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Exploring Intravenous Immunoglobulin (IVIG) efficacy in the Treatment of COVID-19

Abdulgader H. Albar[1,2*] Feras S. Bajaba[1,3] and Bassam O. Aljohany[1]

[1]Biological Sciences Department, Faculty of Science, Microbiology, King Abdulaziz University, Jeddah, **Saudi Arabia**
[2] Department of Microbiology and Parasitology, Collage of Medicine, University of Jeddah, Jeddah, **Saudi Arabia**
[3] Biology Department, Faculty of Science, University of Jeddah, Jeddah, **Saudi Arabia**

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***Correspondence:** abdulkader_albar@hotmail.com **Received: May 02, 2025, Revised: June 22, 2025, Accepted: June 24, 2025 e-Published: June 30, 2025**

The management of COVID-19 and its associated problems has become exceedingly challenging. This disparity has prompted the investigation and utilization of available therapeutic options, including supportive interventions, immunomodulatory drugs, convalescent plasma transfusions, and antiviral treatments. Although several treatments have demonstrated efficacy in treating COVID-19, there is a growing emphasis on immunoglobulins, especially intravenous immunoglobulin (IVIG), as a valuable therapeutic option for moderate and severe cases of COVID-19. The application of IVIG in the management of COVID-19 is guided by the anti-inflammatory properties of the immunoglobulins. The principal pathophysiological observation in severe COVID-19 cases is hyperinflammation, marked by increased levels of interleukin (IL)-2, IL-6, IL-7, tumor necrosis factor-alpha, inducible protein, and interferon gamma, which signifies a cytokine cascade and cytokine release syndrome. One of them is IVIG, which is used against inflammatory, immune-mediated diseases or infectious diseases. Numerous studies assert that IVIG treatment cured COVID-19 patients. The use of IVIG as an adjuvant treatment for COVID-19 has shown encouraging outcomes. Its clinical efficacy is attributed to its immunomodulatory and anti-inflammatory effects. While this is so, there exists a need for further research on the clinical efficacy of IVIG, given the use of relatively small sample sizes in the clinical trials conducted so far. This review has to show the potency of IVIG as a treatment for COVID-19. Further, other challenges that limit the use of IVIG therapy in COVID-19 include issues of cost and safety concerns that need to be addressed.

Keywords: COVID-19, IVIG, SARS-CoV-2, IVIG Immunomodulation, IVIG Immunological mechanisms

INTRODUCTION

The onset of the COVID-19 pandemic and the events that followed, include the massive lockdowns worldwide, have significantly changed the norm across nations. The initial outbreak of COVID-19 occurred in late December 2019, involving the outbreak of a mysterious pneumonia that was at the time characterized by fever, fatigue, dry cough and occasional gastrointestinal symptoms (Wu, Chen, and Chan 2020). While the outbreak was initially limited to the Huanan Seafood Wholesale Market, the following months saw a rise in reported cases of individuals with similar symptoms across China, and eventually in other parts of the world. Given the fast spread and negative health and economic implications, the World Health Organization (WHO) on March 11, 2020, declared COVID-19 a pandemic (World Health Organization, 2020). In the months that followed the pandemic accelerated in both spread and impact, drawing attention by researchers in search of treatment. As of 10 April 2025, the increase in the spread of COVID-19 was over 777 million confirmed cases and nearly above 7 million deaths worldwide, data was shown at the WHO webpage. A study showed that 73.2% of Saudi samples exhibited enduring symptoms for over three months following SARS-CoV-2 infection, with memory issues, arrhythmia, and fatigue being the predominant complaints (Alwafi et al. 2024).

