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COVID-19: room for treating T cell exhaustion?

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Dear Editor,

Immunosuppressive therapy has emerged as promising therapeutic approach in the management of Coronavirus disease-19 (COVID-19) patients, who are often overwhelmed by dysfunctional immune responses [1]. However, some authors highlighted the risk related to unbalanced use of immunosuppressive treatments, since failure of antiviral immunity to control SARS-CoV-2 replication could underlie the hyper-inflammatory responses characterizing severe COVID-19 [2]. In critically ill COVID-19 patients, indeed, massive cytokine storms (including IL-6, TNF-α, and other inflammatory biomarkers), as well as increments of circulating neutrophils and monocyte activation, are typically observed together with low T lymphocyte counts and functional exhaustion of effector T cell responses [1, 3, 4]. Such ineffective and detrimental expansions of innate/humoral responses, alongside T cell suppression, are reminiscent of classical features of sepsis, which is currently defined as a life-threatening organ dysfunction induced by dysregulated host response to infection, being characterized not only by systemic hyperinflammation (SIRS) with related endothelial and organ damage, but also by impairment of adaptive T cell immunity. Moreover, the relevant coagulation disorders observed in end-stage COVID-19 could also well fit with the idea that severe COVID-19 possibly represents a peculiar clinicopathologic manifestation of viral sepsis.

To date, while clinical trials with immunosuppressive treatments (e.g., anti-IL-6 tocilizumab) are ongoing in COVID-19 patients [1], therapeutic approaches to enhance T cell functions have not yet been attempted in this setting. Importantly, immune checkpoint inhibitors (ICIs), such as anti-PD-1 and anti-PD-L1 monoclonal antibodies, originally developed to improve antineoplastic T cell immunity, are undergoing clinical investigation in septic patients [5]. Thus, it should be conceivable that, also in COVID-19 patients, ICIs may be tested to restore immune competence of exhausted T cell subsets and, in this context, to specifically improve the pivotal process of virus elimination, likely blunted in severe COVID-19. Of course, as for septic patients, the risk of immune-mediated complications (including inflammatory flares, pneumonitis, and systemic cytokine-release syndrome) could raise some concerns about the use of ICIs in COVID-19 patients. However, it should be noted that (i) autoimmune-like adverse events were not clinically evident in septic patients treated with ICIs [5] and (ii) tocilizumab represents a standard treatment for the management of such complications in cancer patients and could be promptly associated with ICIs in COVID-19 patients. While awaiting for the development of effective antivirals and vaccines against this life-threating coronavirus, we could harness the opportunity to try tuning patients' immune system by using different immunomodulatory strategies now available, aiming to obtain more proper immune responses to SARS-CoV-2 infection and, hopefully, to reduce COVID-19-related mortality.

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