Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Commentary

Intravenous immunoglobulins for the treatment of the hyper-inflammatory response in COVID-19. Another failure of immunomodulatory therapy?

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Diphtheria toxin was discovered in 1880, and shortly after this the treatment of infectious diseases with the serum of convalescent patients was proposed for the first time [1]. Since then, a long chapter has been written in the history of medicine about the use of serum or plasma containing immunoglobulins for the treatment, pre-emptive therapy or prophylaxis of infectious diseases. In the pandemic of influenza virus infection in 1918, called the 'Spanish flu', convalescent human serum was used for patients with pneumonia [2]. In Spain and in other European countries 'anti-pneumococcal' and 'anti-streptococcal' sera were also used during this devastating 20th-century pandemic [3]. Hyperimmune intravenous immunoglobulins (IVIGs) have been used, with greater or lesser success, for the treatment or post-exposition prophylaxis of diphtheria, tetanus, botulism, rabies, hepatitis A and B viruses, cytomegalovirus, dengue, varicella–zoster virus and Ebola virus infections [4].

A single serum for the infusion of IVIG is usually prepared from the samples collected by pooling sera from thousands of donors. There are at least four different strategies for the use of immunoglobulins for the treatment of infectious diseases: (a) immunoglobulins containing specific antitoxins obtained after deliberate immunization, (b) immunoglobulins obtained from the serum of previously vaccinated individuals or from convalescents, sera of a determined infection used due to their neutralizing properties against a certain microorganism, (c) sera from donors of the general population on the assumption that they contain specific neutralizing immunoglobulins active against infections that are prevalent in that population, and (d) non-specific immunoglobulins from healthy donors used because of their supposed immunomodulatory effects in counteracting immunological hyper-activation secondary to a certain infection.

The exact mechanism of action of immunoglobulins when they are used for this latter purpose is not completely understood. Immunoglobulin G (IgG) presents two functional domains, known as the $F(ab)_2$ fragment (dimeric antigen-binding fragment) and the Fc fragment (crystallizable fragment). The first is responsible for specific antigen binding and the second for binding to the receptor and complement system. Several hypotheses have been proposed to explain their anti-inflammatory and immunomodulatory effects [5]. For example, IVIGs include antigen-specific IgG targeting endogenous antigens—mediated by the $F(ab)_2$ fragment—as cytokines, chemokines or complement factors. High levels of Fc can saturate their receptors in endothelial cells, decreasing the activity of the innate immunity (macrophages, dendritic cells, natural killer cells and neutrophils) and decreasing the activation of the complement system. Other mechanisms mediated by the Fc fragment

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have adaptive immunity as their target; some Fc receptors (mainly FcγRIIB: type IIB γ receptor of Fc) negatively regulate the inflammatory response. High-dose IVIGs produce an upregulation in FcγRIIB that induces the apoptosis of B cells as well as the death of Th1, Th2 and Th17 cells [6].

In this issue of *Clinical Microbiology and Infection* Liu J et al. [7] present the results of a multicentre retrospective study to evaluate the effect of IVIG, as immunomodulatory therapy, in patients admitted to hospital due to severe pneumonia caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (according to prespecified criteria that included $PaO_2/FiO_2 \leq 300$ mmHg). The investigators included 406 patients who had received IVIG according to a decision at the "discretion of the physician in charge of the patient". They compared them 1:1 to controls, matched by confounding factors, who did not receive IVIG. The authors did not find a significant difference in 28-day mortality (that was established as the main outcome): average treatment effect was 0.008 (95% confidence interval −0.081 to 0.097; p 0.86). There were no differences between the two groups for most of the secondary outcomes.

