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The Reset-α Study: A Double Blind, Randomized, Multi Centre, Phase III Trial for the Efficacy and Safety of Thymosin α-1 (Tα1) in Sepsis Patients

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Abstract

Aims and Background: Thymosin alpha 1 (Tα1) has shown promise as an adjuvant treatment for sepsis. This study evaluated the efficacy and safety of Tα1 versus placebo, both combined with standard care, in patients with sepsis.

Methods: This was a multicenter, randomized, double-blind, placebo-controlled Phase III trial. Patients received four injections of Tα1 (2 vials twice daily) or placebo subcutaneously from Day 1 to Day 7 along with standard care. The primary endpoint was the change in Sequential Organ Failure Assessment (SOFA) score. Secondary endpoints included incidence of emerging infections, pathogen clearance rate, ICU/ventilator/vasoactive-agent-free days, changes in lymphocyte markers (CD4/CD8, NLR), TNFα , CRP, mortality, and adverse events (AEs).

Results: Of 131 screened, 123 patients were enrolled across 10 sites. Mean SOFA score reduction was greater in the Tα1 arm (-3.5 ±1.7) versus placebo (-1.13 ±1.2), showing statistical significance. ICU and vasoactive-agent-free days were also significantly higher in the Tα1 arm. Both groups showed reductions in TNF, NLR, and CRP; however, only the Tα1 group showed statistically significant reductions from baseline on Day 7. Mortality was lower in the Tα1 group. Treatment-emergent AEs occurred in 48.4% of Tα1 patients and 72.1% of placebo patients, mostly mild and resolved without sequelae. Septic shock occurred in 3 (Tα1) vs. 5 (placebo) patients.

Conclusion: Tα1 appears to be a safe and effective adjunct to standard care in sepsis, demonstrating significant improvements in organ dysfunction and clinical outcomes.

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Keywords: Thymosin alpha1; Sepsis; SOFA score; CTRI/2022/09/045538.

1. Introduction

A dysregulated host's vulnerable response to infection can result in sepsis, a potentially fatal organ failure. In absence of medical help, it can cause severe tissue damage and organ failure. [1] Three stages of sepsis are sepsis, severe sepsis, and septic shock. Sepsis associated with hypotension and perfusion abnormalities despite the provision of adequate fluid resuscitation is septic shock. [2] According to figures published in 2020, 48.9 million sepsis cases and 11 million deaths occurred worldwide, accounting for 20% of all deaths worldwide. [3] In 2019, antimicrobial resistance was responsible for 4.95 million deaths, with 1.27 million being directly related to it.[4] Sepsis is a multi-dimensional breakdown of the sensitive immunological equilibrium between inflammation and anti-inflammation. Upregulation of pro- and anti-inflammatory pathways causes systemic release of cytokines, mediators, and pathogen-related molecules, activating coagulation and subsequent cascades leading to progressive tissue damage, leading to multi-organ dysfunction.[5, 6] Therefore, modifying the host immune response may help eliminate systemic infection and facilitate the recovery of organ function.

Thymosin alpha 1 (Tα1), an immunological modulator, may help for the physiologic stimulation and restoration of the dysregulated immune response in sepsis patients. Earlier preclinical research has demonstrated that Tα1 influenced innate immunity in a variety of ways. Tα1 can activate innate immune system effector cells, such as macrophages, DCs, and peripheral blood mononuclear cells. [7, 8] Furthermore, Tα1 enhances the effectiveness of adaptive immunity. [9] It can enhance T cell response, attenuate antibody production, and improve cytotoxic T cell and natural killer cell responses. [10] A review study by F. Pei et al. on studies of Tα1 alone demonstrated that it is a promising adjuvant therapy for sepsis and shown that Tα1 by itself or in combination with anti-inflammatory drugs has the potential to increase sepsis survival. [11] In the early 21st century, several small-scale trials have been carried out to evaluate the efficacy of Tα1 for septic patients. The results unexpectedly showed that Tα1 can improve the survival rate of sepsis. [12, 13]

A large-scale, multi-Centre, single-blind, randomized control trial (ETASS) in patients with severe sepsis in six hospitals in China showed lower 28 day all- cause-mortality in the Tα1 subgroup than that of the non-Tα1 subgroup.[14, 15] Pharmacological studies showed that Tα1 stimulates release of endogenous IFN-γ enhancing T cells and overall immune system. [16-20] A systematic review conducted by Yu et al. concluded that Tα1 may improve the immune response resulting from severe sepsis. However, no significant improvement in mortality was observed. [21] Recent promising data have been published on the use of Tα1 for treatment of severe sepsis and for prevention of invasive infections in bone marrow-transplanted patients. Tα1 has an excellent safety profile. [22] Tα1 looks a potential treatment that could be dosed in combination with standard of care in patients with sepsis. Hence, in this present study we evaluated and compared the efficacy and safety of Tα1 in combination with SOC versus placebo with SOC in sepsis patients.