The etiology of the COVID-19 pandemic is attributed to a virus. The virus is known as the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (Lotfi, Hamblin, and Rezaei 2020). The virus is a coronavirus and belongs to the subfamily Orthocoronavirinae, with the name suggesting the characteristic “crown-like” spikes on the surfaces of these viruses (Wu, Chen, and Chan 2020). Four essential structural proteins the S, E, M, and NC proteins are encoded by the approximately 30,000 nucleotides that make up SARS-CoV-2's genetic code (Satarker and Nampoothiri 2020; Yadav et al. 2021; Kakavandi et al. 2023). Moreover, the virus bears some similarities with other coronaviruses. Notably, it is similar to the Middle East respiratory syndrome coronavirus (MERS-CoV) and the severe acute respiratory syndrome

coronavirus (SARS-CoV), given that these three viruses use the Angiotensin-Converting Enzyme 2 (ACE2) receptor for entry into cells (Lotfi, Hamblin, and Rezaei 2020). This similarity has been fundamental in facilitating an understanding of the novel SARS-CoV-2.

The mode of transmission of SARS-CoV-2 has been critical in facilitating its rapid spread and development into a pandemic. While the exact origin, location, and natural reservoir of SARS-CoV-2 is not well known, the virus is considered to be zoonotic, having originated from bats owing to the sequence identity of bat coronavirus (Wu, Chen, and Chan 2020). Despite being a zoonotic virus, human-to-human transmission has been implicated as an important factor in the spread. Human-to-human spread of the virus has been attributed to direct contact with an infected person, with exposure occurring during coughing, sneezing, and the release of respiratory droplets (Shereen et al. 2020). A review by (Alshehri et al. 2023) has effectively demonstrated significant findings regarding the various factors that critically influence the composition and diversity of the nasal microbiota, particularly the notable changes that occur following COVID-19 infection. Further, the virus can also be spread through indirect contact. Indirect contact involves the transmission of the virus through contaminated objects and airborne contagion (Lotfi, Hamblin, and Rezaei 2020). The identification of the mode of transmission of the virus was fundamental in informing infection control and prevention measures. In minimizing human-human transmission, directives that have throughout the pandemic been imposed include massive lockdowns to restrict movement and social-distancing measures to limit human contact. Further, there have been rallying calls on the need for washing hands using soap and water or the use of hand sanitizers, with this aimed at curbing infection through contact with contaminated surfaces.

Despite the efforts aimed at curbing the spread, the pandemic has since its onset imposed negative health implications worldwide. This has led to extensive research and clinical trials in the exploitation of potential therapeutic measures against the virus. While there has been no cure found yet, the discovery of a vaccine against the virus has been a major feat. The successful sequencing of the entire genome of the virus has facilitated the search for vaccines in both pre-clinical and clinical trials. Approved vaccines that continue to be used include Moderna, and Pfizer, with clinical trials of these vaccines showing that these vaccines conferring immunity against the virus through antibody formation (Mohamed et al. 2021). Statistics show that as of December 2023, 67% of the global population had received as in Our World in Data, 2022. This is tremendous progress in the ongoing efforts in public health for disease prevention.

Even though the massive vaccination efforts, the need for a cure against COVID-19 is still ongoing. This is attributed to the random mutations in the virus occurring over time, with the antigenic variation of the spike proteins leading to reduced recognition by neutralizing antibodies generated by natural infection of vaccination (Bok et al. 2021). This calls for further research on potential therapeutic and preventative strategies. Despite the gap in an effective and standardized treatment for COVID-19, the current research focus is aimed at exploring the efficacy of presently used approaches. Notably, Intravenous Immunoglobulin (IVIG) use has conferred promising results on its efficacy as an adjuvant treatment for COVID-19. As such, an understanding of the effectiveness of IVIG treatment for COVID-19 is fundamental.

Intravenous Immunoglobulin (IVIG):

Over the years, IVIG has been employed as a medicinal treatment due to its anti-inflammatory properties. Extracted and pooled polyclonal immunoglobulins from healthy donors make IVIG (Cao et al. 2021). IVIG has been authorized for use in autoimmune conditions by the European Medicines Agency and the US Food and Drug Administration, which include Immune Thrombocytopenic purpura (ITP), Kawasaki disease (KD), Multifactorial Motor Neuropathy (MMN), Chronic Inflammatory Demyelinating Polyradiculoneuropathy (CIDP), with the therapy has also been approved for Guillain-Barre syndrome (GBS) (Galeotti et al. 2017) (Sapir et al. 2005).

