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Letter to the Editor

Outcome of hospitalized patients with COVID-19 pneumonia treated with high-dose immunoglobulin therapy in a prospective case series

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To the Editor,

Control of hyperinflammation might be crucial to decrease COVID-19 severity, and intravenous immunoglobulins (IVIGs) may be useful due to their immunomodulatory properties. IVIGs can neutralize cytokines and autoantibodies, prevent innate cell activation by blocking activating Fc-receptors, reduce the half-life of autoantibodies, promote the generation of regulatory T cells and block the activation of the complement, among many other functions [1]. Preliminary data support the benefit of high-dose IVIG at the time of respiratory distress initiation in COVID-19-infected patients [2–4], and early initiation of this treatment may be critical for survival [4]. Here, we describe five patients treated with IVIG for COVID-19.

Data were prospectively defined and collected, with a follow-up of 4–5 weeks, including post discharge, at the Germans Trias i Pujol hospital between 2 April and 18 June 2020. All patients received hydroxychloroquine, as no guidelines at that time recommended the use of other treatments. We received an exemption from ethics approval because IVIG was used in an off-label indication; it was approved by the Pharmacy and Therapeutics Committee of the hospital, and all informed subjects signed an informed consent (PI-20-266). Five patients received a 5-day course of IVIG, consisting of 400 mg/kg/day of Flebogamma® 10% DIF (Instituto Grifols S.A., Barcelona, Spain). IVIG was administered intravenously once daily by continuous infusion, starting at 60 mL/hr, with a 10–mL increase every 30 min if well tolerated, up to 100 mL/hr. In case of renal failure, infusion was performed at a constant rate of 60 mL/hr. Inclusion and exclusion criteria are described in Table S1, while demographic and baseline characteristics of patients are shown in Table S2. Age ranged from 24 to 80 years, and three patients were male. An oropharyngeal swab was positive for SARS-CoV-2 by RT-PCR assay in four patients, while one diagnosis was done with positive IgA serology for SARS-CoV-2 (Table S3).

At inclusion, patients had a medium risk of acute respiratory distress syndrome (ARDS) according to the Berlin definition (Table S2) and a mid to high NEWS (National Early Warning Score) (Fig. 1). All subjects had COVID-19 multilobar pneumonia and PaO2/FiO2 values ≤ 300 mmHg requiring supplemental oxygen therapy (Table S2). Of note, two patients had severe renal failure before treatment administration. No infusion-related complications during IVIG administration nor adverse effects related to therapy were observed. All patients showed no alterations in renal and hepatic function, with the exception of patient 4, who presented a transient elevation of transaminases on day 7 (aspartate aminotransferase, 329; alanine aminotransferase, 266; reference range, 0–35 IU/L). This patient had a normal abdominal ultrasound, negative hepatitis virus markers and improved transaminases level after ibuprofen was withdrawn (Table S3). The levels of immunoglobulins were determined before treatment; blood counts, chemistry and biomarkers were detected previously to IVIG administration and during 14 days; and chest X-ray was done on day 3, day 5 and when discharged (Table S3).

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After IVIG infusion, the NEWS score showed a progressive decline in all subjects, reaching minimal values by day 14 (Fig. 1). All patients required supplemental oxygen at admission, but their respiratory conditions (PaO2/FiO2 and pO2) improved rapidly after starting treatment (Fig. 1). The mean time to normalization of oxygen saturation and pO2 (>80 mmHg) was 3.6 days (Fig. 1). Lymphocyte count progressively increased until day 14 (Fig. 1), while neutrophil counts normalized by day 3 (Table S3). The main inflammatory biomarkers (interleukin-6, C-reactive protein and fibrinogen) decreased by day 7, reaching normal values by day 14 (Fig. 1). However, D-dimer did not normalize in all individuals by day 14 (Fig. 1). No patients developed any thrombotic event during the study or subsequent follow-up after hospital discharge. Overall, the infusion of IVIG in these five patients resulted in a good recovery, showing resolution of the pulmonary infiltrates by chest radiography, normalization of the inflammatory markers and recovered lymphocyte count.

The main limitations of this case series are the small number of patients enrolled and the absence of controls. Yet our results concur with previous observations indicating the clinical utility of IVIG for treating COVID-19 pneumonia [2–4]. Although patients included in this study showed a PaO2/FiO2 value ≤ 300 mmHg and had a medium risk of ARDS according to the Berlin definition, all of them successfully recovered upon IVIG infusion, and none developed ARDS or required ICU admission. Thus, our experience corroborates the clinical applicability of IVIG for treating COVID-19 pneumonia, and warrants future randomized clinical trials to confirm these observations. Antivirals like remdesivir, neutralizing antibodies against cytokines or our approach using IVIG are more expensive than immunomodulators such as dexamethasone. However, dexamethasone only reduces 2.9% of deaths in patients who require oxygen but not invasive mechanical ventilation [5]. Thus, comparative safety and effectiveness trials are still needed to prioritize the best strategy for treating COVID-19.

**Transparency declaration**

B.C. is founder and shareholder of AlbaJuna Therapeutics, S.L. J.C. is co-founder and Chief Scientific Officer of AlbaJuna Therapeutics, S.L. B.C., J.C. and N.I.-U. are part of the CBIG consortium funded by Grifols. The authors declare no other conflict of interests. This work has been supported by the #JoEmCorono crowdfunding initiative. Grifols provided free of charge all the IVIG required for this study, but had no role on study design or decision to publish.

**Author contributions**

Protocol design: E.R., M.L.P.B., B.C. Patient management and inclusion: E.R., J.R.S., S.R., L.M., R.P., M.L., M.L.P.B. Data analysis: E.R., J.C., J.R.S., S.R., L.M., R.P., B.C., N.I.U., M.L.P.B. Wrote the paper: E.R., J.C., N.I.U., M.L.P.B.

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**Appendix A. Supplementary data**

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cmi.2020.10.010.

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