2. Material and methods

2.1. Study Design

This was a Phase III, two-arm, randomized, placebo-controlled, multi-center, prospective, double-blind, comparative trial. Assuming a 3-point difference in SOFA score between the active and control arms, a standard deviation of 3.8, a randomization ratio of 1:1, and a two-sided level of significance of 5%, 120 patients (60 in each arm) produced power greater than 80%. The trial enrolled 123 sepsis patients from 10 different locations across India. The Institutional Ethics Committee of each of the 10 study sites examined the clinical trial protocol and other study related documents. The study was registered under Clinical Trial Registry of India (CTRI) before enrolment of first patient (CTRI/2022/09/045538). Prior to taking part in the trial, each patient gave written, informed consent. For eligible patients, a blinded treatment plan was followed with four injections of Immunocin α 1.6 mg (Thymosin α) or placebo with SOC in a 1:1 ratio, (2 vials twice a day) from day 1 to day 7 . International Guidelines for Management of Sepsis and Septic Shock: 2021 was followed in treating all patients with standard of care in both arms. Blinding was ensured by the identical look of both study medicine vials, preventing patients, investigators, and staff from distinguishing between them.

2.2. Eligibility Criteria

Male/ female aged ≥ 18 years diagnosed with sepsis according to the diagnostic criteria of " Surviving Sepsis Campaign: International Guidelines for Management of Sepsis 3 and Septic Shock: 2021", with total SOFA scores ≥2, with confirmed or suspected infection and satisfy at least one (pathogenic microbes grow in blood and at aseptic locations, presence of abscess or partially infected tissue, suspected infections identified by leukocytes at normal aseptic locations or organic perforation (confirmed by imaging evidence, examination result or intestinal content leak during drainage) or imaging evidence of pneumonia accompanied by purulent secretion or related syndromes with high infection risk, were included. Patients < 18 years of age, in need of immediate surgery, with history of organ or bone marrow transplantation, survival period less than 28 days with given their preexisting uncorrectable medical condition were not included. Pregnant and lactating mothers, patients participating in any other trial with an investigational drug within 1 month prior to this trial were excluded.

2.3. Study Endpoints

The primary endpoint was change in SOFA score. The secondary endpoints were incidence of emerging infection within 7 days of treatment, clearance rate of pathogenic microorganism over a period of 7-days, change in absolute lymphocyte count, change in CD4/CD8 ratio, change in neutrophil-lymphocyte (NLR) ratio, change in tumor necrosis factor α (TNF α) levels, change in C-reactive protein (CRP) levels from baseline to end of treatment. The other endpoints were duration of hospitalization, ventilator and ICU free days and vasoactive agent free days, number of antibiotics free days, incidences of all-cause mortality and number of treatment emergent adverse events and serious adverse events, over a period of 28 days.

2.4. Study Assessments

Patients' demographics were collected along with their medical/surgical history, medication history and current medical conditions during screening. Patients' SOFA score was recorded at screening and at the end of the treatment. All patients underwent clinical laboratory tests for biomarkers and safety. Blood samples were collected for microbiological findings (primary infection source and the identified microorganisms). Vital sign assessments with SpO2were recorded twice daily. Indices for disease severity were assessed for all patients daily from day 1 to day 7. AEs and serious AEs occurring during the study period were monitored until satisfactory resolution or stabilization.

2.5. Statistical Analysis

The estimated treatment difference in the SOFA score was provided, along with the 95% confidence interval and p-value. Two sample t-tests were utilized to accomplish this. The Modified Intent-to-treat (ITT) group included all patients who received at least one dose of study therapy and underwent at least one post-baseline evaluation. The per protocol (PP) set included all patients who received at least one dose of the study therapy and did not have any significant protocol violations. The safety set included all participants who had received at least one dosage of the study medication. All categorical variables were presented as frequencies and percentages. All continuous variables were summarized as n, mean, and SD. The Kaplan-Meier method was used for obtaining 'time to event' data. The statistical significance of secondary endpoints was determined using a two-tailed t-test with a significance level of 5%. All statistical analyses were carried out with R software version 4.3.2 and SPSS version 29.0.0.0.