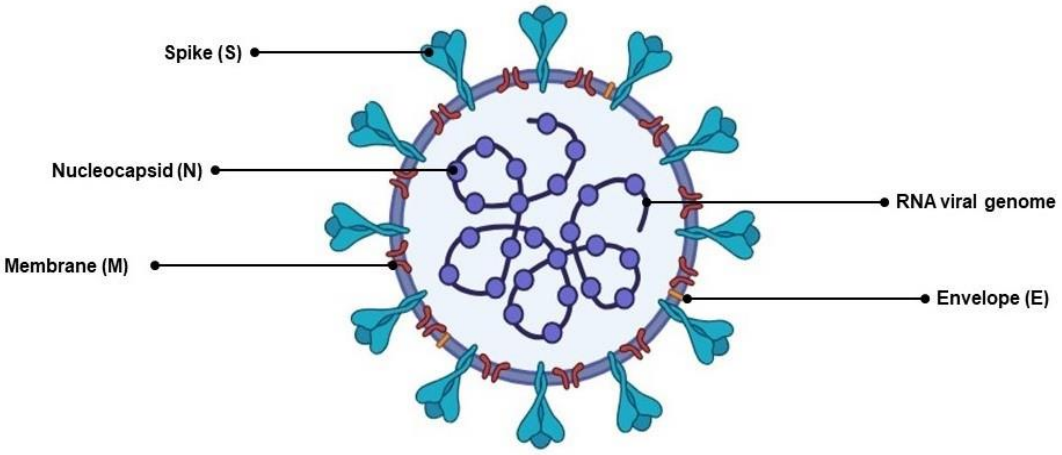

Figure 1: Structures of SARS-CoV-2 structural proteins.

Furthermore, IVIG is widely used off-label for treating immune-mediated, neurological, hematological, and dermatological diseases, as well as there is evidence about the possibility of using IVIG to treat some forms of cancer, and to treat COVID-19 infection. The blockade of Fc receptors, the regulation of complement, the modulating action on cytokines, and the neutralizing function of pathogenic autoantibodies are all critical immunomodulatory activities that immunoglobulin appears to possess (Sapir et al. 2005).

Despite the recent increase in the utilization of IVIG, its application dates back several decades. Behring was given the 1901 Nobel Prize (Raju 2006), for developing a serum therapy for diphtheria in 1890, signifying the inception of immunotherapies in medicine (Guo et al. 2018). This set the course for the pursuit of immunotherapies in the following years. Notable advancements in immunotherapy since then include the 1941 large-scale production of human immunoglobulin by (Cohn and Strong 1946) and the 1952 milestone in which Bruton became the first to administer immunoglobulin as a treatment for an immunodeficient patient (Guo et al. 2018; BRUTON 1952). Following Bruton's successful treatment in 1952 (BRUTON 1952), researchers in the United States reported corroborative results in 9 patients, while a further confirmatory study involving 176 patients in the United Kingdom validated the effectiveness of immunoglobulin in increasing circulating gamma globulin levels and enhancing immunity (Hooper 2015). Immunotherapy, which uses immunoglobulin to treat a variety of diseases, is now widely used throughout the world because of developments in research and clinical trials.

IVIG has many components and is a preparation of antibodies predominantly consisting of polyspecific immunoglobulin G (IgG), along with tiny amounts of immunoglobulin A (IgA) and immunoglobulin M (IgM) (Bongomin et al. 2021). The industrial manufacturing of IVIG involves antibodies that target microbial antigens, self-antigens, and anti-idiotypic antibodies designed to recognize other antibodies (Barahona Afonso and João 2016). Plasma is the essential element employed in the production of IVIG. Therefore, to expedite the collection of plasma, the process of manufacturing IVIG begins with the identification and selection of donors (Novaretti and Dinardo 2011). Plasma collection from blood donors accounts for 20% of the total, whilst plasma donors contribute the remaining 80% (Barahona Afonso and João 2016). A substantial quantity of donors is essential to fulfill the specified plasma volume for product manufacture. Due to their cumulative environmental exposure, the large number of donors creates a plasma pool for immunoglobulin isolation that includes a wide range of antibodies specific to different bacterial, viral, and self-antigens (Barahona Afonso and João 2016). After collecting a sufficient quantity of plasma, each producer proceeds to the production phase, employing various methods or processes instead.

