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Commentary

Complex immune deregulation in severe COVID-19: More than a mechanism of pathogenesis

Evangelos J. Giamarellos-Bourboulis

4th Department of Internal Medicine, National and Kapodistrian University of Athens, Medical School, ATTIKON University Hospital, 1 Rimini Str, Athens 12462, Greece

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The generated impression early at the beginning of the pandemic by SARS-CoV-2 (also called COVID-19) was that severe COVID-19 is due to a cytokine storm with the over-production of interleukin (IL)-6 as the predominant feature [1]. As more and more experience was acquired and IL-6 became a routine biomarker in many countries, it was realized that although IL-6 was increased this was not at the extent found in cytokine storm syndrome (CSS). CSS, also known as macrophage activation syndrome (MAS), bears clinical features of high fever, hepatic dysfunction, cytopenias and coagulopathy and is manifested by rapidly evolving organ dysfunction leading to early death (2). Infectious disorders, amongst which SARS-CoV-2, are considered aetiological factors. However, not all patients with severe COVID-19 are suffering from MAS.

MAS is classified using the HScore introduced by the American College of Rheumatology and provides separate scoring for core temperature, number of cytopenias, organomegaly, aspartate aminostransferase, triglycerides, fibrinogen, ferritin, history of immunosuppression and bone marrow hemophagocytosis [2]. HScore 169 or more is linked with 82% sensitivity for MAS. By applying the HScore as gold standard for diagnosis in 5121 Greek patients with bacterial sepsis split into one test and one validation cohorts and by also testing one cohort of 109 Swedish patients, serum ferritin was introduced as diagnostic tool; serum concentrations above 4420 ng/ml had 98% specificity and 97.1% negative predictive value [3]. However, MAS was found in only 3 to 4% of participants.

At the beginning of COVID-19 pandemic, we sought for ferritin in patients with severe respiratory failure (SRF) under mechanical ventilation (MV). We also isolated peripheral blood mononuclear cells (PBMCs) for stimulation for cytokine production and we measured the number of HLA-DR (Human leukocyte Antigen DR) molecules on CD14-monocytes (mHLA-DR). Results were compared to patients with bacterial community-acquired pneumonia (CAP) and sepsis; less than 5000 mHLA-DR was diagnostic of immunosuppression. Two immunological entities were recognized in patients with SRF; 25% had MAS and 75% had complex immune dysregulation (CID) with less than 5000 mHLA-DR. The CID of severe COVID-19 was distinct from sepsis-induced immunosuppression since PBMCs maintained their functionality for cytokine production, mainly for tumour necrosis factor-alpha (TNFα) and IL-6; in sepsis immunosuppression this functionality was lost [4]. Low mHLA-DR in severe COVID-19 has also been described in a small cohort of patients from Norway [5].

These findings were solidified by the study of Bonnet et al. in the current article of EBioMedicine [6]. The authors studied a cohort of 134 patients with SRF under MV split into two periods, March-June and September-November 2020, corresponding to the first two waves of COVID-19 in France. The two periods were also different regarding the standard-of-care (SOC) management since dexamethasone was added in the SOC of patients in the second wave following the results of the RECOVERY trial [7]. The authors identified strong traits of CID i.e. low mHLA-DR and moderate circulating levels of IL-6. Unfavourable outcome was associated with less than 5000 molecules of mHLA-DR and predisposition for secondary infections. The authors tried to make this more applicable for the routine evaluation of patients and introduced the serial measurement of the ratio of IL-6 to mHLA-DR. Values of this ratio above 18.1, within the first three days, and above 48.6 between days 7 and 10 were associated with 100% positive predictive value for death. mHLA-DR was increased amongst survivors on days 7 and 10 compared to baseline and amongst patients treated with corticosteroids. When ferritin was measured in plasma, nil patient had levels more than 4420 ng/ml

The findings reinforce the notion than severe COVID-19 is dominated by CID and not by MAS. CID is characterized by an interplay between IL-6 and mHLA-DR. When inflammation is attenuated IL-6 decreases and mHLA-DR increases so the IL-6/mHLA-DR ratio is decreased and the prognosis of favourable. The opposite is taking place amongst non-survivors. These data become even more important since the authors described an increase of mHLA-DR following corticosteroid treatment [6]. We have also described similar increase of mHLA-DR after the ex vivo treatment of monocytes with the IL-6 receptor antagonist tocilizumab [5]. These findings explain, at least partly, the mechanism of the clinical benefit provided by dexamethasone and tocilizumab in patients with SRF as this has been described in the RECOVERY and REMAP-CAP trials, respectively [7,8].

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E-mail address: egiamarel@med.uoa.gr

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These findings become most important in the light of a recently published case-series of five COVID-19 patients remaining under MV for extended periods. SARS-CoV-2 viral load was spectacularly decreased following start of treatment with recombinant interferon-gamma (rhIFNγ); four patients were eventually discharged alive [9]. rhIFNγ has been suggested as treatment for patients with immunosuppression and septic shock [10] where low mHLA-DR is one main feature [5]. To this end, the importance of the IL-6/mHLA-DR ratio introduced by the authors may pave the way for future guided immunotherapy in COVID-19.

Contributors

EJGB conceived the idea of the manuscript, wrote the manuscript and gets the responsibility for submission.

Declaration of Competing Interest

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