3. Results

3.1. Patient disposition

As per protocol, 131 men and women with sepsis were screened and 123 eligible patients in intensive care unit were enrolled and treated in this study. Out of enrolled patients, 120 completed the study (Fig. 1).

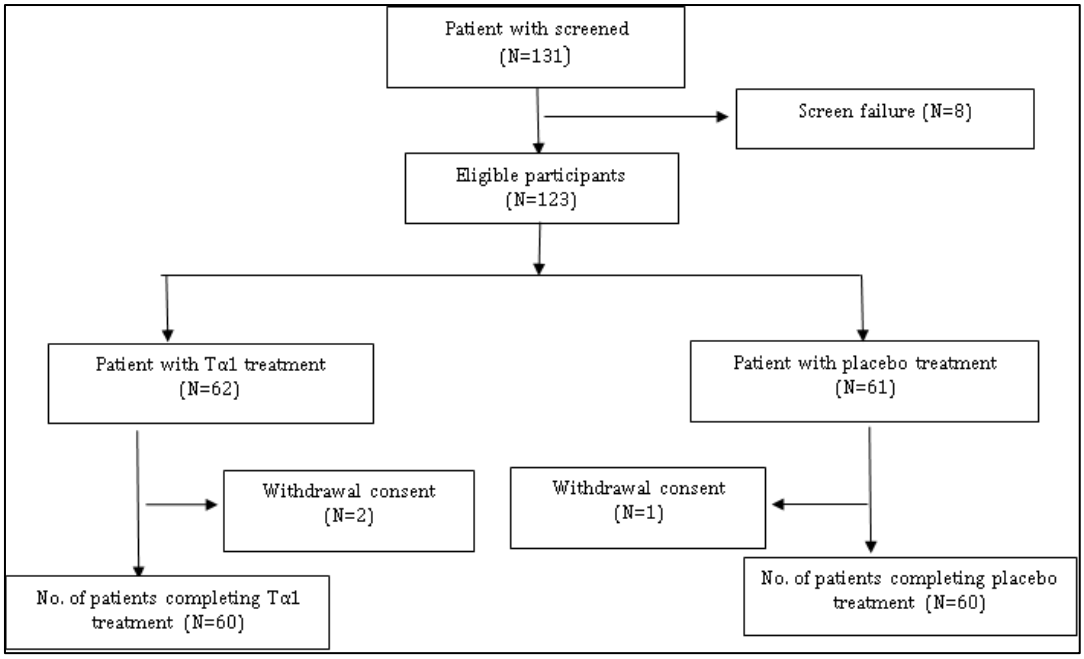


Figure 1 Strobe diagram

In the Thymosin arm, patients' mean (SD) age was 60.1 (12.77) years, while in the placebo arm, it was 58.1 (16.9). The patients' mean (SD) height was 156.7 (19.67) cm and 157.3 (8.25), in Thymosin arm and placebo arm, respectively. The mean (SD) weight of patients in Thymosin arm was 62.96 (20.97) kg and in placebo arm it was 59.26 (10.84). The mean (SD) BMI was 24.47 (9.34) kg/m2and23.89 (3.67), in Thymosin arm and placebo arm, respectively. (Table 1).

Table 1 Summary of Demography and Baseline Characteristics

Characteristics	**Thymosin α 1 with SOC (n = 62)**	**Placebo with SOC (n = 61)**	**Overall (n =123)**
Age(years)Mean(Min; Max)	60.1 (37- 83)	58.1 (24-82)	59.1 (24- 83)
Gender(Male, Female)	33 (53.2%) - 29 (46.7%)	31 (50.8%) - 30 (50.2%)	64(52.03%)-59 (47.96%)
Height(cm)Mean (Min; Max)	156.7 (154, 178)	157.3 (141- 174)	156.9(141- 178)
Weight(kg)Mean (Min; Max)	62.96 (42.0, 119.0)	59.26 (31.7- 85.0)	61.3(31.7- 119.0)
BMI(kg/m2)Mean (Min; Max)	24.47 (18.22, 45.27)	23.89(13.90- 33.20)	24.12(13.90 -45.27)

Analysis was done on ITT population. In Thymosin arm, the mean (SD) SOFA score of 4.8 (2) at baseline was reduced drastically to 1.4 (0.96) at end of treatment. In placebo arm, the mean (SD) SOFA score of 4.9 (2.17) at baseline was reduced to 3.77 (2.18) at end of treatment. The mean (SD) change from baseline was -3.5 (1.7) in Thymosin arm and -1.13 (1.2) in placebo arm. The difference between the two arms was statistically significant with p value < 0.001(Table 2 and Figure 2).

