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Review

Thymosin alpha1 based immunomodulatory therapy for sepsis: a systematic review and meta-analysis

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ABSTRACT

Objectives: Thymosin alpha1 (Tα1) is considered a promising immunomodulatory drug. However, it is still unclear whether Tα1 should be recommended for the management of sepsis. Here we conducted a systematic review and meta-analysis to assess the efficacy of Tα1 based immunomodulatory therapy on the clinical outcomes of septic patients.

Methods: We searched for relevant clinical trials published before Dec. 12, 2014 through electronic databases. All articles about Tα1 based immunomodulatory therapy for sepsis were included regardless of language. Two authors independently selected studies, extracted data and assessed the quality of each included study. We polled the data related to all-cause mortality with Review Manager 5.1.

Results: Twelve controlled trials were evaluated in all. Tα1 based immunomodulatory therapy had a significant trend toward lower all-cause mortality among patients with sepsis (pooled risk ratio 0.68, 95%CI 0.59-0.78, $p < 0.00001$, 12 trials, n = 1480).

Conclusions: Tα1 based immunomodulatory therapy was associated with a lower mortality in septic patients. Nevertheless, these findings should be interpreted cautiously because of the poor quality and small number of participants of the included trials. More well-designed worldwide multicenter clinical trials are needed to provide a conclusive guideline for clinical practice.

1. Introduction

Severe sepsis remains one of the major causes of mortality among critically ill patients, even under modern critical care management, and it also leads to heavy economic burden worldwide[1–3]. It affects more than 751,000 patients just in the United States per year[1], with a mortality ranges from 20% to 45.8%[4–6]. It is well known that sepsis is a syndrome characterized by systemic inflammation resulting from severe infection, followed by acute multiple-organ failure, and even death[7–9]. Early appropriate use of antibiotics, aggressive source control and hemodynamic management were related to improved outcomes in terms of mortality in severely septic patients[9–11]. However, there are still no specific drugs or treatment strategies for this serious disorder. Although there were several promising drugs under investigating for the treatment of sepsis, such as drotrecogin alfa (human recombinant activated protein C)[12], eritoran (Toll-like receptor 4 blocker)[13], and talactoferrin (human recombinant lactoferrin)[14], none of them achieved a satisfactory result because of failure to confirm the efficacy[12], unsuccessfully getting efficacious endpoint[13] and toxic effects[14], respectively. For these reasons, it is urgent to find new directions for sepsis studies[14–18].

Two studies conducted by Limaye et al.[19] and Luyt et al.[20] shed light on this challenge. They uncovered an underlying mechanism of this critical illness by proving the concept that the critical illness can induce immunosuppression. Since they found that most septic patients admitted to intensive care units had septic foci[21], growing evidence has indicated that early sepsis is characterized by hyperinflammatory symptoms, such as fever, altered mental status and organ dysfunction[22]. As sepsis persists, immune depression occurs, which is mediated by mechanisms including depletion of $CD4^+$ T, $CD8^+$ T, B, and dendritic cells as well as decreasing production of both proinflammatory and antiinflammatory cytokines[23–29]. Therefore, as discussed by Richard Hotchkiss[30], sepsis could be considered to be a complex immune disorder with both a hyperinflammatory stage and subsequently a hypoinflammatory stage[31]. So severely septic patients might benefit from therapies that reinforce host immunity[23,24,32].

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Thymosin alpha1 (Tα1), a thymus derived immunomodulatory peptide[33], is widely used in clinical trials for the treatment of immunodeficiency related diseases[34–36]. It has been proven efficient in the treatment of chronic B and C hepatitis as well as some types of cancers[34–37]. It has also been extensively described as the immunomodulatory activity on innate immune cells, such as polymorphonuclear leucocytes, dendritic cells, and macrophages[38]. Adaptive T helper immunity was also reported as being able to be affected by Tα1[39]. The results of animal experiments significantly implied that Tα1 can help mice survive sepsis[40], whereas the clinical trials regarding the effect of Tα1 based immunomodulatory therapy on mortality of severely septic patients did not achieve a consistent conclusion.

In order to unequivocally ascertain the role of Tα1 on sepsis, many efforts have been made. A systematic review conducted by Yu et al.[41] concluded that Tα1 could ameliorate immunosuppression caused by severe sepsis. However, a significant improvement in mortality was not observed. After that, some trials with more participants were reported. Therefore we performed this review of the controlled trials involving Tα1 based immunomodulatory therapies in septic patients to assist practitioners and researchers appropriately in determining the efficacy of this strategy and guiding further research in this area.

2. Methods

The literature search, study selection, data extracted and assessment of risk of bias were performed independently by two authors (CC Li and LY Bo) using the standard strategy mentioned below. All discrepancies were firstly discussed and resolved by consensus, and the senior reviewer (Jin FG) was consulted for the final decision if consensuses were not reached.