There are some methodological issues in this article [7] that must be highlighted. First, the authors included patients with "lung imaging" lesions that had progressed "more than 50% within a period of 24–48 hours". In our opinion, this criterion might be difficult to define in hindsight, especially if simple chest x-rays were used to establish this criterion. Second, we are not informed about the percentage of patients receiving steroids, other immunomodulatory drugs (such as tocilizumab) or antiviral drugs (such as remdesivir) in both groups. Third, we are informed about the time from hospitalization to IVIG treatment but not about the time from symptom onset to the initiation of treatment with IVIG (albeit both groups presented the same grade of inflammation as determined by the level of C-reactive protein). Fourth, we know neither the exact dates on which the study was developed (beginning and end of recruitment) nor its geographical localization. This information would be relevant for the study as it might have influenced the prevalence of specific anti-SARS-CoV-2 antibodies in the plasma samples collected from the donors (albeit IVIG might have been pooled before the pandemic). Fifth, despite matching, and due to the retrospective design of the study, the presence of occult confounders influencing the result cannot be excluded.

We would also like to call attention to the fact that the median dose of IVIG that was used was 9.8 g/day for survivors and 10.42 g/day for non-survivors [7]. These doses seem to be much lower than those usually prescribed when an immunomodulatory effect of IVIG is sought. For example, in a recent study evaluating IVIG treatment for patients developing septic shock in the context of necrotizing fasciitis, the median dose was 1 g/kg (this will mean a dose of 70 g/day for a standard weight of 70 kg) [8]. This difference in dosage might justify the negative results obtained in the current study. In another study reporting negative results, developed in Japan, low-dose IVIGs were used in sepsis [9].

As previously specified, IVIG can be used for the treatment of infectious diseases in different ways, and it is important not to confuse them. The authors of the present study propose using non-specific IVIGs based on their immunomodulatory effect. But they cite, as previous relevant studies in the same line of research, three studies that used IVIG in a different way. In one of them IVIGs were used for an autoimmune disease [10]. In the second plasma with high-titre anti-influenza antibodies was used due to the supposed direct neutralizing properties of the specific immunoglobulins [11] but not based in their immunomodulatory properties. The third refers to a study based on the use of convalescent plasma for Middle East respiratory syndrome coronavirus (MERS-CoV) pneumonia but, again, it was not based on the use of non-specific IVIG [12]. The use of convalescent plasma has also been extensively studied in the context of coronavirus 2019 (COVID-19) [13].

The primary outcome for the study by Liu et al. [7] was 28-day mortality, which is the standard for many trials and other comparative studies searching for therapeutic alternatives in COVID-19. In our opinion, many other determinants for mortality might be implicated when the outcome is set 4 weeks away from a punctual and short-in-time therapeutic decision, as IVIG treatment is. Maybe alternative outcomes—such as 14-day mortality or improvement in respiratory and/or inflammatory parameters—might be more appropriate for measuring the effect of this type of immunomodulatory treatment.

Previous experiences of the use of non-specific IVIGs with an immunomodulatory purpose in the context of severe COVID-19 have been published. Two comparative studies demonstrated a benefit of IVIG in terms of mortality rate [14,15]. Both studies included fewer than 30 patients in the arm receiving IVIG. Another study demonstrated a benefit of IVIG in terms of clinical parameters [16]. A randomized controlled trial, also including a very limited number of patients, did not demonstrate a reduction in the mortality rate [17]. The methodological limitations of all the studies preclude the extraction of any definitive conclusion about the role of IVIG in the context of SARS-CoV-2 infection.

Treatment with immunoglobulins is not exempt from adverse events such as a serum sickness reaction or thrombotic events (not specifically assessed in their study) as well as the potential transmission of some microorganisms [18]. Maximum caution and quality control should be applied in IVIG preparation [18].

We acknowledge the effort of Liu J et al. [7] to bring some light into a field in which available scientific information is scarce. Despite its negative results, their study must be considered as an exploratory approach to a complex clinical situation, paving the way for the development of prospective clinical trials to study the immunomodulatory effect of non-specific IVIG in the context of the COVID-19 pandemic.

Author contributions

Both FLM and JMA participated in the conceptualization and writing of the original draft of this Commentary.

Transparency declaration

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