Table 2 Change in SOFA score from baseline

Statistics	**Thymosin α 1 with SOC**		**Placebo with SOC**	
	Day 1	Day 7/EOT	Day 1	Day 7/EOT
Mean (SD)	4.8 (2)	1.4(0.96)	4.9 (2.17)	3.77 (2.18)
	Change from Baseline		Change from Baseline	
Mean (SD)	-	-3.5 (1.7)	-	-1.13 (1.2)

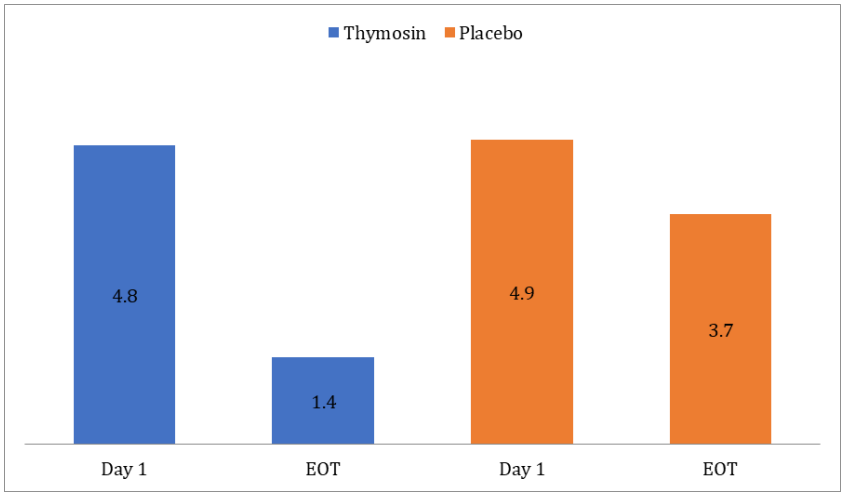


Figure 2 Changes in SOFA scores from baseline (day 1) to end of treatment (EOT)

The median duration of hospitalization was 12 days and 14 days in Thymosin and placebo arm, respectively(p value: 0.0002) (Table 3, Figure 3&4).The median duration of ventilator free days was 6 and 4 in Thymosin and placebo group respectively. (p value: 0.0015) (Table 3, Figure 3&5). Median ICU free days were 5 in thymosin arm as against 2 days in placebo arm (p value: 0.0001) (Table 3, Figure 3&6).In Thymosin arm median vasoactive agent free days were 11 and 8 in placebo arm(p value 0.63) (Table 3, Figure 3&7). The Thymosin arm showed a statistically significant difference over placebo arm in hospitalization, ventilator-free days, and ICU-free days with p values of 0.0002, 0.0015 and 0.0001 respectively. Only 5 incidences of emerging infection were reported in Thymosin Arm and in Placebo Arm 7 incidences were reported. The clearance rate of pathogenic microorganisms was 100% in both arms.

Table 3 Kaplan-Meier estimate of duration of Hospitalization, Ventilator-free days, ICU-free days and Vasoactive agents-free days

	Thymosin α 1 with SOC	**Placebo with SOC**
Duration of hospitalization [Median (95% CI)]	12(11, 12)	14(12, 21)
Ventilator-free days[Median (95% CI)]	6(5, 8)	4(3, 5)
ICU-free days [Median (95% CI)]	5(5, 9)	2(2, 4)
Vasoactive agents-free days [Median (95% CI)]	11(9, NA)	8(8, NA)

