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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Review

Intravenous immunoglobulins (IVIG) in severe/critical COVID-19 adult patients

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ABSTRACT

The coronavirus disease 2019 (COVID-19) pandemic has become a huge obstacle to the health system due to the high rate of contagion. It is postulated that intravenous immunoglobulins (IVIG) can lower the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)-related inflammation and prevent the development of acute respiratory distress syndrome (ARDS). The main advantages of IVIG treatment might be targeting cytokine storm in severe and critical COVID-19 by influences on complement, innate immune cells, effector T-cells, and Tregs. Randomized clinical trials (RCTs) and non-RCTs evaluating the safety and efficacy of IVIG in patients with severe/critical COVID-19 were performed. It seems that early administration of high-dose IVIG (in the acceleration phase of the disease) in severe or especially critical COVID-19 may be an effective therapeutic option, but there are no strong data to use it routinely. The results regarding mortality reduction are inconclusive. Additionally, IVIG treatment carries a risk of complications that should be considered when initiating treatment. However, given the COVID-19 mortality rate and limited therapeutic options, the use of IVIG is worth considering. This review summarizes the development and highlights recent advances in treatment with IVIG of severe/critically ill COVID-19 patients.

1. Introduction

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causes coronavirus disease 2019 (COVID-19) [1]. Thus far, globally over 6 million people have died from COVID-19, and more than 700 million have been infected with SARS-CoV-2 [2]. Most patients experience mild symptoms of SARS-CoV-2 infection [3]. However, nearly 15% of patients, especially elderly with comorbidities such as diabetes and cardiovascular diseases, can suffer from severe pneumonia, acute respiratory distress syndrome (ARDS), and multiple organ failure, which finally can lead to death [3,4].

Intravenous immunoglobulin (IVIG) preparation consists of highly purified immunoglobulins obtained from thousands of healthy donors [5]. The IVIG is used as antibody replacement therapy in primary or acquired immunodeficiencies (low dose; usually 0.2–0.8 g per kg of body weight/month) and as immunomodulatory treatment in auto-immune or auto-inflammatory diseases (high dose; usually 0.8–2 g per kg of body weight) [6]. In replacement therapy in primary immunodeficiency syndromes, the recommended starting dose is 0.4–0.8 g/kg given once, followed by at least 0.2 g/kg given every three to four weeks. Generally, the required dose is of 0.2–0.8 g/kg/month and dose interval usually varies from 3 to 4 weeks [7]. For patients with secondary immunodeficiencies, the recommended dose of IVIG is 0.2–0.4 g/kg every three to four weeks [7]. Higher doses of IVIG are used to reach the immunomodulation effect in patients with e.g., primary immune thrombocytopenia (0.8–1 g/kg given on day one and this dose may be repeated once within 3 days or 0.4 g/kg given daily for two to five days), Guillain Barré syndrome (0.4 g/kg/day over 5 days what gives a total dose of 2 g/kg), Kawasaki disease (2 g/kg should be administered as a single dose), chronic inflammatory demyelinating polyradiculoneuropathy (2 g/kg divided over 2-5consecutive days, followed by 1 g/kg over 1–2 consecutive days every 3 weeks), multifocal motor neuropathy (2 g/kg given over 2–5 consecutive days, followed by 1 g/kg every 2–4 weeks or 2 g/kg every 4–8 weeks over 2–5 days [7–13]. The immunomodulatory effect of IVIG can be potentially used in the treatment of COVID-19 patients.

Generally, it seems that IVIG neutralizes different pathogenic exogenous and endogenous antigens which can help fight against bacterial or viral infections and lower the level of cytokines [6,14]. Fc-mediated and Fab-mediated mechanisms are potentially responsible for the

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immunomodulatory action of IVIG [6]. The main receptors of immunoglobulin G (IgG) are Fc gamma receptors (FcγRs) (Fig. 1) which of different affinities for monomeric IgG are found on B cells, NK cells, dendritic cells, macrophages, monocytes, and neutrophils [6]. Therefore, immunomodulatory actions triggered by IVIG are manifold [6,15]. Administration of IVIG leads to saturating the FcγRs (fewer FcγRs are available). However, too high concentration of monomeric IgG (above the normal plasma levels) may lead to dysfunction of FcγRs, and the immunomodulatory effects can be explained in part by this mechanism [6,16]. Therefore, it seems that for immunomodulatory effects, high doses of IVIG are needed [6,17,18]. The second theory of IVIG action as an immunomodulator is related to an upregulation of the inhibitory FcγRIIb on effector cells [6,19]. Moreover, shortening the half-life of all IgG, together with harmful auto-antibodies, can be made by saturation of the neonatal FcR (FcRn) receptor with a high dose of IVIG (Fig. 1) [6]. IVIG may also reset the balance at the level of dendritic cells and reduce responses to interferon (IFN) [6]. IVIG modifies also dendritic cell function by reducing their activation, maturation, differentiation, antigen processing, and presentation. It also inhibits the proliferation and antigen-presentation functions of autoreactive B lymphocytes, leading to a decrease in pathogenic autoantibodies [20]. IVIG achieves this by neutralizing B cell survival factors, preventing activation of FcγR, reducing proliferation, sequestering autoantigens, decreasing receptor-mediated activation, and inducing apoptosis of autoreactive B cells [20]. It is suggested that IVIG may take some role in the inhibition of the complement cascade [6,21]. Complement activation C5a is a potent proinflammatory and chemoattractant factor for neutrophils, monocytes, and macrophages, increases the production of tumor necrosis factor (TNF), macrophage inflammatory protein-1α (MIP-1α), and interleukin 6 (IL-6), and is associated with tissue damage and disease severity in COVID-19 [22,23]. It seems that the C5a-C5aR1 axis has a role in the pathophysiology of ARDS, while C5a plasma level can be lowered by IVIG [22,23]. To evaluate how IVIG reduce inflammation in COVID-19 patients, a study analysis level of 41 inflammatory biomarkers in plasma was conducted [22]. Blood samples were collected at several time points from five COVID-19 patients who received IVIG (Flebogamma 10% at the dose of 400 mg/kg/d for 5 days) [22]. It was demonstrated that the plasmatic levels of TNF, interleukin 10 (IL-10), interleukin 5 (IL-5), interleukin 7 (IL-7), MIP-1α, hepatic growth factor, C5a, fatty acid–binding protein 2 and lipopolysaccharide (LPS)-binding protein (LBP) steadily declined over the two weeks following the start of treatment [22].

