Reply to Dorgham et al., "Considering Personalized Interferon Beta Therapy for COVID-19"

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We read with great interest the comments by Dorgham et al. (1) with regard to our recently published article (2). Also, we appreciate sharing the results of their valuable work reporting a correlation between interferon beta (IFN-β) serum levels and COVID-19 mortality, which was summarized in their letter. It helps us to understand the role of IFNs in the pathogenesis and treatment of COVID-19.

Type I IFNs are a part of the innate immune system. Although they are used for the treatment of some autoimmune diseases, like multiple sclerosis, some patients with other immune-mediated diseases, like systemic lupus erythematous, have high levels of IFNs related to activation of the disease (3). Also, IFNs are prescribed for viral hepatitis owing to their antiviral activities (4).

During the emergence of the COVID-19 pandemic, the role of IFNs in the prevention and treatment of this disease was proposed. Some promising results in two other epidemics of coronavirus, i.e., SARS (severe acute respiratory syndrome) and MERS (Middle East respiratory syndrome), have been reported (5). As with other family members, SARS-CoV-2 possesses some mechanisms (like the proteins ORF6 and ORF8) that can inhibit the production of type I IFNs (6).

It was proposed that administration of IFNs to COVID-19 patients with increased serum IFN-β levels might have detrimental effects. However, the role of type I IFNs in COVID-19 pathogenesis has been proposed to be reduced. Most patients with severe COVID-19 displayed impaired IFN activity that also correlated with lower viral clearance (7). The culprit proteins (like nuclear shuttle protein [NSP]-type and open reading frame [ORF]-type proteins) of the virus can antagonize the production of IFNs, so SARS-CoV-2 may evade the innate immune system (8). Some findings have been reported (9, 10). In the Dorgham et al. study (1), COVID-19 patients with increased serum IFN-β levels experienced significantly higher mortality. Only 11 out of 112 patients were categorized in this subpopulation. Also, it should be considered that IFNs are components of the cytokine storm phase. Patients in this stage have high serum levels of IFNs and probably high mortality (11).

We agree with Dorgham et al. that early administration of IFNs for the treatment of COVID-19 should be taken into account. It is suggested not only because of the probable deterioration of the patient's condition and because IFN may promote cytokine release in the later stages of the disease but also because of the diminished antiviral effect of IFN in late phases of the disease (12, 13). After about 8 to 12 days, the immune system will encounter the cytokine storm, and the use of IFNs at this stage did not show beneficial effects (14). In addition, sampling for measurement of serum levels of IFN-β in this study was done during days 0 to 25 of hospital admission; therefore, patients were probably in different stages of the disease.

Finally, in agreement with Dorgham et al., we acknowledge the concept of personalized IFN-β therapy with a consideration of the pathogenesis of COVID-19 and the stage of the disease. Unfortunately, many aspects of the pathogenesis of COVID-19 have not been clarified yet. Future studies are needed to determine which intervention at which stage of the disease might help certain patients.

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ACKNOWLEDGMENT

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