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ORIGINAL RESEARCH

EVALUATION OF ROLE OF THYMOSIN ALPHA 1 IN MODERATE TO SEVERE COVID 19 PATIENTS: A RETROSPECTIVE STUDY

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ABSTRACT

Background. Immune-mediated lung injury and complex changes of the immune system, such as lymphopenia and cytokine storm, that have been associated with adverse outcomes underlining a fundamental role of host response in severe acute respiratory syndrome coronavirus 2 infection and the pathogenesis of the disease.

Thymosin alpha 1 (Tα1) is one of the molecules used in the management of COVID-19, because it is known to restore the homeostasis of the immune system during infections and cancer.

AimIn this study we aim to observe the role of thymosin alpha 1 in moderate to severe COVID-19 disease.

Methodology:A retrospective, single-centred study including 244 patients with laboratory-detected moderate to severe SARS-CoV-2 infection admitted to designated COVID-19 centre in a tertiary care hospital from March to October, 2020 was done. 100 patients received thymosin alpha 1 and their results were compared with 144 patients who received standard care without thymosin alpha. Clinical records, laboratory data, and radiological findings were analysed of patients treated with thymosin alpha 1 to evaluate the role oftreament outcome.

Results. 94% (n=94) patients in the thymosin group required oxygen at more than 6 L per minute as compare to 97.2% (n= 140) of the patients in the non- thymosin group. 35% of patients in the thymosin group (n=35) required high flow nasal oxygenation as compare to 49% (n=77) in the non thymosin group. 6% (n= 6)of the patients in the thymosin group required mechanical ventilation as compare to 11.6% (n=16) in the non thymosin group with the p-value of 0.17. Then hospital mortality was 6% (n= 6) in the thymosin group as compared to 9.02% (n=13) in the non thymosin group. The median hospital stay was 10 days in the thymosin group as compared to 8 days in the non thymosin group with the p-value of 0.001. 76 patients in the thymosin group had increased CRP levels on day 1 as compared to 119 in the non-thymosin group. On day 5, 21 patients in thymosin group had increased levels

as compared to 89 patiemts in the non thymosin group with a significant p-value of < 0.001. Statistically significant results were obtained on day 10, only 13 patients in the thymosingroup had increased levels as compare to 57 in the non thymosin group. On day 1, 89 patients in the thymosin group had increased level of IL-6 as compare to 102 in the non thymosin group. Serial monitoring on day 5 showed that in thymosin group, 35 patient had increased levels as compare to 85 patients in the non thymosin group (with a significant value of <0.05). Again on day 10, the difference was a statistically significant when only 10 patients in the thymosin group had elevated levels as compare to 43 in the non thymosin group.

Conclusion.

Significant difference was seen in terms of biochemical parameters but that could not be translated to clinical improvement measured in terms of need for non invasive/invasive mechanical ventilation and in hospital mortality rates.

Introduction

The pandemic of 2019, caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), has been a critical threat to global health.[1]Although considerable efforts have been made to treat COVID-19 yet well-established treatment and control options appear to lack. The treatment of COVID-19 is mainly symptomatic and supportive therefore current clinical treatment strategies for critical COVID-19 patients mainly include oxygen therapy, antiviral and Steroids. Most COVID-19 cases displayed severe lymphocytopenia, especially in aged and severe cases.[2] Lymphocytes play an essential role in fighting against viral infections, therefore, boosting the number and enhancing the antiviral function of T cells in COVID-19 patients which is of paramount value for successful recovery.[3]

Thymosin alpha 1 is a 28 amino acid peptide originally isolated from the thymus which has been extensively studied in terms of its functions in the immune system. It is recognized as an immune enhancing, immune modulating, as well as an immune restoring agent, and as such it has been utilized in several clinical and research settings.[4]Thymosin alpha 1 is an immune function modifier. Therefore, Thymosin-a1 has been used in diseases with impaired immune function, particularly infections including viral infections. In 2003, Thymosin-a1 had been used as an immune enhancer in SARS patients, demonstrating efficacy in controlling the progression of SARS.[5] The immune response of the host has an important effect on the development and prognosis of infectious diseases. Studies showed that total lymphocytes, CD3+T cells, CD4+ T cells and CD8+ T cells decreased in COVID-19 patients, and significantly decreased T cell lymphocyte subset counts were related to the severity and prognosis of COVID-19. Therefore, Thymosin-a1 has potential as a drug for the treatment of COVID-19 patients.[6]

Aim:

In this study we aim to assess the role of thymosin alpha 1 in moderate to severe COVID-19 disease. We assessed the progression of disease measured in terms of various laboratory markers, need for a need for high flow oxygenation/ non-invasive ventilation, invasive mechanical ventilation, in hospital mortality and duration of hospital stay.