The SARS-CoV-2 induces a strong activation of the interleukin IL-1β/IL-6 pathway but not the IFN-I and -III [1]. During SARS-CoV-2 infection an IL-6 and interleukin-1 receptor antagonist (IL1RA) are elevated [1]. Hence, controlling the inflammatory mediators for treating cytokine release syndrome (CRS) is essential to managing severe COVID-19 cases [1,24]. Neutrophils could also play some role in COVID-19 patients, which is supported by study results showing that elevated circulating neutrophils may have prognostic value for identifying patients at risk for developing severe COVID-19 [1]. Generally, it seems that the COVID-19 patient`s treatment should be more focused on controlling inflammation than on influencing IFN-related responses [1].

IVIG has been observed to reduce the levels of inflammatory

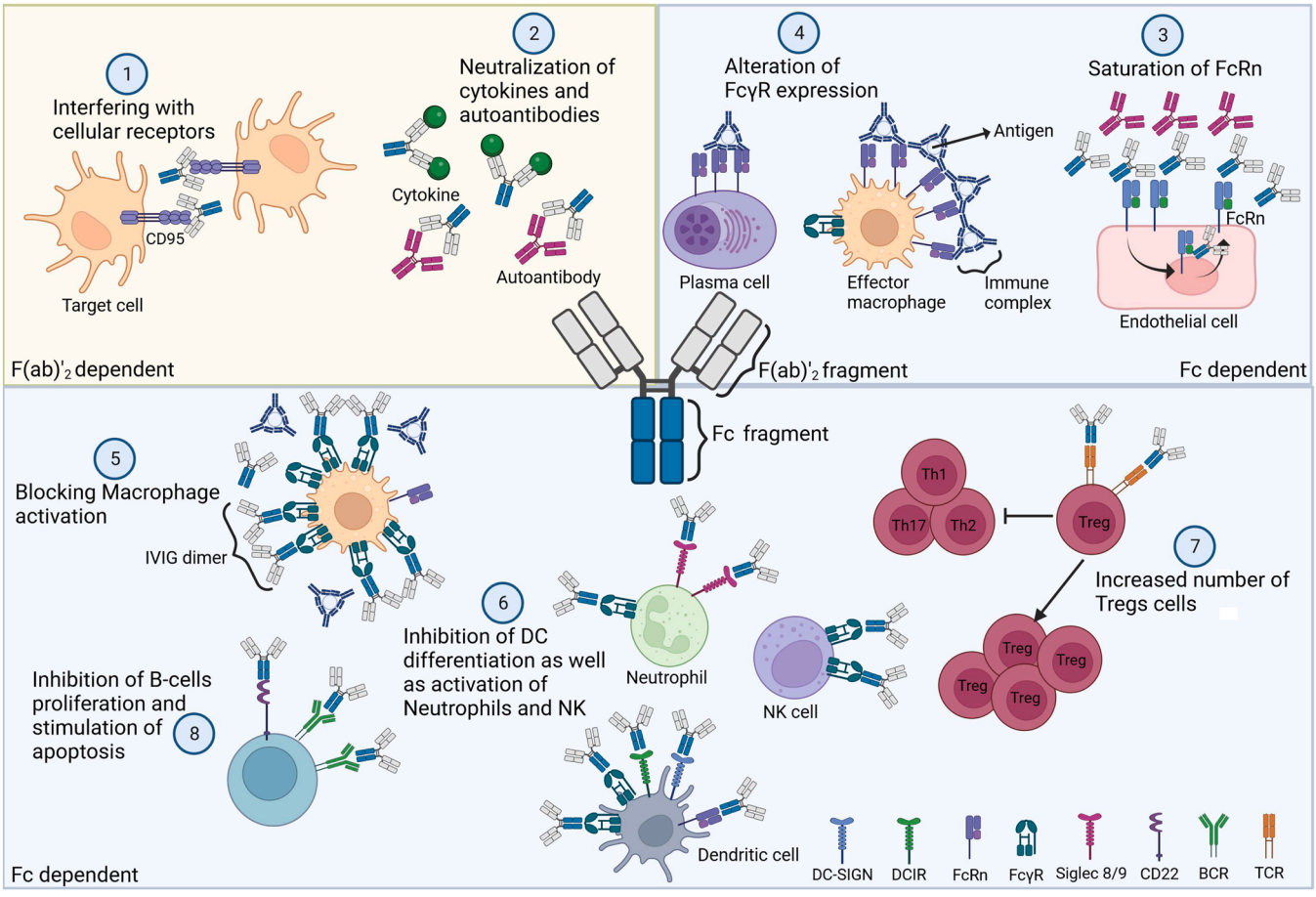

Fig. 1. Potential IVIG anti-inflammatory and immunomodulatory effects. IVIG influence the immune system both direct and indirect. IVIG reduce the synthesis of cytokines, supress the complement system and restrict immune cells growth as well as the maturation of T cells and DCs. On the contrary, these molecules stimulate the FcγR receptor and increase the number of Tregs cells, macrophages and B cells. DC-dendritic cell, NK-natural killer cells, BCR-B-cell receptor, TCR – T-cell receptor. Created with BioRender.

cytokines, may affect the regulatory T cells (Tregs) activity, and inhibit the production of TNF-α, IL-6, and matrix metalloproteinase 9 (MMP9) [25]. Therefore, IVIG may prevent the cytokine-mediated interstitial and alveolar wall edema responsible for ARDS among patients with SARS-CoV-2. Additionally, it has been proposed that the polyreactivity of IVIG might contribute to faster elimination of the virus [25]. It seems that for immunomodulatory action a high IVIG dose is required (e.g., 2 g/kg given in 2–5 days) to guarantee an optimal binding of antibody-pathogenic antigen, and a sufficient saturation of FcγRs mentioned above [6,25].

Data collected in studies involving IVIG conducted among various populations of COVID-19 patients, appear to indicate that it has the greatest potential in the treatment of severe and critically ill COVID-19 individuals. Therefore, this review summarizes the development and highlights recent advances in the severe/critically ill COVID-19 patients treatment with IVIG.

2. Methods

A systematic literature search was performed through Medline (PubMed), EMBASE, SCOPUS, and Cochrane Library electronic databases. Studies were selected to assess the efficacy of IVIG in treating patients with severe/critical COVID-19. In this review, all randomized clinical trials (RCTs) and non-RCTs evaluating the safety and efficacy of IVIG in patients with severe/critical COVID-19 were included. Clinical case reports or clinical case series were not included.

3. Results

3.1. Retrospective, single-center studies