2.1. Search strategy

We performed a computer-aided literature search using databases including EMBASE, MEDLINE (PubMed), Cochrane Central Register of Controlled Trials in English and China National Knowledge Infrastructure (CBM), VIP Database for Chinese Technical Periodicals (VIP) in Chinese to retrieve potentially relevant controlled trials. We mainly used the following search terms: Thymosin alpha1, Thymosin, Thymus, Maipuxin, Thymalfasin, and Zadaxin. All articles and conference abstracts about Tα1 based immunomodulatory therapies for sepsis were identified regardless of language.

2.2. Study selection

Studies were included if they met all of the following criteria: (1) Participants: patients had to be diagnosed with sepsis. (2) Type of studies: studies were eligible only if they were controlled clinical trials. (3) Type of interventions: studies used Tα1 based immunomodulatory therapies. Studies were excluded if they did not provide outcomes related to mortality or were duplicated publications.

2.3. End points and data extraction

The primary end point was all-cause mortality, and the second end point was adverse events. For all-cause mortality, we used 28-day mortality. If 28-day mortality could not be acquired, we used ICU or hospital mortality instead. We also extracted and collected the relevant information about each study, such as characteristics of studies, characteristics of participants, immunomodulatory therapy strategies and types of outcomes.

2.4. Quality assessment

We evaluated the quality of the included trials independently by two authors (CC Li and LY Bo). The methodological qualities of included controlled trials were evaluated using a modified Jadad Scale[42]. The full score is 7, with 4-7 being regarded as high quality and 1-3 as low quality. We also assessed the risk of bias using the domain-based evaluation that includes: selection bias, performance bias, detection bias, attrition bias, reporting bias and other bias[43].

2.5. Data processing and statistical analysis

Treatment effects on total mortality were pooled to obtain estimates of summary effect. For dichotomous outcomes, we calculated relative risk (RR) and 95% confidence interval (CI) of every study and estimated the overall Mantel-Haenszel (M-H) RR as well as the 95% CI. I^2 statistic and Chi^2 test were used to examine the heterogeneity, and if significant heterogeneity ($p \leq 0.10$ for Chi^2 test results or $I^2 \geq 50\%$) was obtained we used a random-effects model, and otherwise a fixed-effects model was used. Subgroup analyses were performed according to the immunomodulatory therapy strategy, type of blind, outcome measures and Tα1 dose. Sensitivity analyses were performed by excluding every single study or subgroup, re-analyzing and comparing with the original RR to test the robustness of our results. In addition we reanalyzed the data by excluding the low quality studies and only pooling the data from high quality studies (modified Jadad Score ≥ 4). To evaluate publication bias, we constructed a funnel plot and calculated a classic fail-safe number to estimate the number of missing studies that needed to yield a statistically non-significant overall effect. Hypothesis testing was considered statistically significant if two-side p-value≤ 0.05. Data synthesis and subgroup analyses were done using Review Manager (version 5.1), and classic fail-safe N was estimated using Comprehensive Meta Analysis (V2).

3. Results

We identified 465 potentially relevant articles in the initial search, and twelve studies (N = 1480 patients)[44–55] satisfied the inclusion criteria. All of them were included in the meta-analysis (Figure 1). The key characteristics of included trials were summarized in Additional file 1. When stratified by types of immunomodulation therapy strategies, 6 studies were treated with thymosin alpha1 and 6 studies with thymosin alpha1+ulinastain (Tα1+UTI). Stratified by outcome measures, 10 studies reported 28-day mortality and 2 studies reported ICU mortality. Stratified by Tα1 doses, 8 studies used high dose Tα1 (>1.6 mg/day) and 4 studies used low dose Tα1 (≤1.6 mg/day). The mean age of the participants ranged from 43.5 to 67.37. The mortality rate of control groups ranged from 33.33% to 65.45%.

When assessing the quality of the included studies, we found 7 studies were rated as high quality according to the modified Jadad Scale. As presented in Additional file 2: Table S2, most of the included studies were of high risk or unclear in reporting random sequence generation as well as allocation concealment. Blinding of participants and personnel was adequate only in three studies. All studies were of low risk for detection bias and attrition bias. The results about the quality of the studies indicated that the final results of this meta-analysis may be potentially not robust, and need further subgroup and sensitivity analysis.

Overall, as shown in Figure 2, the effect of Tα1 based immunomodulatory therapy on all-cause mortality was statistically significant (M-H RR, 0.68 [95%CI, 0.59-0.78]; $p < 0.00001$). Overall mortality of 12 studies was 35.27% and the mortality in the