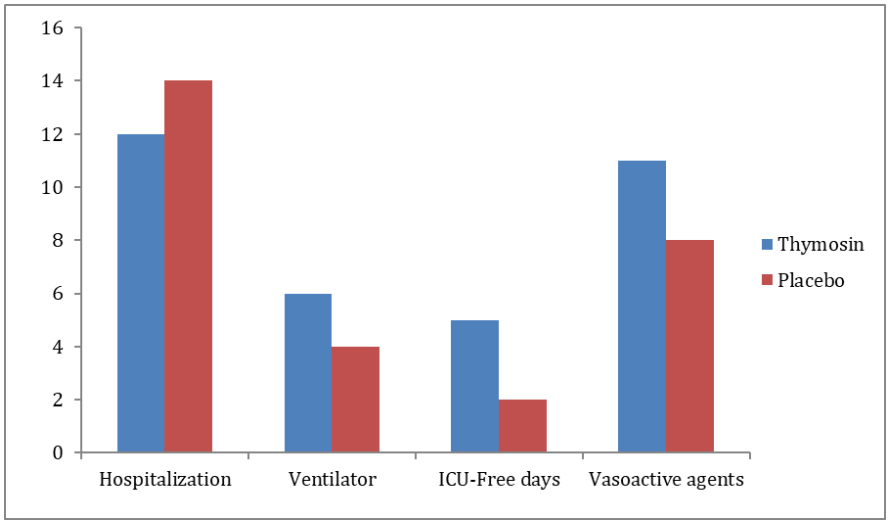
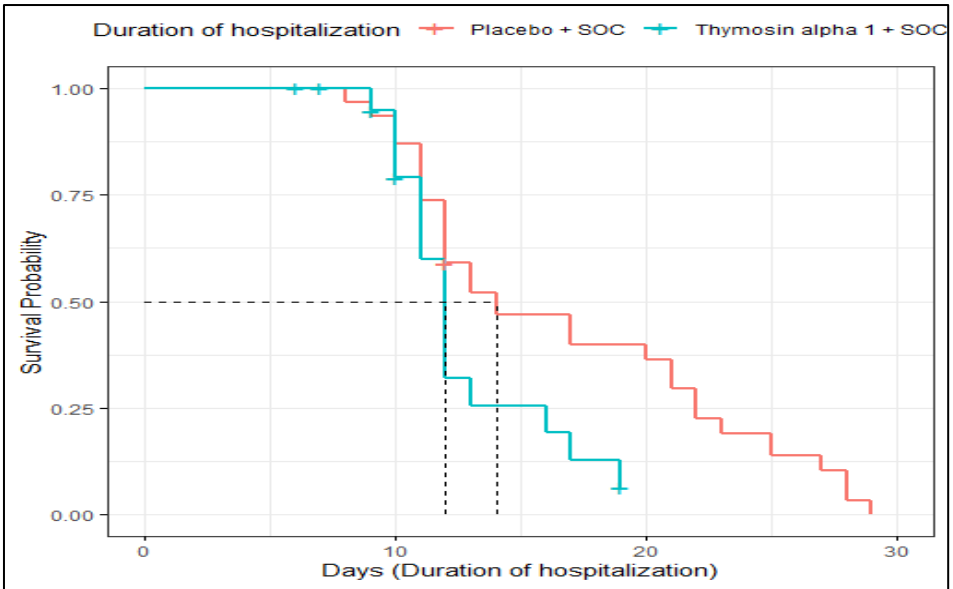


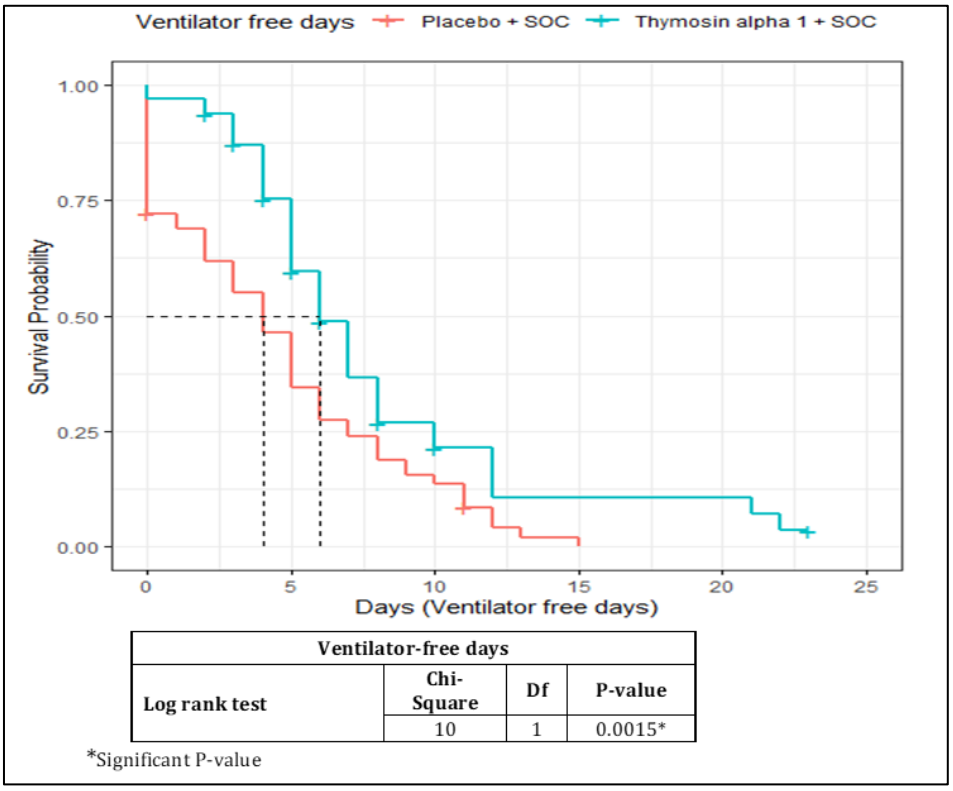
Figure 3 Median duration of Hospitalization, Ventilator, ICU and Vasoactive agent -free days