The study by Xie and colleagues investigated retrospectively the effect of treatment of patients with severe or critical COVID-19 pneumonia divided into two groups: those who received IVIG $\leq$ 48 h or $>$ 48 h after admission to the hospital [26]. The 28-day mortality rate among patients who received IVIG within $\leq$ 48 h was significantly lower [26]. Additionally, the 28-day survival time was significantly longer, while hospitalization and the intensive care unit (ICU) stays were considerably reduced when compared to the $>$ 48 h group (Table 1) [26]. The survivors received IVIG earlier than no-survivors [26]. The results of this study indicate the advantage of IVIG administered within 48 h after admission. However, the study was conducted in one center and without a control group [26].

In another study, the main criteria of severe COVID-19 were respiratory rate $>$ 30/min, signs of dyspnea and respiratory distress, peripheral capillary oxygen saturation (SpO2)$<$ 90%, and arterial partial pressure of oxygen (PaO2)$<$ 70 mmHg, despite nasal oxygen support of $>$ 5 L/min, PaO2/fraction of inspired oxygen (FiO2)$<$ 300 (mild ARDS), multi-lobular involvement or pleural fluid in the lung, as well as hypotension [27]. Patients received standard treatment with or without IVIG [27]. In the IVIG group, the Sequential Organ Failure Assessment (SOFA) score at admission was significantly lower, while more chronic cardiac disease incidences were observed in the non-IVIG group [27]. A significantly higher median survival time was noted in the IVIG group (Table 1) [27].

Patients with COVID-19-related moderate-to-severe ARDS (PaO2/FiO2 $\leq$ 200 mmHg), as defined by the Berlin criteria, were included in the next study [28]. Patients were divided into the IVIG group (a minimum one dose of 0.4 g/kg of IVIG, to a maximum of 5 doses given on consecutive days plus standard of care) and the non-IVIG group (standard of care) [28]. Concerns about IVIG treatment in this study are related to subjective decisions made by physicians about whether or not to administer IVIG and its total doses which vary in this study. However, the median cumulative dose of IVIG and the median number of doses received were 152.0 g (108.0 – 235.0 g) and 5.0 (3.0 – 5.0) in a matched cohort, respectively [28]. Among them, the median time from ICU admission to initiation of IVIG therapy was 6 days [28]. ICU mortality in the IVIG group was significantly higher than in the non-IVIG group regardless of the time from ICU admission to IVIG therapy ($<$5 days vs $\geq$5 days) and the number of given doses ($\leq$3 vs. $>$3 doses) [28]. Moreover, in the IVIG group, the incidence of acute kidney injury (AKI) was significantly higher, and it was already established that individuals with both AKI and COVID-19 tend to have a high mortality rate [28,29]. In addition, on day 28, the IVIG cohort had a smaller number of ventilator-free and ICU-free days [28]. In this work, patients received IVIG relatively late compared to other studies which showed some benefit of IVIG treatment.

The study conducted in China evaluated IVIG treatment in severe COVID-19 patients according to the definition of the World Health Organization (WHO) (Table 1) [30]. After adjusting for some confounding factors, it was shown that patients receiving IVIG experienced longer periods of hospitalization compared to the non-IVIG group [30]. The greatest limitation of this work is the lack of information regarding the time of initiation of IVIG administration, doses of IVIG, and duration of treatment. Although the authors indicated that most patients received 0.5 g/kg/d [30].