The techniques used in industrial manufacture of IVIG vary from the historical techniques, to more modern modifications. Significantly, the techniques that were used by Cohn and his coworkers during the World War 1 in 1952 have been modified, leading to the development of methods for the separation of plasma proteins into the individual stable fractions that have different biologic functions (Cohn and Strong 1946). Besides the separation techniques, the industrial production further involves techniques to facilitate safety of the end-product. Prior to the application of these techniques, all donations are screened for virus infections, including Hepatitis B,

Human Immunodeficiency Virus and Hepatitis C (Barahona Afonso and João 2016). In reducing the viral load, manufacturers utilize pasteurization, treating with solvent/detergents, treating with caprylic acid, nano-fitration and treating with methylene blue (Novaretti and Dinardo 2011). These techniques aimed at ensuring safety are further applied during handling and transportation to address safety concerns and minimize risk of adverse reactions. Given the advancement in science and technology, more advanced techniques are being utilized in ensuring the safety of the final products. This has therefore lead to increased efficacy, increased consistency, greater tolerability and efficacy, thus increasing its application in the treatment and management of several diseases.

The use of IVIG is informed by the immunomodulatory activity of the formulation. IVIG is administered as a substitution therapy in primary and secondary immunodeficiencies at either a low dose of 400 mg kg−1, or as an immunotherapy in autoimmune and inflammatory diseases at a dose of 1–2 g kg−1 (Galeotti et al. 2017). In replacement therapy, the low doses used achieves a peak serum level of 12-12 mg/ml, while high doses in immunotherapy lead to a peak serum level of 25-25 mg/ml (Kolahchi et al. 2021). Once administered, IVIG is aimed at replacing antibodies in the human body. The mechanism of action involved in restoring the levels of IgG and enhancement if immunity include the functional blockade of Fc receptors, antibody neutralization and inhibition of autoantibody production, complement inhibition, modulation of cytokine and cytokine antagonist production, expanding the lymphocyte repertoire diversity and the activation of functional blockade of the death receptor fas (Barahona Afonso and João 2016). As such, owing to the role of IVIG in modulating biological processes that are involved with the innate or acquired immunity, IVIG is used in the treatment and management of several diseases as aforementioned.

Introduction and Background of Intravenous Immunoglobulin (IVIG) in the Treatment of COVID-19

The absence of a defined treatment protocol. The management of COVID-19 and its associated problems has become exceedingly challenging. This disparity has prompted the investigation and utilization of available therapeutic options, including supportive interventions, immunomodulatory drugs, convalescent plasma transfusions, and antiviral treatments (Lanza et al. 2020). Although several treatments have demonstrated efficacy in treating COVID-19, there is a growing emphasis on immunoglobulins, especially intravenous immunoglobulin (IVIG), as a valuable therapeutic option for moderate and severe cases of COVID-19. The application of IVIG in the management of COVID-19 is guided by the anti-inflammatory properties of the immunoglobulins. The principal pathophysiological observation in severe COVID-19 cases is hyperinflammation, marked by increased levels of interleukin (IL)-2, IL-6, IL-7, tumor necrosis factor-alpha, inducible protein, and interferon gamma, which signifies a cytokine cascade and cytokine release syndrome (Kolahchi et al. 2021). Additionally, in COVID-19, the hyperinflammatory condition is evidenced by increased levels of C-reactive protein, D-dimer, ferritin, and lactate dehydrogenase (Zhou et al. 2020). The subsequent inflammation leads to the infiltration of monocytes and lymphocytes in the lungs and heart, resulting in the recruitment of inflammatory IL-6-secreting monocytes and, consequently, significant lung disease in infected individuals (Kolahchi et al. 2021). The utilization of medicines like IVIG, which modulate immune responses, has increased in the treatment of severe acute respiratory distress syndrome.