Duration of hospitalization			
Log rank test	**Chi-Square**	**Df**	**P-value**
	13	1	0.00026*

*Significant P-value

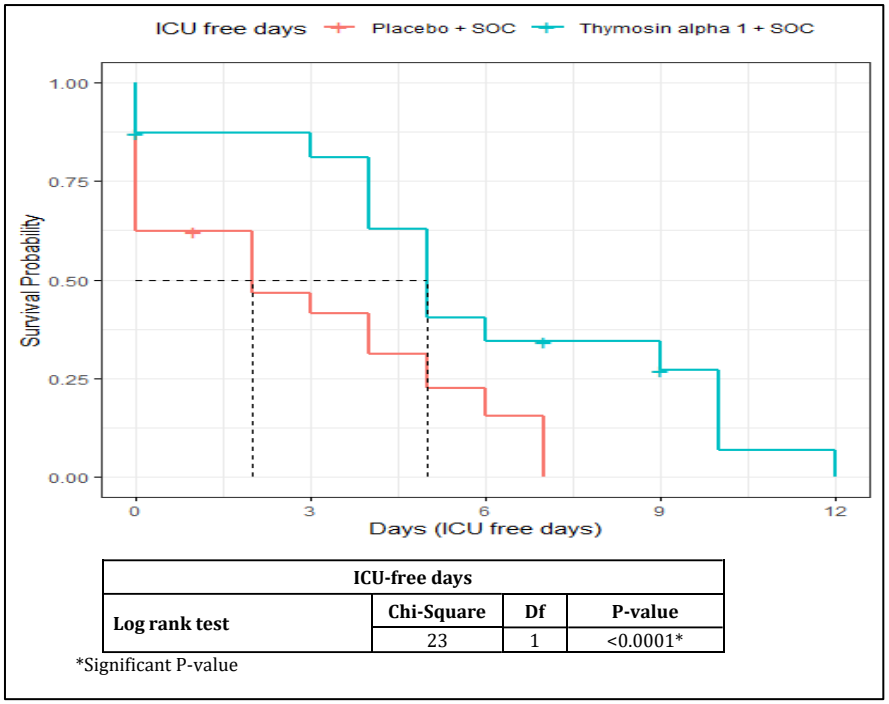
Figure 4 Kaplan-Meier estimate of Duration of hospitalization



Ventilator-free days			
Log rank test	**Chi-Square**	**Df**	**P-value**
	10	1	0.0015*