A study for severe and critical COVID-19 patients as per WHO classification (except those who were already on invasive mechanical ventilation) admitted to the ICU was conducted in India [31]. Patients who received tocilizumab, thymosin alpha-1, or steroids before invasive mechanical ventilation, or convalescent plasma after IVIG administration were excluded from the study [31]. IVIG was administered as a continuous infusion for 3 days if patients' oxygenation worsened, and was administered with a median time of 5 days from ICU admission (Table 1) [31]. In the IVIG group, a lower number of patients needed invasive ventilation, in-hospital mortality and the 28-day mortality were lower, and the length of stay in the ICU was shorter [31]. Based on the results, it seems that early administration of IVIG ($\leq$7 days from ICU admission) had significantly better outcomes regarding the need for mechanical ventilation and in-hospital mortality [31]. Limitations of this retrospective study are as follows: lack of inflammatory markers evaluation, lack of baseline immunoglobulin levels, and lack of long follow-up with imaging tests performing what could give additional information regarding the effectiveness or adverse events of IVIG treatment [31].

3.2. Retrospective, multicenter studies

The impact of IVIG administration was assessed in critical (severe type and critical type) COVID-19 patients [32,33]. The same percentage of patients died within 28 days in both groups, and 4% more patients died within 60 days in the IVIG group (Table 1) [32]. The hospitalization and duration of disease were longer in the IVIG group, and 20% more patients in the IVIG group had the critical type [32]. Researchers pointed out also that IVIG doses of $>$ 15 g/day significantly reduced 28-day and 60-day mortality, and increased survival time as compared with the group receiving IVIG of $\leq$ 15 g daily, however, the statistical significance was modest. The IVIG treatment could significantly reduce 60-day mortality, total in-hospital stay, and total course of the disease, and significantly increase survival time when IVIG is administered $\leq$ 7 days from admission [32]. Nevertheless, it seems that the dose and the time of administration are important only in the critical type. In the multivariate analysis and in the Cox proportional hazards model, only in the critical-type patients, IVIG could significantly decrease the 28-day mortality, but not the 60-day mortality [32]. Lymphopenia was the risk of poor prognosis as it was found in previous studies [32,34]. Taken together, IVIG administration did not have a beneficial effect on the whole cohort, but only in the critical-type patients (respiratory failure and needing mechanical ventilation; shock occurs; multiple organ failure, needing ICU monitoring) [32,33]. The different IVIG doses, as well as the time of IVIG administration, and retrospectively collected data, are the main limitations of this study [32].

Table 1
Results of studies with the use of IVIG among adult patients with severe/critical COVID-19.

The first author of the study (year of publication) [reference]	Type of study	Target group	Arms (number of patients)	Time of start of IVIG administration	IVIG administration details	Benefit from IVIG treatment
Xie (2020)[26]	Retrospective, single center	Severe and critical COVID-19 pneumonia	IVIG (n = 58) No control arm	> 48 h group and ≤ 48 h group were divided in accordance with use of IVIG in 48 h after admission to the hospital	20 g/day when the absolute lymphocyte count fell to $< 0.5 \times 10^9$/L	For ≤ 48 h group as compared to > 48 h group: - the length of stay in the hospital was significantly shorter - the length of stay in the ICU was significantly shorter - the proportion of patients requiring mechanical ventilation was significantly lower - the 28-day survival time was significantly longer
Esen (2021)[27]	Retrospective, single center	Critically ill COVID-19	1. IVIG (n = 51) 2. non-IVIG (n = 42)	N/A	Octagam 5%; 30 g/day for 5 days	- IVIG significantly prolonged median survival time - significantly reduced plasma levels of C-reactive protein
Ali (2021)[28]	Retrospective, single center	COVID-19 related moderate-to-severe ARDS	1. IVIG (n = 190) 2. non-IVIG (n = 400)	median time from ICU admission to initiation of IVIG therapy was 6 days (2.2–11.1 days)	0.4 g/kg; further doses of IVIG were given on consecutive days, to a maximum of 5 doses	No benefit.
Hou (2021)[30]	Retrospective, single center	Severe COVID-19	1. IVIG (n = 47) 2. non-IVIG (n = 66)	N/A	N/A most patients received 0.5 g/kg/d	- did not improve in-hospital mortality rates or the need for mechanical ventilation
Aggarwal (2022)[31]	Retrospective, single center	Severe and critical COVID-19	1. IVIG (n = 255) 2. non-IVIG (n = 280)	the median time of ICU admission to IVIG administration was 5 (3–8) days	0.5 g/kg body weight/day as a continuous infusion for 3 days	In the IVIG group: - fewer patients required invasive ventilation - lower in-hospital mortality - lower the 28-day mortality - shorter length of stay in the ICU
Shao (2020)[32]	Retrospective, multicenter	Critical (severe and critical type) COVID-19	1. IVIG (n = 174) 2. non-IVIG (n = 151)	> 7 days and ≤ 7 days from admission	> 15 g daily ≤ 15 g daily 0.1–0.5 g/kg per day 5–15 days 15 g per day (equivalent to 0.2–0.3 g/kg per day)	Critical- type: For a group with IVIG > 15 g daily as compared with the group ≤ 15 g daily: - significantly reduced 28-day and 60-day mortality and increases survival time The IVIG treatment could significantly reduce 60-day mortality, total in-hospital stay, and total course of the disease, and significantly increase survival time when IVIG is administered ≤ 7 days from admission.
Cao (2021)[35]	Retrospective, multicenter	Severe COVID-19	1. IVIG (n = 26) 2. non-IVIG (n = 89)	N/A - an average of 13.2 days of disease onset - subgroup analysis within the first week of infection vs the second week	A total dose of 2 g/kg divided over 2–5 days; 0.3 −0.5 g/kg/day for 5 days	In the IVIG group: - lower the 28-day mortality rate - shorter the length of hospitalization - faster normalization of IL-6, IL-10 and ferritin - significantly reduced mortality - administration of IVIG within the first week of the beginning of the disease was associated with a reduced 28-day mortality rate
Liu (2021)[4]	Retrospective, multicenter	Severe COVID-19	1. IVIG (n = 421) 2. non-IVIG (n = 429) 406 were matched	- the median time interval from hospital admission to initiation of IVIG treatment among all patients was 2.8 days (1–3 days)	- duration of IVIG treatment was 9.5 days for all patients Survivors: - The median duration of IVIG treatment was 11 days with a median dose of 9.85 g/day Non-survivors: - 7 days with a median dose of 10.42 g/day	In general no benefit. - No significant difference in 28-day mortality No significant differences between the IVIG group and the non-IVIG group: - for ARDS, diffuse intravascular coagulation, myocardial injury, acute hepatic injury, shock, acute kidney injury, non-invasive or invasive mechanical ventilation, continuous renal replacement therapy, and extracorporeal

