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A randomized trial of Mycobacterium w in severe sepsis

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ABSTRACT

Purpose: The aim of this study was to evaluate the efficacy of Mycobacterium w (Mw), an immunomodulator in severe sepsis.
Methods: Patients 18 years or older with severe sepsis were randomized within 48 hours of first organ dysfunction to receive either intradermal Mw or saline. The primary end point was 28-day mortality, whereas the secondary end points were ventilator days, intensive care unit (ICU) and hospital length of stay, and delta Sequential Organ Failure Assessment (SOFA) score.
Results: Fifty patients with severe sepsis (25 Mw, 25 control) were included in the study. There were 7 and 8 deaths in the Mw and control groups, respectively ($P = 0.51$). The days on mechanical ventilator were significantly lesser in the Mw group compared with control (median, 6 vs 9; $P = 0.025$). The median ICU and hospital length of stay was significantly less in the Mw arm (7 vs 12 days [$P = 0.006$] and 10 vs 16 [$P = 0.007$], respectively). The delta SOFA score was significantly higher in the control arm ($P = 0.027$). There was a higher incidence of secondary bacterial infections in the control group ($P = 0.009$).
Conclusion: The use of Mw in severe sepsis was associated with significant reduction in days on mechanical ventilation, ICU and hospital length of stay, lower incidence of nosocomial infection, and delta SOFA score.

1. Introduction

Sepsis accounts for 6% to 30% of all intensive care unit (ICU) admissions with a mortality rate of 10% to 80% depending on the severity [1,2]. In the last 2 decades, no treatment has been shown to reduce mortality in patients with severe sepsis. Several large trials directed against inflammatory pathway and coagulation cascade have failed to demonstrate any benefit in sepsis [3–6]. Sepsis represents a complex cascade of events occurring in response to invading microbial agents. Recent evidence suggests that sepsis continuum includes an immune paralytic state, which may play a significant role in sepsis [7]. Lipopolysaccharide, a cell wall component of gram-negative organisms combines with toll-like receptor 4 (TLR4) on the host leukocyte and other immune cells (macrophages, neutrophils, dendritic cells, and natural killer cells). The binding of lipopolysaccharide with TLR4 activates 2 major intracellular pathways, MyD88 pathway, involved in proinflammatory responseand a toll/interleukin-1 (IL-1) receptor domain–containing adaptor protein inducing interferon-β (IFN-β) (TRIF) pathway, leading to production of type 1 IFNs that stem the inflammatory response and cause a state of immune suppression [8–10].

In a postmortem analysis of 40 patients who died of sepsis, it was demonstrated that significantly reduced levels of cytokine secretion (tumor necrosis factor, IFN-γ, IL-6, and IL-10) occurred at 5 hours by anti-CD3/anti-CD28–stimulated splenocytes. The cytokine secretion was generally less than 10% in sepsis compared with controls and was independent of age, duration of sepsis, corticosteroid use, and nutritional status [7]. The concept of immune suppression in sepsis is further exemplified in a study involving 41 patients with sepsis [11]. In this study, there was a marked reduction in the T cell receptor β chain diversity that was associated with increased mortality and a higher risk of developing nosocomial infection [11]. It has also been demonstrated that there is decreased ex vivo proliferation of Th1 and an increased Th2 immune response [12,13]. Thus, it seems that sepsis is characterized by an initial "cytokine storm" and a later "immune paralysis." Modulating this response and overcoming immune paralysis may help in improving the outcome in severe sepsis.

Mycobacterium w (Mw) is a nonpathogenic, rapidly growing atypical mycobacterium classifiable in Runyon group IV. It shares T and B cell determinants with *Mycobacterium leprae* and *Mycobacterium tuberculosis*. When heat-inactivated and administered intradermally, Mw is an immune modulator that evokes antigen-specific cell-mediated immunity and augments Th1 type of cross-reactive response [14–16]. We hypothesized that Mw by its TLR4 agonist activity may help in restoring immunity, thereby improving outcomes in severe sepsis. In this randomized trial, we evaluate the efficacy of Mw in severe sepsis.

2. Materials and methods

2.1. Study design

This was a randomized, double-blind, 2–parallel arm, comparative controlled prospective study to assess the efficacy of Mw in combination

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with standard therapy in patients with severe sepsis. The study protocol was approved by the Institute Ethics Committee, and a written informed consent was obtained from all patients or their next of kin.

2.2. Setting

The study was conducted in the respiratory intensive care unit (RICU) of this Institute. All patients with suspected gram-negative sepsis admitted in the RICU between October 2012 and November 2013 were enrolled in the study. The RICU is an 8-bed ICU catering to the care of medical critically ill patients. It comprises a team of 11 physicians (6 consultants and 5 residents specialized in pulmonary and intensive care). Two physicians (residents) are present round the clock and are supported by the nursing staff with a nurse-to-patient ratio of 2-3:1.

2.3. Randomization

Patients were randomized 1:1 to the experimental or the control arm. Randomization sequence was computer generated, and the sequence code was placed in an opaque sealed envelope, which was opened by a physician at the time of enrollment of a particular patient.