The application of IVIG in the treatment and management of respiratory disorders is not a novel notion. IVIG has already been utilized in the treatment of SARS, acute respiratory distress syndrome (ARDS), influenza pandemics, seasonal influenza, and MERS (Kolahchi et al. 2021). In both SARS and MERS, the coronaviruses involved elicited virus-neutralizing antibodies, making plasma therapy beneficial in treating SARS and MERS during their respective pandemics (Díez, Romero, and Gajardo 2020). Research investigations have demonstrated the clinical efficacy of IVIG in treating respiratory disorders.

IVIG treatment of COVID-19: Immunological mechanisms:

The mechanism of action of IVIG treatment for COVID-19 targets the mitigation of hyper-inflammatory conditions. In hyper-inflammatory conditions, IVIG functions by obstructing the intact Fc-gamma receptors on immune cells, so impeding their activation, signaling, and cellular function, mitigating complement-mediated tissue damage, and down-regulating pro-inflammatory cytokines (Bongomin et al. 2021). Comparable strategies are utilized in the management of COVID-19 patients. In COVID-19, IVIG functions by suppressing inflammatory processes and promoting anti-inflammatory responses. This encompasses the suppression of IL-6 production, the inhibition of matrix metalloproteinase nine activity, and the attenuation of T-cell activation, alongside the activation of anti-inflammatory mechanisms such as IL-10 production in the gut, an augmentation of macrophages, and an elevation of Peroxisome Proliferator-Activated Receptor gamma (PPARγ) (Kolahchi et al. 2021).

Moreove (Rojas et al. 2020) indicate that IVIG influences the progression of Covid-19 by inhibiting dendritic cell maturation, enhancing the synthesis of IL-33, IL-4, and IL-13, and diminishing the expression of IL-12. In vitro studies demonstrate that IVIG inhibits the development of dendritic cells, hence impacting their activities as essential regulators of innate immunity and specialized antigen-presenting cells (Bayry et al. 2003). In addition to these mechanisms, IVIG exerts an

immunomodulatory effect on macrophages. The activation of macrophages is identified as the primary immunological component implicated in inflammation and lung injury in COVID-19 illness (Rojas et al. 2020). (Blanco-Melo et al. 2020; Rojas et al. 2020) assert that IVIG regulates excessive cytokine production and mitigates pulmonary damage resulting from macrophage activation syndrome-like conditions linked to innate immune migration to lung tissues. This suggests that IVIG administered for COVID-19 therapy may also function by enhancing an anti-inflammatory macrophage profile. Although numerous studies elucidate the mechanism of action of IVIG, research continues to enhance the understanding of its immunological mechanisms in the treatment of COVID-19. The mechanism of IVIG in producing its immunological effects for treating COVID-19 is consistent, however varied reactions occur depending on the disease stage. COVID-19 comprises three clinical stages. (Kolahchi et al. 2021) identify three stages: the acute or pneumonia stage, the viremia stage, and the recovery stage. In the initial phases of the disease, lymphocyte levels are normal or marginally reduced, with lymphopenia manifesting in the latter stages during viremia. Consequently, during the initial stage of the disease, IVIG diminishes the viral load and mitigates the synthesis of elevated inflammatory mediators, whereas in the advanced stages of severe disease, IVIG enhances antibiotic effectiveness and aids in addressing the pronounced immune dysfunction (Coloretti et al. 2021). Lymphopenia in COVID-19 signifies a substantial reduction in lymphocytes, which may be lethal, as immune suppression predisposes an individual to viral, fungal, and bacterial infections (Nabih 2021). According to this, the prognosis of patients with severe COVID-19, such as those admitted to intensive care units (ICUs), and the prevention of disease development depend critically on the timing of IVIG therapy in the management and treatment of COVID-19.