(*continued on next page*)

Table 1 (*continued*)

The first author of the study (year of publication) [reference]	Type of study	Target group	Arms (number of patients)	Time of start of IVIG administration	IVIG administration details	Benefit from IVIG treatment
						membrane oxygenation except for prone position ventilation
Salehi (2022)[36]	Retrospective, multicenter	Critically ill COVID-19	1. IVIG (n = 74) 2. non-IVIG (n = 109)	N/A	- groups with the low, medium, and high doses (0.25, 0.5, and 1 g/kg) during 3–5 days; Intratect	No benefit regarding duration of hospitalization, ICU length of stay, duration of mechanical ventilation or mortality rate.
Chen (2022)[37]	Retrospective, multicenter	Critically ill COVID-19	1. IVIG (n = 392) 2. non-IVIG (n = 362) score-matched cohort: 253 patients in each group	Median 11 days (8–16) of illness onset. Prior to ICU admission, 30.1% of patients received IVIG treatment	Most patients received a dose of 0.5 g/kg/day	No benefit
Sakoulas (2020)[38] NCT04411667	Randomized, prospective, open label Pilot study	Moderate-to-severe hypoxia (sPo2 $\leq$ 96% on $\geq$ 4 L O2 by nasal cannula) but not on mechanical ventilation	1. IVIG (n = 16) 2. non-IVIG (n = 17)	beginning on the day of enrollment	IVIG 0.5 g/kg/d for 3 days beginning on the day of enrollment; Octagam 10%	In the IVIG group: - significantly reduced IL-6 serum concentration - the rate of patients requiring mechanical ventilation was reduced (not statistical significance) - patients with alveolar - arterial gradient greater than 200 mmHg showed: 1) reduction in progression to mechanical ventilation (statistically significant), 2) shorter of duration of length hospital stay, 3) shorter ICU length of stay, 4) improvement in oxygenation (Pao2/Fio2) at day 7.
Gharebaghi (2020) [39]	Randomized, double-blind placebo-controlled	Severe COVID-19	1. IVIG (n = 30) 2. non-IVIG (n = 29)	N/A	four vials daily for 3 days; Flebogamma 5% DIF GRIFOLS	In the IVIG group, the overall duration of hospitalization was longer and the in-hospital mortality rate was significantly lower
Tabarsi (2021)[40]	Randomized, single center	Severe COVID-19	1. IVIG (n = 52) 2. non-IVIG (n = 32)	The mean time from admission to IVIG initiation was 3.84 $\pm$ SD 3.35 days (1–22)	Intratect® (Biotest); 400 mg/kg daily for three doses	- A significant positive relationship between the time from hospital admission to IVIG initiation and the length of stay in the hospital and ICU among the survivors - no other benefits
Mazeraud (2021) [41] ICAR study	Randomized, phase III, multicenter double-blind, placebo-controlled	COVID-19-associated moderate-to-severe ARDS	1. IVIG (n = 69) 2. non-IVIG (n = 77)	IVIG infusion had to start before the end of the 96 h after the onset of invasive mechanical ventilation	CLAYRIG a total dose of 2 g/kg 0.5 g/kg each given over at least 8 h over 4 days	No benefit

IVIG, intravenous immunoglobulins; COVID-19, coronavirus disease 2019; ICU, intensive care unit; ARDS, acute respiratory distress syndrome; SD, Standard deviation Severe def. according to the World Health Organization (WHO) interim guidance, severe COVID-19 was defined as having one of the following three conditions: respiratory rate $\geq$ 30 breaths/min, severe respiratory distress, or peripheral capillary oxygen saturation (SpO2) $\leq$ 93% when inhaling room air [50].

