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SARS-CoV-2 infection complicated by inflammatory syndrome. Could high-dose human immunoglobulin for intravenous use (IVIG) be beneficial?

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Dear Editor,

We have read with interest your editorial [1]. Indeed, the pandemic infection coronavirus disease 2019 (COVID-19), caused by the new coronavirus named severe acute respiratory syndrome coronavirus 2-related (SARS-CoV-2), is a major concern worldwide because of its highly contagious nature, the great number of patients requiring intensive care therapy and the high mortality rate. In the absence of vaccine or passive immunotherapy, one of the principal aim in the treatment of these patients is to prevent the potent virus-induced inflammatory stimuli from leading to the acute respiratory distress syndrome (ARDS), that has a severe prognosis. Indeed, following SARS-CoV-2 infection, different clinical pictures may arise. They range from: 1) asymptomatic, or mild fever with a dry cough with or without seasonal flu-like symptoms, to 2) dyspnea ranging from effort to spontaneous respiratory problems requiring hospitalization. This clinical condition can resolve or progress in 17–19.6% of symptomatic patients to 3) ARDS, requiring positive pressure oxygen therapy and often, intensive care therapy. In this phase, disseminated intravascular coagulation [2] and multi-organ failure can also be observed (5%). This rapidly evolving condition is the main cause of death worldwide in infected patients [3–5]. Clinical recovery can occur at any of the above-mentioned stages, but more rarely from stage 3 (3.4%) [3–5]. Stage 3 is preceded by a marked rise of serum ferritin and C-reactive protein (CRP) levels and increased erythrocyte sedimentation rate, and is associated to severe edema due to an alveolar capillary leak-like syndrome (responsible for the ground glass picture seen at chest high resolution CT scan), leading to a marked impairment of gas exchange, requiring assisted ventilation. Overall, these clinical and laboratory pictures suggest a pro-inflammatory cytokines-driven ARDS.

Thus, ARDS is induced by a potent virus-mediated inflammation, resembling the inflammation observed in some auto-immune/−inflammatory diseases such 1) juvenile idiopathic arthritis [6]; 2) Kawasaki disease [7], 3) the catastrophic anti-phospholipid syndrome (CAPs) [8] and 4) the systemic capillary leak-like syndrome (SCLLS) [9], the latter two being complications of the antiphospholipids antibodies syndrome (APS) [10].

Before ARDS takes place, only one drug with immunomodulatory properties, namely hydroxy-chloroquine, is currently being used in these patients. Different mechanisms of action have been hypothesized or assessed for it, including down-modulation of natural and adaptive immunity [11], reduction of the intracellular viral replication and uptake [12].

At ARDS stage, the targeting of IL-6 seems to be promising and after successful attempts in stabilizing the alveolar capillary membrane and shortening the intensive care unit stay [13–16], a number of controlled clinical trials are ongoing with anti-IL-6 monoclonal antibody (mAb) (NCT04306705, NCT04317092, and EudraCT Number: 2020–001110-38). It cannot be excluded that small molecules given per os, like the JAK-1 inhibitor, which interfere with IL-6-triggered intracellular signals, may eventually be used instead of mAb to prevent ARDS.

1. Human immunoglobulin for intravenous use (IVIG) can be useful to lower inflammation in SARS-COV-2 infection and preventing ARDS

The IVIG preparation consists of highly purified immunoglobulins (Ig), mostly of the IgG class, obtained from between 1,000 and 15,000 healthy donors per batch [17,18]. Therefore, the majority of these molecules are natural antibodies with polyreactive properties, that can recognize and neutralize different pathogenic exogenous antigens (viral or bacterial antigens / toxins and superantigens) [19], as in the case of coronavirus infection, or endogenous antigens (i.e., cytokines, chemokines and metalloproteases), as in the case of CAPs and SCLLS [9,20] or of Kawasaki disease, parvovirus infection or streptococcus-derived superantigens, hypothesized to trigger the vasculitis [21]. The anti-inflammatory / immune-regulatory role of IVIG also relies on their Fc region interaction with the corresponding Fcγ receptors (FcγRs). Since FcγRs are expressed on cells involved in natural (phagocytes) and adaptive (T cells, B cells) immunity, and on cells (antigen presenting-cells) bridging natural and adaptive immunity, the interaction may modulate signaling through FcγRs, ultimately inducing potent anti-inflammatory effects [18,22,23]. IVIG may also influence the number and function of regulatory T cells (Tregs) which help to control inflammation and inhibit T cell activation [24], tumor necrosis factor (TNF)-α production, IL-6 and matrix metalloproteinase 9 activity, primarily

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Table 1
Infectious and autoinflammatory diseases considered for the off-label use of human normal immunoglobulin for intravenous (IVIG) [18].

