EDITORIAL

Thymosin α1 for COVID-19: Look before You Leap!

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Indian Journal of Critical Care Medicine (2022): 10.5005/jp-journals-10071-24297

It is now over two-and-a-half years since coronavirus disease-2019 (COVID-19) struck in late 2019. As our knowledge and response to the disease have evolved, with identifying the SARS-CoV-2 virus and its genome, understanding the mode of transmission, pathophysiology, therapeutic strategies, and the development of vaccines, so has the SARS-CoV-2 virus, with the emergence of new variants. The pathophysiology of COVID-19 can be broadly divided into an incubation phase, where the virus is present but the patient is asymptomatic, a symptomatic viremic phase where the patient develops symptoms that could progress to pneumonia with the virus invading the lungs, and a late phase associated with a declining viral load but with an uncontrolled inflammatory response, often described as a "cytokine storm" leading to lung and multiorgan failure.[1] Therapeutic strategies, therefore, included antiviral therapy and augmentation of the immune response in the early viremic phase and modulating or "cooling" the immune response in the hyperinflammatory phase. Large randomized controlled trials would eventually lead to evidence-based treatment including vaccination against the SARS-CoV-2 virus, antiviral drugs such as remdesivir, nirmatrelvir–ritonavir, and molnupiravir, enhancing passive immunity with monoclonal antibodies, and immune-modulating drugs like dexamethasone, tocilizumab, and baritictinib.[2–10]

In the early months of the pandemic, before the emergence of a large evidence base for current treatments, several empirical treatments were tried in an attempt to reduce morbidity and mortality. One such drug was thymosin α1 (Tα1), a polypeptide hormone produced by thymic epithelial cells. Thymosin α1 increases the T-lymphocyte count as well as T-cell differentiation and maturation and reduces cell apoptosis.[11,12] These effects could be beneficial in combating viral invasion. Further, Tα1 has been shown to mitigate the cytokine-release syndrome suggesting that it might be beneficial in the hyperinflammatory phase.[13] It was used in critically ill patients in Wuhan early in the pandemic, and retrospective data suggested that Tα1 may improve outcomes in patients with COVID-19, especially those with severe lymphocytopenia.[14] However, attractive treatments such as Tα1 may appear, but they must be tested in well-designed clinical trials. Therefore, Shetty et al. are to be commended for undertaking a randomized controlled trial evaluating the efficacy of Tα1 in patients with moderate and severe COVID-19.[15]

From the trial registry data, this was a pharmaceutical industry-sponsored trial, with Gufic Biosciences Limited as the primary sponsor. Patients were randomized from October 2020 onwards, during the first "wave". The authors studied 105 COVID-19 patients. Of these, 75 patients (48 patients with moderate COVID-19 and 27 with severe COVID-19) received Tα1, while 30 patients (17 patients with moderate COVID-19 and 13 with severe COVID-19) received placebo in addition to standard therapy prevailing at that time. The authors report that the mortality was 11.1% in the Tα1 group, and 38.5% in the placebo group, a statistically significant result that appears to be dramatic. Patients with moderate and severe COVID-19 had faster resolution of symptoms and a shorter hospital stay in the Tα1 group compared with placebo. However, a closer look at the data reveals that the percentages for mortality are calculated using only the severe COVID-19 patients in the denominator. There were eight deaths totally, three in the Tα1 group and 5 in the placebo group. Hence, the overall mortality is 3/75 or 4.0% in the Tα1 group and 5/30 (16.6%) in the placebo group. This is a fragile result. One additional death in the Tα1 group would have resulted in a nonsignificant *p*-value of 0.07. Further, all deaths occurred in severe COVID-19 patients, suggesting that the mortality benefit was confined to those with severe COVID-19 and not to those with moderate COVID-19. This benefit in a subgroup of patients cannot be considered definitive and must be seen as hypothesis generating. In this context, it would be useful to know the distribution of comorbidities, the initial oxygenation therapies, and the other drugs (remdesivir, corticosteroids, tocilizumab, etc.) that patients received in the Tα1 and placebo groups. In the absence of such information, it is difficult to interpret the data presented.

Further, the current situation with COVID-19 is vastly different than it was at the beginning of the pandemic. A large proportion of the population has developed some immunity to SARS-CoV-2, by vaccination, infection, or both. The current variants are different from the original Wuhan strain. Dexamethasone and tocilizumab reduce mortality in hypoxemic patients. Effective antiviral drugs such as nirmatrelvir–ritonavir and molnupiravir reduce the severity of the infection and improve outcomes.[9] The study by Shetty et al. presents a signal on the role of Tα1 that needs re-evaluation in a vastly changed scenario. In conclusion, Tα1 is an interesting molecule that should be used in the context of a clinical trial before it can be recommended as an adjunct to standard evidence-based therapy of COVD-19 in routine clinical practice.

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How to cite this article: Divatia JV. Thymosin α1 for COVID-19: Look before You Leap! Indian J Crit Care Med 2022;26(8):892–893.

Source of support: Nil

Conflict of interest: None

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