In the second study, the main inclusion criteria (severe type) were as follows: respiratory distress ($\geq$30 breaths/min); or SaO2 $\leq$ 93% at rest; or PaO2/FiO2 $\leq$ 300 mmHg, and hospitalization took place within 2 weeks of the onset of symptoms [35]. Patients were divided into two groups: the IVIG group (IVIG plus standard care) and the non-IVIG group (standard care) (Table 1) [35]. Patients in the IVIG group received IVIG at an average of 13.2 days from the beginning of the disease. The 28-day mortality rate of the IVIG group was lower and the use of IVIG was associated with significantly reduced mortality [35]. Moreover, in the IVIG group, the duration of hospitalization was shorter, and generally, the normalization of IL-6, IL-10, and ferritin was faster than in the non-IVIG group [35]. In the subgroup analysis, those who received IVIG within the first week of the beginning of the disease were associated with a reduced 28-day mortality rate compared to those who started IVIG in the second week of the disease. The authors also pointed out that those without comorbidities appear to benefit more from IVIG treatment [35]. There were no IVIG-related thrombotic complications in the study. Limitations of this work are: no randomization, retrospective nature of the study, and exclusion of patients treated with remdesivir.

Patients with respiratory rate $>$ 30 breaths/min, SaO2 $<$ 93% at rest, PaO2/FiO2 $\leq$ 300 mmHg (severe patients), and lung imaging showing that the lesions had progressed more than 50% within a period of 24–48 h were enrolled in the study [4]. The median duration of IVIG treatment was 9.5 days for all patients, while for the survivors group the median duration of IVIG treatment was 11 days with a median dose of 9.85 g/day and for non-survivors 7 days with a median dose of

10.42 g/day [4]. The IVIG was administered with a median of 2.8 days from admission. The IVIG treatment did not significantly improve 28-day mortality in severe COVID-19 patients (Table 1) [4]. Although this is a study with a large group of patients, it has its limitations such as a retrospective study, the decision of IVIG administration was made by the physician, heterogeneity (patients treated in ICU and outside ICU), no data regarding baseline immunoglobulin levels, lacks data from long-term follow-up (including adverse events), patients receiving other medical treatments have not been included in this study, lack of information about weight-adjusted doses to each patient [4].

In 2022, the retrospective matched cohort study comprising data from three tertiary centers was published [36]. Critically ill COVID-19 patients (SaO2 <90% with a non-rebreather mask, those who needed noninvasive ventilation (NIV) or intubation) were divided into IVIG group (standard of care plus IVIG) and non-IVIG group (standard of care) [36]. Interestingly, the authors evaluated also separately the effect of IVIG in different dosages (low (0.25 g/kg), medium (0.5 g/kg), and high (1 g/kg)), administered during 3–5 consecutive days [36]. The standard treatment plan for patients contained hydroxychloroquine plus atazanavir/ritonavir [36]. There was no significant difference between IVIG and non-IVIG groups regarding ICU length of stay, the number of intubated patients, duration of mechanical ventilation, and mortality rate [36]. Only the duration of hospitalization was found to be significantly longer in the IVIG group. Furthermore, the longest duration of hospitalization was in the medium-dose IVIG subgroup and was significantly longer than in the non-IVIG group, but generally, different doses of IVIG had no major impact on the results. The different timing of IVIG administration was one of the limitations of this study. Outcomes do not support the advantages of IVIG addition to standard treatment in critically ill COVID-19 patients [36].

Another multicenter study was conducted with critically ill COVID-19 patients with severe respiratory failure requiring advanced respiratory support, circulatory shock, or multiorgan failure [37]. A total of 754 patients were included in the study, of which 392 patients received IVIG [37]. Most patients received a dose of 0.5 g/kg/day at day 11 from illness onset, of which around 30% received IVIG before ICU admission [37]. In the non-IVIG group, the median of days from illness onset to ICU admission was higher and more patients required vasopressin. There were no significant differences regarding survival between the groups and 28-day mortality for either hyperinflammation or hypoinflammation patients. Unfortunately, no data are available in this study regarding the total IVIG dose received by patients and the duration of IVIG treatment [37]. In addition, IVIG was administered relatively late. This study was especially insightful due to its large sample size, application of propensity score matching and inverse probability of treatment weighting to compare 28-day mortality of patients who were treated and not treated with IVIG, and consideration of the varied phenotypes of COVID-19 (hyperinflammation and hypoinflammation) [37].

3.3. Randomized studies

In the open-label randomized controlled pilot study, patients were randomly assigned to IVIG group (Octagam 10%, 0.5 g/kg/d with methylprednisolone 40 mg before infusion for 3 days plus standard of care) and the non-IVIG group (standard of care) [38]. Adult patients with moderate-to-severe hypoxia (SpO2 $\leq$ 96% on $\geq$ 4 L O2 by nasal cannula) but not on mechanical ventilation were included in the study, also tocilizumab treatment was not allowed. Glucocorticoids were received by all patients in the IVIG group and 59% of patients in the non-IVIG group [38]. In the IVIG group, a significant reduction of IL-6 serum concentration was noted, and the rate of patients requiring mechanical ventilation was reduced (not statistical significance). However, this reduction was statistically significant in favor of the IVIG group among patients with an alveolar-arterial gradient greater than 200 mmHg [38]. Moreover, these patients needed shorter hospitalization, and ICU length of stay, and had improvement in oxygenation at day 7. In addition, there were no thrombotic events [38]. The limitations of the study are as follows: conducted only in two hospitals, the small sample size, most patients were Hispanic/Latino, not a blinded study, and concomitant steroids were used. However, after performing an analysis among patients taking steroids in both groups it seems that IVIG benefit is independent of these drugs [38].