Methodology:

This is a prospective observational study conducted in the Department of respiratory medicine at Government Chest Disease Hospital Srinagar. Patients with moderate to severe COVID-19 disease (microbiologically confirmed/clinic-radiological) and those giving consent were included in the study. A total of 244 patients were included, 100 patients received thymosin alpha 1 and their results were compared with 144 patients who received

standard care without thymosin alpha. Patients in thymosin alpha group were given three subcutaneous doses of thymosin alpha 1, 18 hours apart in addition to the standard treatment. Patients on invasive mechanical ventilation, patients with multiple organ dysfunction, lactating and pregnant females, patients who were deliberately on immune-suppression and those not giving consent were excluded from the study. Oxygen requirement, need for mechanical ventilation, mortality rate, median hospital stay and biochemical markers like CRP, IL6 were compared among the two groups.

Results:

A total of 244 patients were included in the study. 100 patients received thymosin alpha plus standard care and 144 patients received only standard care. 140 patients were males(63 in the thymosin group and 77 in the non thymosin group) and 114 patients were females (37 in thymosin group and 68 in non-thymosin group). A total of 44.2% (n=108) patients had associated comorbidities. Hypertension was the most common commodity present in 23.7% (n= 58) of the patients, followed by Type II diabetes in 17.2% (n=42), hypothyroid in 11.4% (n= 28), coronary artery disease in 4% (n= 12) and chronic kidney disease in 1.6% (n=4).(Table 1)

We included patients with moderate to severe disease in our study and they required oxygen therapy at lower flow rates (1 to 6 L per minute) on admission. Over the period of time 94% (n=94) patients in the thymosin group required oxygen at more than 6 L per minute as compare to 97.2% (n= 140) of the patients in the non- thymosin group with the p-value of 0.212 (Table 2). 35% of patients in the thymosin group (n=35) required high flow nasal oxygenation as compared to 49% (n=77) in the non thymosin group with a p-value of 0.08.(Table 3) 6% (n= 6)of the patients in the thymosin group required mechanical ventilation as compare to 11.6% (n=16) in the non thymosin group with the p-value of 0.17 (Table 4). Then hospital mortality was 6% (n= 6) in the thymosin group as compared to 9.02% (n=13) in the non thymosin group with the p-value of 0.5 again non-significant. Therefore we could not establish any significance in treatment with thymosin alpha in terms of these parameters.(Table 5)

The median hospital stay was 10 days in the

Variable	No of patients
All	244
Patients receiving alpha thymosin plus	100
Patients receiving standard care	144
Male	140 (63 in the thymosin group and 77 in the non thymosin group
Female	114 (37 in thymosin group and 68 in non-thymosin group)
Associated comorbidities	44.2% (n=108)
Hypertension	23.7% (n= 58)
Type II diabetes	17.2% (n=42)
Hypothyroidism	11.4% (n= 28)
Coronary Artery Disease	4% (n= 12)
Chronic Kidney Disease	1.6% (n=4).

thymosin group as compare to 8 days in the non thymosin group with the p-value of 0.001, which means the duration of significantly less in the non-thymosin group. (Table 6)

Table 1: Shows Demographic data and grouping of patients

Patients in the thymosin group required oxygen at more than 6 L per minute	94% (n=94)	
Patients in the non thymosin group required oxygen at more than 6 L per minute	97.2% (n= 140)	p-value= 0.212

Table 2: No of patients requiring oxygen in the thymosin and non thymosin group

Patients in the thymosin group required high flow nasal oxygenation	35% (n=35)	
Patients in the non thymosin group required high flow nasal oxygenation	49% (n=77)	p-value= 0.08

Table 3: No of patients requiring oxygen in the thymosin and non thymosin group

Patients in the thymosin group required mechanical ventilation	6% (n= 6)	
Patients in the non thymosin group required mechanical ventilation	11.6% (n=16)	p-value= 0.17

Table 4: No ofpatients requiring mechanical ventilation in the thymosin and non thymosin group

Hospital mortality rate in the thymosin group	6% (n= 6)	
Hospital mortality rate in the non thymosin group	9.02% (n=13)	p- value= 0.5

Table 5: No ofmortality in the thymosin and non thymosin group

Median hospital stay in the thymosin group	10 days	
Median hospital stay in the non thymosin group	8 days	p-value= 0.001

Table 6: median hospital stay in the thymosin and non thymosin group

Biochemical markers (CRP levels on Day 1, 5, 10)		
Patients in the thymosin group had increased CRP levels on Day 1	76	p-value= 0.02
patients in the non thymosin group had increased CRP	119	

levels n Day 1		
Patients in the thymosin group had increased CRP levels on Day 5	21	p-value < 0.001
Patients in the non thymosin group had increased CRP levels on Day 5	89	
Patients in the thymosin group had increased CRP levels on Day 10	13	p- value<0.001
Patients in the non thymosin group had increased CRP levels on Day 10	57	

