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LETTER TO THE EDITOR

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Immunostimulation with interferon-γ in protracted SARS-CoV-2 pneumonia

Dear Editor,

We read with great interest the recent publication describing two coronavirus disease 2019 (COVID-19) patients with protracted severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pneumonia with rituximab treatment treated by convalescent plasma (CP) by Gerber et al.[1] Deep immunosuppression is a major hallmark of those patients with altered interferon (IFN)-release, low monocyte HLA-DR expression (mHLA-DR), and profound lymphopenia accompanied by functional CD8 + T cell impairments.[2–4] In this context, patients under chronic use of immunomodulatory therapeutics with pre-existent altered immune surveillance and defective antiviral immunity may be at increased risk for protracted SARS-CoV-2 pneumonia. We report here the COVID-19 pneumonia course in a 68-years-old female patient with rheumatoid arthritis chronically treated with rituximab (anti-CD20 monoclonal antibody). Her medical history also included Sjogren's syndrome, renal impairment, and polyneuropathy. Due to rapid clinical deterioration and viral persistence despite CP therapy, treatment with IFN-γ was successfully instituted.

Twenty days after symptoms onset and COVID-19 diagnosis (polymerase chain reaction [PCR] positive nasopharyngeal swab), the patient was admitted to the intensive care unit (ICU) with respiratory distress requiring high flow oxygen therapy (inspired oxygen fraction at 70%, 50 L/min gas flow). Dexamethasone (6 mg daily) was initiated before ICU arrival (i.e., on Day 14) and was continued until day 28. On admission, positive SARS-CoV-2 PCR in both bronchoalveolar lavage and serum were observed (Table S1), in association with severe lymphopenia with a complete lack of B cells, low mHLA-DR, and absence of anti-SARS-CoV-2 immunoglobulin G (IgG) despite normal total immunoglobulin levels (5.8 g/L, Table S2). Therefore, two infusions of two units of CP were performed at Days 22 and 23 after symptoms but did not elicit any improvement as shown by development of progressive pulmonary injury (bilateral ground-glass opacities 70%, compared to 30% 6 days before) and fibrosis (Figure S1). Meanwhile, PCR results remained positive. An additional infusion of CP was performed on Days 28 and 30. On Day 32, as the patient continued to deteriorate while maintaining features of marked immunosuppression, immunotherapy with IFN-γ, 100 mcg daily subcutaneously [5] was administrated for 3 days. Within few days, the patient clinically improved, immune alterations reversed (increase in mHLA-DR and lymphocyte count) and nasopharyngeal swab and blood SARS-Cov-2 PCR became negative on Days 36 and 39 (Figure 1, Supplemental Tables). Meanwhile, IgG anti-SARS-CoV-2 remained negative. During IFN-γ treatment, the patient complained of only slight joint pain, easily managed with acetaminophen or Tramadol. Finally, the patient never

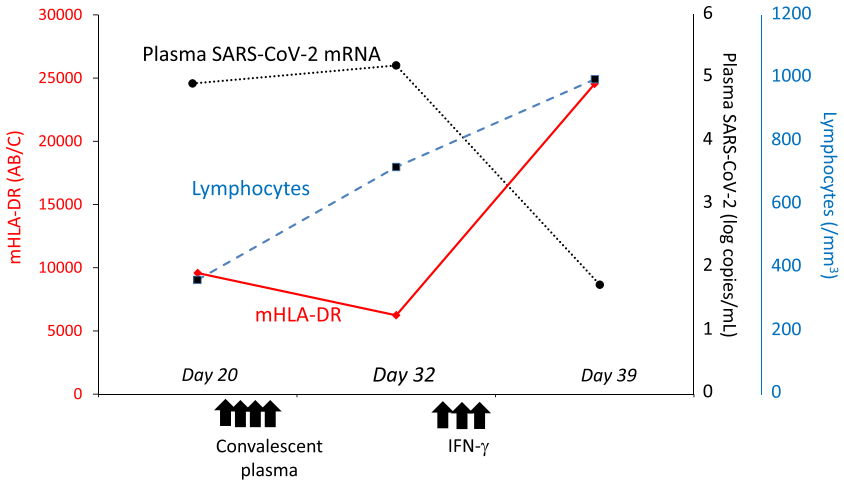

FIGURE 1 Overtime evolution of virus detection, lymphocyte count, and mHLA-DR in a COVID-19 patient under immunotherapy. Black arrows at the bottom depict the timing of convalescent plasma (CP) therapy and IFN-γ injections. Rapidly after IFN-γ therapy onset, SARS-CoV-2 plasma mRNA decreased (black dashed line) while immune parameters rose up to reference values: lymphocyte count (blue dashed line, reference value >1000/mm^3), mHLA-DR (red line, reference value >13,500 AB/C). COVID-19, coronavirus disease 2019; IFN, interferon; mHLA-DR, low monocyte HLA-DR expression; mRNA, messenger RNA; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

required mechanical ventilation. She left the ICU on Day 41 and the hospital on Day 54.

Here we described the COVID-19 course of a patient under chronic rituximab treatment. Despite several CP infusions, the patient worsened in association with virus persistence. Although we did not monitor specific cellular responses, knowing IFN-γ properties, we can hypothesize that such immunotherapy has improved the antiviral response by reinforcing CD8 + T cell cytotoxicity and expression of major histocompatibility complex molecules on different types of cells (reflected by mHLA-DR rise) and infected cells. Most importantly, immunostimulation by IFN-γ prevented the need of mechanical ventilation, which would have increased the risks of secondary ventilator-associated pneumonia. We conclude that, in severe COVID-19 patients presenting with features of severe immunosuppression, the benefit of immunostimulation deserves to be further assessed.

CONFLICT OF INTERESTS

The authors declare that there are no conflicts of interest.

AUTHOR CONTRIBUTIONS

Anne-Claire Lukaszewicz, Fabienne Venet, Alexandre Faure, Emmanuelle Vignot, Guillaume Monneret conceived and planned the medical strategy. Anne-Claire Lukaszewicz, Fabienne Venet, Alexandre Faure, Emmanuelle Vignot, Guillaume Monneret contributed to the interpretation of the results. Anne-Claire Lukaszewicz took the lead in writing the manuscript. All authors provided critical feedback and helped shape the manuscript.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.