Another randomized, but placebo-controlled double-blind clinical trial was conducted among 59 adult patients with severe COVID-19 infection who did not respond to initial treatments and were assigned to the IVIG group or placebo group [39]. Patients were included in the study if they had acute respiratory syndrome, involvement of more than 30% of both lungs in high-resolution computed tomography, SaO2 < 90%, and did not respond to initial treatment (at least both one antiviral and one chloroquine-class drug) [39]. Thirty patients received IVIG (Table 1) and in this group, the overall duration of hospitalization was longer and the in-hospital mortality rate was significantly lower [39]. This study was unfortunately limited to a small number of participants. The authors concluded, that the longer duration of hospitalization in the IVIG group could be due to differences in survival between groups (patients in the placebo group had shorter survival) [39].

In Tabarsi and colleagues` randomized trial severe pneumonia was defined as respiratory rates: $\geq$ 30 breaths/min, SpO2 $\leq$ 93%, and PaO2/FiO2 $\leq$ 300 mmHg. Patients were randomly assigned to the IVIG group and non-IVIG group (Table 1) [40]. Patients in both groups received oxygen, fluids, lopinavir/ritonavir, and hydroxychloroquine [40]. As in line with other studies, it seems that early administration of IVIG has a critical impact on the results, which in this study was expressed by the shorter length of hospital and ICU stay among the survivors from the IVIG group [40]. The time from admission to IVIG administration was 1–22 days (Table 1). In general, this study did not support the therapeutic benefits of administering IVIG for severe cases of COVID-19 (taking into account e.g., mortality rate, the need for mechanical ventilation, and more than 50% improvements in chest CT scan) [40].

Finally, to evaluate the usefulness of IVIG among patients with the COVID-19, the multicentre, double-blind, placebo-controlled, phase III ICAR clinical trial was conducted [41]. Patients with invasive mechanical ventilation for up to 96 h and associated moderate-to-severe ARDS received either IVIG or placebo [41]. The median time between symptom onset and initiation of invasive mechanical ventilation was 8 days in both groups [41]. In addition, in both groups, the COVID-19 treatment before and 2 days after random assignment consisted mainly of corticosteroids and antibiotics [41]. The severity of critical illness and ARDS was similar in both groups [41]. The number of ventilation-free days by day 28 was chosen as the endpoint. It seems that IVIG and corticosteroids do not make any synergistic effects in COVID-19-associated ARDS [41]. There was no statistical difference in the prespecified endpoint between the groups, which suggests no superiority in the use of IVIG in these patients [41]. The IVIG administration had also no effect on the mortality rate or proportion of extubated patients at day 28. Moreover, serious adverse events occurred at a numerically higher rate among patients in the IVIG group than in the placebo group [41]. Ten and three patients had deep vein thrombosis in the IVIG group and in the placebo group, respectively. While, among the IVIG and placebo groups was a total of four and one cases of pulmonary embolism, respectively [41]. This study was conducted in one country among only 146 patients and with median follow-up time of 90 days [41]. Although the benefit of IVIG has not been demonstrated in the prespecified group of patients in the ICAR study, it is suggested that further studies with IVIG should focus on the earlier phase of COVID-19-related pneumonia (prevent progression to ARDS) [41]. It is also speculated, that IVIG could have a positive influence on the recovery phase of ARDS by promoting the tissue repair processes [41].

3.4. Meta-analysis

Six studies from China (5 retrospective and observational and one

randomized clinical trial) with a total of 1142 patients were included in the meta-analysis [42]. Limited data regarding the use of IVIG were available and pooled results from 4 retrospective studies showed no survival benefit among patients receiving IVIG [42]. There are many limitations of this meta-analysis and results should be interpreted with caution.

In the next meta-analysis with 825 hospitalized patients, carried out by Xiang and colleagues, 4 clinical trials and 3 cohort studies mentioned above were included [27,32,38–40,43–45]. The authors scored the quality of the seven included studies as low. Based on the information gathered from the studies and the WHO definition of severity, all patients were divided into 'non-severe', 'severe', and 'critical' subgroups [45]. The analysis showed that IVIG could reduce the mortality compared with the control group in a critical subgroup, but not in the severe or non-severe subgroups [45]. Moreover, the results suggest that IVIG prolonged hospitalization in a critical subgroup (limited data) and showed a trend of prolonging the hospitalization in the severe subgroup (no statistical significance) [45]. It is postulated that longer hospitalization is related to the higher survival rate in the IVIG group. The use of IVIG had no bearing on the duration that patients of the severe subgroup spent in the ICU [45]. Importantly, this meta-analysis as the studies cited earlier shows that the efficacy of IVIG seems to be related to the COVID-19 disease severity. The results of IVIG treatment could be influenced by many factors such as dosage, time of IVIG treatment initiation from admission and duration of IVIG treatment, other concomitant treatments, and perhaps even the type of used IVIG. The number of randomized clinical trials was limited, and only one was blinded. Moreover, there was a relatively small number of patients in each study. Notably, the assessment of the advantages of IVIG treatment may be interfered with the therapeutic effect of the parallel use of other drugs for COVID-19. This effect can be partially counteracted by analyzing a control group, not receiving IVIG. Of note, in this meta-analysis severe and non-severe COVID-19 patients were included.

