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Letter to the Editor

Ulinastatin and Thymosin *a*1 Therapy in Adult Patients with Severe Sepsis: A Meta-analysis with Trial Sequential Analysis of Randomized Controlled Trials

Heng FAN [1, 2], ***Yu ZHAO*** [3], ****Jian Hua ZHU*** [1], ***Ji Hui YE*** [1], ***Xue Qing YAO*** [2]

1. *Dept. of Intensive Care Unit, Ningbo First Hospital, Ningbo, China*
2. *Dept. of General Surgery, Guangdong General Hospital, Southern Medical University, Guangzhou, China*
3. *Dept. of Nephrology, Ningbo Urology and Nephrology Hospital, Ningbo, China*

***Corresponding Author:** Email: peterbenny@163.com

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Dear Editor-in-Chief

Sepsis is an important cause of critical illness and represents a global problem with increased number of death for the patients of critical care unit. Removal of the inflammatory mediators and/or bacterial components from bloodstream may down-regulation of an overactive immune response that result in end-organ damage for patients with severe sepsis (1). A large number of studies have investigated the association between Ulinastatin (UTI) plus Thymosin α1 (Tα1) therapy and severe sepsis, but the results were inconsistent. We performed a meta-analysis of randomized controlled trials (RCTs) to definite the relationship between UTI plus Tα1 therapy and severe sepsis from all eligible studies via analyzing the effects of the potential confounding variables. We searched MEDLINE, EMBASE, the Cochrane library database and Chinese databases (CNKI, Wanfang Data, CBM, and VIP) that evaluated the effect of UTI plus Tα1 therapy on clinical outcomes in adults with severe sepsis. The search terms used were ("ulinastatin" or "UTI" or "Urinary Trypsin Inhibitor") and ("thymosin" or "zadaxin" or "thymalfasin") combined with ("sepsis" or "systemic inflammatory response syndrome" or "multiple organ dysfunction syndromes"). The Cochrane collaboration tool was used to evaluate the risk of bias, and Grades of Recommendation, Assessment, Development and Evaluation approach to assess the quality of evidence. The primary outcome was 28-d mortality. We calculated risk ratios (RRs) or mean differences (MDs) and 95% confidence intervals (CIs) using a random effects model. A two-tailed *P* value less than 0.05 was considered a significant level except for where a certain *P* value has been given. Data analysis was performed by using Review Manager, version 5.2 (RevMan; The Nordic Cochrane Centre, The Cochrane Collaboration 2010, Copenhagen, Denmark).

Four RCTs enrolling 818 patients were included in the meta-analysis (2–5). The main characteristics of the four included RCTs are presented in the Electronic Supplementary Material (ESM). Overall, two RCTs were categorized as at lower risk of bias (2, 3), and two as at unclear risk of bias (4, 5). Data on primary outcome were provided in all four trials (818 patients) (2-5). The cumulative z curve crossed the conventional boundary for benefit but did not cross the trial sequential monitoring boundary for benefit, showing that currently cumulative evidence is inconclusive. UTI plus Tα1 therapy was associated with a reduction in mortality (RR: 0.68, 95% CI: 0.57 to 0.81, $P < 0.00001$, $I^2 = 0\%$, Fig.

1). For secondary outcomes, UTI plus Tα1 therapy had no effect on length of ICU stay (weighted mean difference, WMD -2.95 days, 95% CI -6.79 to 0.89, four RCTs (2-5)) and duration of supportive ventilation (WMD -0.61 days, 95% CI -3.39 to 2.16, four RCTs (2-5)). The UTI plus Tα1 therapy level of evidence was moderate for 28-d mortality, and low for length of hospital stay and length of ICU stay.

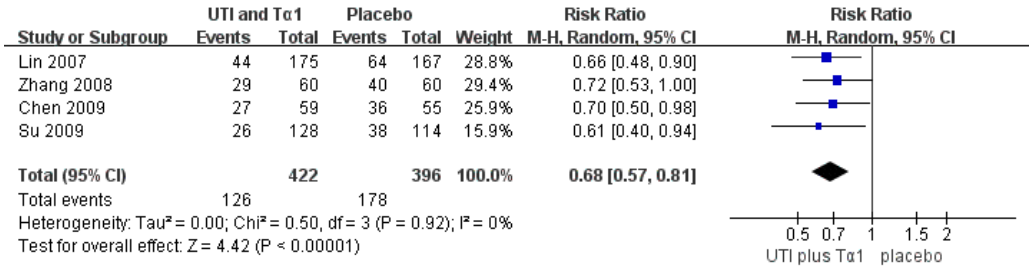

Fig. 1: Forest plot depicting mortality

In conclusion, our meta-analysis suggests that UTI plus Tα1 therapy can reduce the ICU mortality and improve the progress of adult patients with severe sepsis. However, caution should be used to translate these findings to clinical protocols, because data were limited by insufficient information size. Further, RCT trials with larger sample studies are necessary, and the suitable dose of UTI and Tα1 remain need more investigation.

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