type of organ dysfunction, ( n ) (%)</td>
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<td></td>
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<tr>
<td>Shock</td>
<td>101 (66.0)</td>
<td>98 (64.5)</td>
<td>0.811</td>
</tr>
<tr>
<td>Respiratory</td>
<td>83 (54.2)</td>
<td>84 (55.3)</td>
<td>0.909</td>
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<td>Renal</td>
<td>40 (26.1)</td>
<td>46 (30.3)</td>
<td>0.447</td>
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<tr>
<td>Hematologic</td>
<td>25 (16.3)</td>
<td>21 (13.8)</td>
<td>0.632</td>
</tr>
<tr>
<td>Metabolic</td>
<td>60 (39.2)</td>
<td>54 (35.5)</td>
<td>0.554</td>
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</table>

Figure 3. Kaplan-Meier plot of overall survival at 28 days for the two groups of patients.
the withdrawal of activated protein C after a second random-ized controlled trial (18) failed to confirm the survival benefits seen in a first pivotal study (22). Over the years, various sug-gestions have been made to explain our apparent inability to translate plausible interventions from the laboratory to large-scale clinical trials. It is becoming increasingly clear that the main problem lies with correct identification of the population of patients who would actually benefit from the intervention under study (23). Correcting this problem remains a challenge because our ability to diagnose sepsis accurately and early in its course is still limited, as is our capacity to rapidly identify immunologic and other biologic phenotypes to determine optimal timing and dosing of an intervention. Our understand-ing of the mechanisms by which many of the proposed interventions act in the complex sepsis patient, compared to well-controlled and carefully selected animal models, is also frequently inadequate to be able to appropriately target interventions at one or more clinical or laboratory variables. The development of more specific inflammatory/immunological/biochemical biomarkers to diagnose sepsis and characterize these patients is urgently needed to better identify suitable patient populations for therapeutic studies in the future.

CONCLUSION
Administration of oral talactoferrin was associated with a trend to increased 28-day mortality in patients with sepsis, despite promising results from an earlier phase II study. Clinical trials of sepsis interventions need to be based on improved patient characterization to focus on those who are most likely to benefit from the treatment in question.

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<table>
<thead>
<tr>
<th>Variable</th>
<th>Talactoferrin (n = 157)</th>
<th>Placebo (n = 148)</th>
<th>p</th>
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<tr>
<td>Any adverse event, n (%)</td>
<td>145 (92.4)</td>
<td>141 (95.3)</td>
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<td>Treatment-related adverse events, n (%)</td>
<td>16 (10.2)</td>
<td>21 (14.2)</td>
<td>0.298</td>
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<td>Serious adverse events, n (%)</td>
<td>74 (47.1)</td>
<td>51 (34.5)</td>
<td>0.027</td>
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<td>Treatment-related serious adverse events, n (%)</td>
<td>2 (1.3)</td>
<td>3 (2.0)</td>
<td>0.677</td>
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<td>Adverse events resulting in study drug discontinuation, n (%)</td>
<td>4 (2.5)</td>
<td>9 (6.1)</td>
<td>0.160</td>
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<tr>
<td>Adverse events resulting in death, n (%)</td>
<td>44 (28.0)</td>
<td>28 (18.9)</td>
<td>0.079</td>
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REFERENCES