2.4. Patients

All consecutive patients 18 years or older with severe sepsis were screened for participation. Severe sepsis was defined by presence of at least 2 or more criteria for systemic inflammatory response syndrome (temperature >38.5°C or <36.0°C; heart rate >90 beats/min; respiratory rate >20 breaths/min or $Paco_2$ <32 mm Hg; and leukocyte count >12 000 cells/μL or <4000 cells/μL or >10% immature band forms) with presumed or documented evidence of gram-negative infection, and one or more organ dysfunction. Patients with any of the following were excluded: pregnancy, gram-positive culture, only fungal infection as source of sepsis, received cardiopulmonary resuscitation, on immunosuppressive therapy, and unwilling to provide consent.

2.5. Study protocol

Patients in the experimental arm (Mw) in addition to standard care received single daily dose of 0.3 mL of Mw (heat-inactivated Mw [0.5×10^9]; Immuvac, Cadila Pharma, Ahmedabad, India) in the deltoid region for 3 consecutive days. The drug was administered within 24 hours of randomization and/or 48 hours of first organ dysfunction (cardiovascular system dysfunction: systolic blood pressure ≤90 mm Hg or the mean arterial pressure ≤70 mm Hg for at least 1 hour despite adequate fluid resuscitation or the use of vasopressors to maintain a systolic blood pressure or mean arterial pressure of >90 and >65 mm Hg, respectively; renal dysfunction: urine output <0.5 mL kg^{-1} h^{-1} for 2 consecutive hours despite adequate fluid resuscitation; respiratory system dysfunction: Pao_2/Fio_2 ≤300; hematologic dysfunction: platelet count <100 000/mm^3 or decrease by 50% in the 3 days preceding enrollment; unexplained metabolic acidosis: pH ≤7.30). Patients were observed for any local or systemic adverse effects that could be associated with institution of the study drug. In the control arm, 0.3 mL/d of saline was injected intradermally at the insertion of deltoid muscle near the middle of the arm, in addition to standard care.

2.6. Study procedures

Baseline demographic and clinical profiles were recorded for all the patients. Patients were followed up for 28 days. Liver and renal function tests, arterial blood gas analysis, complete blood count, and Sequential Organ Failure Assessment (SOFA) scoring were done each day until day 14 and then on day 28, if the patient was still admitted in the hospital. Delta SOFA was calculated by subtracting the initial (day 1) SOFA from maximum SOFA during the hospital stay. A delta SOFA of ≥2 and 3 were taken as organ dysfunction and organ failure, respectively [17]. All cultures were obtained before institution/change of the first dose of antibiotics. Antibiotics were administered as per the local sensitivity pattern and within 1 hour of presentation in the ICU. All patients with shock were given 30 mL/kg of crystalloids as a bolus to achieve a central venous pressure of at least 15 cm and 8 to 10 cm of saline in non–acute respiratory distress syndrome and acute respiratory distress syndrome patients, respectively. Patients not achieving a target mean blood pressure of greater than 65 mm Hg or urine output of 0.5 mL kg^{-1} h^{-1} were started on vasopressor support. All patients received prophylaxis for deep venous thrombosis and stress ulcer, as per protocol. Enteral route was the preferred route for administration of nutrition.

2.7. Study outcomes

The primary outcome of the study was 28-day all-cause mortality. The secondary outcomes were delta SOFA scores, ventilator-free days, time-to-vasopressor withdrawal, and ICU and hospital lengths of stay.

2.8. Statistical analysis

The efficacy was evaluated as per intention-to-treat for all patients randomized in the study irrespective of the doses of the study drug received. The 28-day mortality was evaluated using χ^2 test at 5% type I error level. Mann-Whitney *U* test was used to assess statistical significance of nonparametric measures.

3. Results

There were 278 admissions during the study period, of which 50 patients were enrolled in this study. The baseline parameters were similar in the 2 groups (Table 1). The study population comprised predominantly of male subjects. Patients in the Mw group were younger than the control arm, albeit not statistically significant. The Mw group had lower hemoglobin and platelet count, and higher baseline SOFA scores than the control group (Table 1). Sepsis of unknown origin followed by community-acquired pneumonia was the common presenting diagnosis. Comorbidities were equally distributed in both the groups. Of the 50 patients, 49 needed invasive mechanical ventilation for respiratory support on presentation. At baseline, culture positivity was seen in 4 and 3 patients in the Mw and control groups, respectively (Table 2).

There were 7 deaths in the Mw group and 8 in the control group (Table 3). Patients in the Mw group had significant improvements in the secondary outcomes. The Mw group had improvement in organ dysfunction as reflected by decline in SOFA score over time (Fig. 1) and a significantly lower delta SOFA (Table 3). In a multivariate model, Mw was associated with lower odds of developing organ dysfunction (delta SOFA ≥2) even after adjusting for age, hemoglobin, and platelet count (Table 4). There was significant reduction in days on ventilator, and length of stay in the ICU and hospital in the Mw group; there was also a trend toward lesser requirement of vasopressors (Table 3).

The Mw group had significantly lesser incidence of secondary bacterial infection compared with the control group (Table 3). Ventilator-associated pneumonia (VAP) was the commonest secondary bacterial infection in both groups; 12 patients in the control group developed VAP, whereas 5 patients in the Mw group had occurrence of VAP (Table 5). *Acinetobacter baumannii* was the commonest organism responsible for nosocomial infections. Catheter-related blood stream infection (CRBSI) occurred in 2 and 6 cases in the Mw and control groups, respectively. Six patients had both VAP and CRBSI: 2 in the Mw group and 4 in the control arm.

4. Discussion

The use of Mw in combination with standard care did not reduce 28-day mortality in patients with severe sepsis. Nevertheless, we found a

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