*Significant P-value

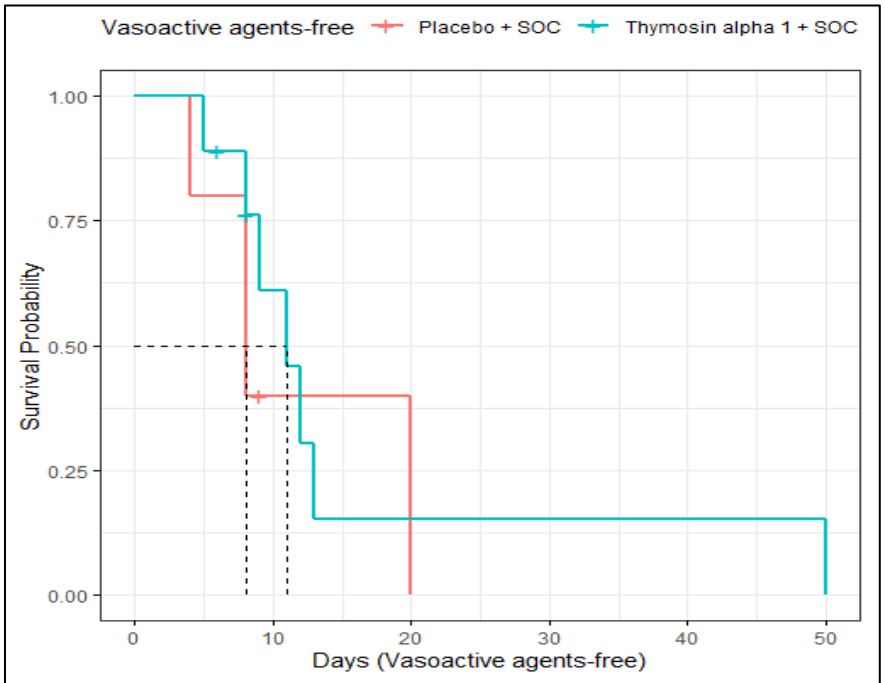
Figure 5 Kaplan-Meier estimate of Ventilator-free days



ICU-free days			
Log rank test	**Chi-Square**	**Df**	**P-value**
	23	1	<0.0001*

*Significant P-value

Figure 6 Kaplan-Meier estimate of ICU-free days



Vasoactive agents-free days			
Log rank test	**Chi-Square**	**Df**	**P-value**
	0.2	1	0.63

Figure 7 Kaplan-Meier estimate of Vasoactive agents-free days

In Thymosin arm the mean (SD) ALC at baseline 973.88 (625.14) increased to 1444.82 (780.51) at the end of treatment and in placebo arm mean (SD) ALC 931.86.13 (560.24) at baseline increased to 1175 (619.92), (Table 4). The change from the baseline in Thymosin arm was statistically significant, p= 0.049.

Table 4 Changes in Absolute lymphocyte count, CD4/CD8 ratio, NLR ratio, TNF levels and CRP levels from baseline

Statistics	**Thymosin α 1 with SOC**		**Placebo with SOC**		**Thymosin α 1 with SOC**		**Placebo with SOC**	
					Change from Baseline			
	Day 1	Day 7/EOT	Day 1	Day /EOT	Day 7/EOT	P-Value	Day 7 /EOT	P-Value
ALC Mean (SD)	973.88 (625.14)	1444.82 (780.51)	931.86 (560.24)	1175.053 (619.92)	413 (960.79)	0.049	235.91 (645.28)	0.112
CD4/CD8 ratio Mean (SD)	1.94 (1.01)	2.69 (1.14)	2.48 (2.50)	1.46 (0.69)	0.7 (1.25)	0.053	-1.074 (2.46)	0.107
NLR ratio Mean (SD)	16.62 (15.47)	6.264 (5.6947)	9.57 (6.2777)	6.028 (4.4061)	-6.77 (10.32)	0.002	-2.64 (7.07)	0.108
TNF levels Mean (SD)	26.1 (13.5)	13.7 (7.2)	25.9 (9.8)	19.6 (13.6)	-12.965 (7.85)	0.003	-6.3 (4.5)	0.864
CRP levels Mean (SD)	79.89 (55.02)	27.87 (37.42)	56.13 (51.60)	40.09 (43.95)	-47.32 (69.68)	0.002	-8.11 (36.76)	0.344

The mean (SD) CD4/CD6 ratio 1.94 (1.01) at baseline in the thymosin arm climbed to 2.69 (1.14) at the end of treatment, while in the placebo arm it reduced from 2.48 (2.50) to 1.46 (0.69) at the end of treatment (Table 4).

The mean (SD) NLR ratio 16.62 (15.47) at baseline in Thymosin arm was very high which significantly reduced (p= 0.002) to 6.26 (5.69) at the end of the treatment. The reduction was not significant in the placebo arm, 9.57 (6.28) at baseline and 6.02 (4.41) at the end of the treatment. Reduction in mean (SD) TNF levels was observed in both the arms. In the Thymosin arm it was 26.1 (13.5) at baseline significantly reduced to 13.7 (7.2), the mean (SD) change was -12.97 (7.85) at the end of treatment (p= 0.003). In the placebo arm, 25.9 (9.8) levels at baseline reduced insignificantly to 19.6 (13.6) at the end of treatment (Table 4).