Disease	Rationale and/or mechanism of action
Prophylaxis in haematopoietic stem cell transplantation	Ig replacement
Infection disease conditions (toxemia, parvovirus 19)	Neutralization of pathogenetic exogenous antigen, anti-inflammatory effects
Infections in solid organ transplantation, surgery, trauma, burns	Ig replacement
Idiopathic arthritis (especially the juvenile inflammatory form)	Fc-mediated
Dermatomyositis and polymyositis	Fc-mediated
Catastrophic antiphospholipid syndrome	Fc-mediated, Fab-mediated
Systemic capillary leak-like syndrome	Fc-mediated, Fab-mediated
Vasculitides (ANCA-associated)	Fab-mediated, Fc-mediated, blocking of CDC and ADCC.
Skin autoimmune diseases (pemphigo, epidermolysis bullosa, atopic dermatitis, chronic urticaria)	mostly Fc-mediated, anti-inflammatory,
Myasthenia gravis	Fab-mediated
Asthma	Anti-inflammatory

ADCC, antibody-dependent cell-mediated cytotoxicity; ANCA, anti-neutrophil cytoplasmic antibody; CDC, complement-dependent cytotoxicity.

responsible for the vascular damage in a mouse model of inflammatory disease [25]. Striking evidence of the anti-inflammatory role of IVIG is the decreased serum levels of inflammatory cytokines following their infusion in patients with Kawasaki disease [26]. The above-mentioned properties are the rationale for suggesting IVIG use in SARS-CoV-2 infection to prevent and counteract the cytokine-mediated interstitial and alveolar wall edema responsible for ARDS. IVIG polyreactivity might also serve to speed virus clearance.

Besides being given to patients with (primary or secondary) IgG deficiency as replacement therapy to prevent infections, at the dosage of 0.4 g/kg administered in one day every three-four weeks [17,18], IVIG preparations were also successful in treating inflammatory, immune-mediated diseases or infectious diseases, at a five-fold higher dosage (2 g/kg given in two to 5 days). High dosage is required to ensure an optimal binding of natural antibodies to pathogenic antigens, considering the relatively low antigen-binding affinity of natural antibodies, and to ensure a sufficient saturation of FcγRs on immune cells.

To support the concept that IVIG may be successfully used in COVID-19 is the similar etiology or inflammatory pathogenesis between SARS-CoV-2 infection and diseases for which the use of IVIG has been approved by the European Medicines Agency (EMA)(https://www.ema.europa.eu/en/) and the US Food and Drug Administration (FDA) (https://www.fda.gov/), including Kawasaki disease, or for which IVIG are employed off-label with beneficial effects (Table 1) [18]. The latter include inflammatory diseases 1) induced by endotoxemia or infectious diseases, especially those observed in subjects with organ(s) function impairment, such as in aggressive viral infections, or in subjects with compromised clinical conditions; or 2) auto-immune/−inflammatory - genetically sustained – rheumatic diseases, such as the aforementioned vasculitides, CAPs and SCLLS, the latter two resembling an inflammatory syndrome likely triggered by endogenous or exogenous antigens in the context of APS [9,10]. SCLLS has also been observed in Kawasaki disease [27]. Last but not least, IVIG were found to be effective in the treatment of patients with SARS [28].

To date, there has been only one report (dated March 25) of the successful administration of IVIG in three patients with severe COVID-19 [29], but randomized clinical trials have been started (NCT 04261426). As several months will pass before these ongoing trials are concluded, we believe IVIG meet all the criteria for off-label use in SARS-CoV-2 infection, in view of their immunomodulatory and protective action against superinfections, which can be arise in the ARDS phase [30,31].

In conclusion, SARS-CoV-2 infection can at a certain point turn into a true inflammatory syndrome. Before ARDS develops, we propose that IVIG can be useful in preventing inflammation through different mechanisms of action. IVIG may also serve as immunological support in SARS-CoV-2 infected patients, protecting them from being overwhelmed by superinfections.

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