Table 7: CRP levels at day 1, 5 & 10 in the thymosin and non thymosin group

Biochemical markers (IL-6 levels on Day 1, 5, 10)		
Patients in the thymosin group had increased IL-6 levels on Day 1	89	p-value= 0.02
patients in the non thymosin group had increased IL-6 levels n Day 1	102	
Patients in the thymosin group had increased IL-6 levels on Day 5	35	p-value <0.05
Patients in the non thymosin group had increased IL-6 levels on Day 5	85	
Patients in the thymosin group had increased IL-6 levels on Day 10	10	p- value<0.001
Patients in the non thymosin group had increased IL-6 levels on Day 10	43	

Table 8: IL-6 levels at day 1, 5 & 10 in the thymosin and non thymosin group

We also assesed the degree of inflammation in terms of biochemical markers including C-reactive protein (CRP) and interleukin 6 (IL-6). A total of 76 patients in the thymosin group had increased CRP levels on day 1 as compared to 119 in the non-thymosin group, the difference being statistically insignificant on day 1 (p-value 0.02). We monitored the parameters on day 5 and day 10. On day 5, 21 patients in thymosin group had increased levels as compared to 89 patiemts in the non thymosin group with a significant p-value of < 0.001. Statistically significant results were obtained on day 10 (only 13 patients in the thymosin group had increased levels as compare to 57 in the non thymosin group with a significant p-value of <0.001) On day 1, 89 patients in the thymosin group had increased level of IL-6 as compare to 102 in the non thymosin group. Serial monitoring on day 5 showed that in thymosin group, 35 patient had increased levels as compare to 85 patients in the non thymosin group (with a significant value of <0.05). Again on day 10, the difference

was a statistically significant when only 10 patients in the thymosin group had elevated levels as compare to 43 in the non thymosin group.We also monitored D dimer level serially in both the groups on day 1, day 5 and 10. However no statistically significant difference was observed between the two groups on day 5 or day 10. (Table 7 and Table 8)

Discussion:

In our study we did not find any statistical significance between the two groups in terms of oxygen requirement, need for non invasive and invasive mechanical ventilation. In a study conducted by JiaoLui et al, 306 received thymosin alpha 1 therapy. The outcomes that they measured included non recovery rate, intubation rate, AKI incidence, ARDs rate, in hospital mortality and length of ICU stay. They found that all these parameters were significantly higher in thymosin alpha group. As per this study, the need for IMV in thymosin group was 10.1% (31/306) as compared to 5.36 % (106/1976) in the non thymosin group, with a p value of 0.001- that is significant increase in need for intubation in thymosin group. The in hospital mortality as per this study for thymosin alpha group was 20% (62/306) as compared to 13.7 (271/19in the non thymosin group with a significant p value of 0.003. the reason for this significant difference could be the fact that although the baseline characters were similar in the two group but the patients included in the thymosin group had slightly larger proportion of critically ill patients.[7]

In other study by YuepingLui et al, a significant mortality benefit was seen in patients who received thymosin alpha with a p value of 0.04. however, the benefit was more in patients with CD8+ count of < 400/microL and CD4+ count <650/microL.[8]

In another study by Ming Wu et al, the 28 day mortality was significantly less in thymosingroup (12.1% vs 14.7%) but there was no difference in the 60 day mortality(16.5% vs 15.1%)[9]

As per study by JiavLui et al, the length of ICU stay was more in the patients who received thymosin alpha (14.9 +/- 12.7 vs 8.7 +/- 8.2 days) with a p value of less than 0.001. we obtained similar results in our study where the median hospital stay was 10 day in the thymosin group as compared to 8 days in the non thymosingroup with a p value of 0.001.[7]In the study by Ming Wu et al, similar results were obtained in terms of duration of hospital stay where the duration was prolonged in patients who had received thymosin alpha ($p < 0.001$).

In our study, however we found a significant reduction in the levels of biochemical markers CRP and IL-6 in the patients who received thymosin alpha 1 with a p value of <0.001. In contrast to our findings, Ming Wu et al in their study did not note any significant improvements in CRP or IL-6 levels. [9]

Conclusion:

Thymosin alpha 1, because of its immunomodulatory properties, has been theoretically proposed as a treatment option for covid 19 disease. The data regarding its role in covid 19 is however limited. Some studies have shown benefit while others have not. In our study, we could not establish a clear cut benefit of thymosin alpha in moderate to severe cases of covid-19. Though significant difference was seen in terms of biochemical parameters but that could not be translated to clinical improvement measured in terms of need for non invasive/invasive mechanical ventilation and in hospital mortality rates.

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