Focosi and colleagues examined 10 studies which were included also in this review. They have found that the use of high-dose IVIG was not associated with a significantly reduced risk of death, however, in moderate COVID-19 patients IVIG significantly reduced the length of hospital stay [46]. In conclusion, their analysis was negative regarding the usefulness of IVIG in COVID-19 patients [46].

Of note, meta-analysis of 48 randomized controlled trials, evaluating several drugs, revealed the efficacious of immunoglobulin gamma in the treatment of severe COVID-19 [47]. A detailed discussion of this meta-analysis is beyond the scope of this article.

4. Future directions

It is postulated that IgM-enriched IVIGs (IGAM), which in addition to IgG also contain IgM and IgA can be more effective than standard IVIG preparations in the treatment of critical COVID-19. It seems that administering IGAM before mechanical ventilation is required to receive the best results of critical COVID-19 disease treatment [48]. Although there are no direct treatment recommendations from Rahmel and colleagues` retrospective multicentric cohort study, the authors suggest that there is a clinically relevant effect of IGAM in certain subgroups [48]. However, this needs to be tested in randomized controlled trials.

In the future, more people who have undergone SARS-CoV-2 infection and after COVID-19 recovery will be donors for IVIG production. It was already shown the appearance of antibodies to SARS-CoV-2 in pooled donor plasma and IVIG products in 2020, and increasing levels of anti-SARS-CoV-2 antibodies in pooled plasma and IVIG products up to September 2021 [49]. IVIG from these donors can show an added benefit in COVID-19 treatment, not only immunomodulatory.

5. Conclusion

Most studies included in the review are retrospective. The difficulty of a fair comparison of the discussed studies lies in their heterogeneity: different daily and total doses of IVIG, the use of various IVIG preparations, duration of therapy, time of initiation of IVIG treatment (which seems to be critical), sometimes a non-homogeneous population, sometimes not taking into account confounders, and even a different definition of severe or critical COVID-19. Moreover, most studies have a short follow-up. However, given the sudden pandemic situation (first infection in 2019) and the need for rapid drug testing, it would be unrealistic to expect to already have many results from multi-center, prospective late-phase clinical trials with long follow-up periods. The most common endpoints were mortality and length of hospital stay.

Currently, most studies show that the timing of IVIG administration is critical, and saying "time is precious" takes on a special meaning in this context. Usually, early administration of IVIG (in the acceleration phase of the disease) in severe or especially critical COVID-19 may be an effective therapeutic option [50]. The effect of immunomodulators is dose-dependent, and high doses of IVIG are needed. However, some authors postulate that mentioned benefit of IVIG relies mostly upon their early administration.

Data on mortality among different studies are not conclusive. In a randomized study conducted by Gharebaghi and colleagues in the IVIG group, in-hospital mortality was significantly lower, however, in the second randomized ICAR study there was no benefit of IVIG treatment [39,41]. Of note, in the first mentioned above randomized study severe COVID-19 patients were included while in the ICAR study COVID-19-associated moderate-to-severe ARDS patients [39,41]. Moreover, randomized trials were conducted with a number of patients ranging from 16 to 77 [38–41]. A large retrospective multicenter study showed a reduction in mortality in the IVIG group, however, the second large retrospective study showed no benefit regarding mortality [4,32]. Taking together, a randomized trial with a large number of patients is needed to finally determine whether IVIG reduces mortality. However, in some studies, IVIG has shown some other benefits. Analyzing the results of the cited studies, it seems that there is a population of patients with severe/critical COVID-19 who may particularly benefit from early high-dose IVIG administration. It seems that immunological and inflammatory biomarkers may be helpful in their identification.

The efficacy of IVIG may improve because a higher percentage of donors will have over time neutralizing antibodies to the SARS-CoV-2. Therefore, new trials are needed to evaluate if the last batches of IVIG will have higher effectiveness.

In conclusion, IVIG may be beneficial, especially in critical COVID-19, but there are no strong data to use it routinely. Additionally, IVIG treatment carries a risk of complications that should be considered when initiating treatment. During IVIG treatment can occur side effects such as hypersensitivity reactions, thromboembolism (myocardial infarction, cerebral vascular accident, pulmonary embolism, deep vein thromboses), acute renal failure, transfusion-related acute lung injury, aseptic meningitis syndrome, hemolytic anemia, or neutropenia/leukopenia [7,51]. Overall, serious adverse events were not statistically significantly more frequently reported in the IVIG arm, based on the mentioned studies. It is worth noting that one of the single-centre retrospective studies reported a significantly higher incidence of AKI in the IVIG group [28]. However, in the randomized ICAR trial, this significance was not confirmed [41]. Therefore, given the COVID-19 mortality rate and limited therapeutic options, the use of IVIG is worth considering. However, caution should be exercised when prescribing and administering IVIG to obese patients and patients with pre-existing risk factors for thrombotic events and ensure that patients are adequately hydrated if IVIG is administered [7].

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Consent to participate

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Conception and design/idea for the article (DK), acquisition of data/literature search (DK), analysis and interpretation of data (DK, JB), draft of the manuscript (DK), writing the paper (DK, JB), preparation of the table (DK), drawing figure (JB), critically revised of the work (DK, JB), approval of the final version of the manuscript (DK, JB).

Declaration of Competing Interest

Authors have no conflicts of interest to declare.

Data Availability

Information/data placed in the manuscript are available in the source articles indicated in references.

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