In the Thymosin arm, reduction in mean (SD) CRP levels was -47.32 (69.68), statistically significant (p=0.022). the mean (SD) 79.89 (55.02) at baseline reduced to 27.87 (37.42) at end of treatment. In the placebo arm 56.13 (51.60) at baseline reduced to 40.09 (43.95) at end of treatment. Statistically significant change was observed between the two arms (p= 0.032) (Table 4).

Except for one patient in the Thymosin arm for six days, all other patients received antibiotics throughout the study. During the trial, one death occurred in the Thymosin arm and four in the placebo arm.

3.2. Safety outcomes

A total of eighty-two (82) adverse events were reported in 123 patients, out of which 35 are in study arm and 47 in placebo arm. 5 were Possible, 4 were Probable, 33 were Unlikely and 39 were unrelated. Majority AEs were either 'unrelated' or 'unlikely' related to Thymosin.

4. Discussion

Sepsis is a potentially fatal organ failure brought on by an aberrant or uncontrollable host immune reaction to an infection. Tα1 is an immune modulator that can activate and restore dysregulated immune responses in sepsis patients. [11] In the current study we evaluated the effectiveness of Thymosin alpha in the treatment of sepsis. The findings of this clinical study provide valuable insights into the efficacy and safety profile of Thymosin alpha in septic patients. According to a retrospective study conducted on 288 patients by Fei Pei, organ dysfunction can be alleviated by Tα1 medication, and the therapeutic efficacy of this treatment can be measured by the SOFA score on day 7.[23] Jianfeng Wu conducted another study on 361 sepsis patients and found similar findings. Combining Tα1 therapy with standard medical interventions may improve clinical outcomes in severe sepsis patients. [24]

By directly changing the lifespan, production, and functionality of the effector cells that maintain homeostasis, sepsis impacts the immune system. Tissue regeneration and wound healing are also facilitated by the hematopoietic and effector cells that uphold immune surveillance against harmful microorganisms. [25]

Tα1 has been shown by Yu et al. to enhance immune activity following severe sepsis. However, no substantial improvement in mortality was observed.[21] A comprehensive literature search revealed that Tα1-based immunomodulatory therapy significantly reduced all-cause mortality in sepsis patients, as per 12 relevant studies. [24, 26] In a study conducted, sepsis patients treated with 1.6 mg Tα1 QD resulted in decreased APACHEII score, the number of organ dysfunction and 28 days all-cause mortality. [13] Another study on sepsis patients with the same dose of Tα1 showed improved APACHEII score, immunological parameters and decreased mechanical ventilation and ICU stay. [27] The current study results showed a statistically significant improvement in the Thymosin arm compared to the placebo arm in key measure of SOFA score ($p < 0.001$). Thymosin arm proved to be better in other measures such as duration of hospitalization, ICU free days, and ventilator-free days. A significant improvement in the majority of the inflammatory marker assessed, absolute lymphocyte count, NLR, TNF and CRP in Thymosin arm compared to placebo arm.

The results suggest that Tα1 can certainly be an effective adjuvant with standard therapy treatment for sepsis patients. The study found that Tα1 has a favorable safety profile and supports its potential as a therapeutic option for sepsis patients, with 80% of adverse events being unlikely or unrelated. Our study's key strength is that it is prospective, controlled, and double blind, with direct comparisons of Thymosin and placebo with standard care in sepsis patients. The comparison to the placebo arm demonstrates that standard therapy with Thymosin can provide higher therapeutic benefits while maintaining an acceptable safety profile. Nevertheless, limited sample size limits the generalizability of the study findings. Further, studying on larger sample size would have further corroborated the positive results of this study.

5. Conclusion

In conclusion, this clinical trial provides encouraging evidence for Tα1's efficacy and safety in the treatment of sepsis. The findings highlight the need for additional research and the potential incorporation of Tα1 into the clinical management of septic patients.

Compliance with ethical standards

Acknowledgments

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Disclosure of conflict of interest

No conflict of interest to be disclosed.

Statement of ethical approval

The study protocol was approved by the clinical sites respective Ethics Committees. This study was conducted in compliance with the International Conference on Harmonization-Good Clinical Practices (ICH-GCP) guidelines E6 (R2), 2016; ICMR guidelines – National Ethical Guidelines for Biomedical and Health Research Involving Human Participants, 2017; Declaration of Helsinki, 2013; applicable local government regulations, and institutional research policies, and standard operating procedures.

Statement of informed consent

Informed consent was obtained from all individual participants included in the study.

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