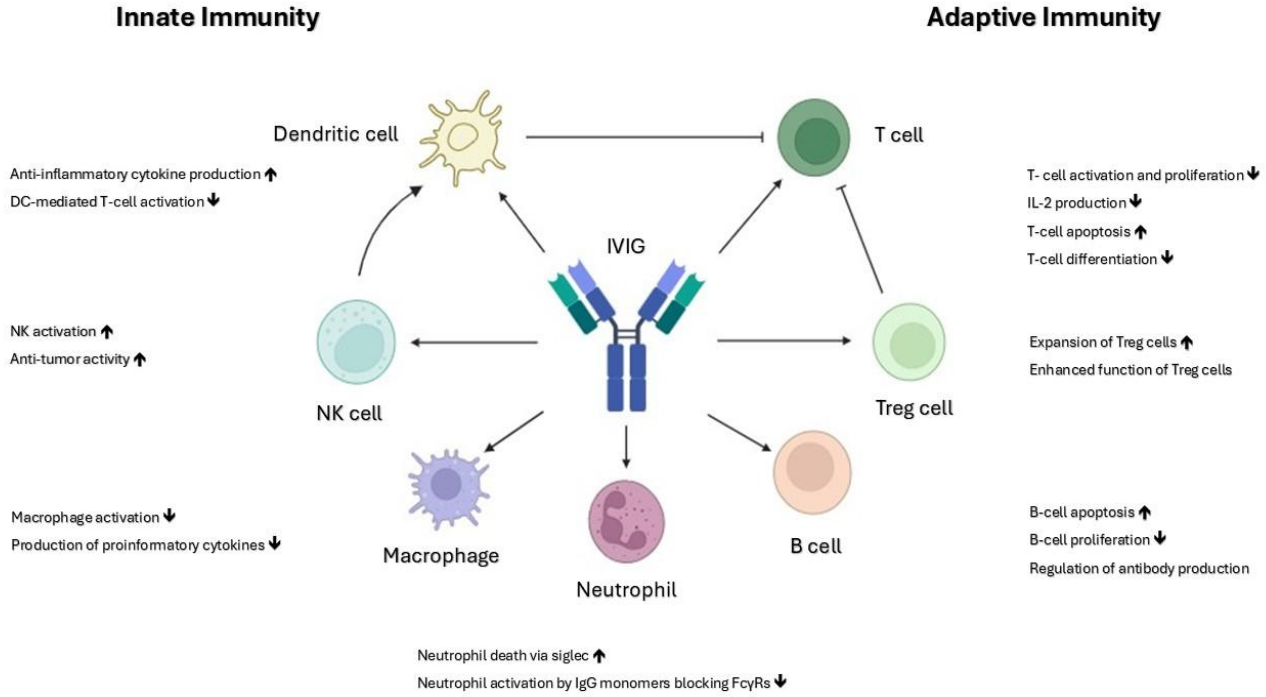

Figure 2: A diagram has proposed the mode of action of IVIG on innate and adaptive cellular immunity.

Currently Used IVIG Formulations: Production and Dosage

The industrial manufacturing of IVIG for COVID-19 treatment adheres to the standard procedures utilized in IVIG manufacture for various illnesses. The initial step entails a pre-donation evaluation of prospective donors to verify adherence to plasma donation regulations, with a crucial stipulation that convalescent donors must be aged 18 to 65, exhibit no infectious symptoms, and possess a negative COVID-19 test conducted 14 days post-recovery (Rojas et al. 2020). Additional screening process requirements encompass the assessment for transfusion-transmitted illnesses, including HIV, syphilis, malaria, and hepatitis B. After donors complete the screening process, convalescent plasma is obtained via plasmapheresis utilizing a therapeutic apheresis machine, with a collection volume ranging from 600 to 800 ml (Ali et al. 2021). The harvested plasma is thereafter preserved in volumes of 200 or 250 ml and is frozen within 24 hours post-collection

(Rojas et al. 2020). Before processing, the titers of anti-SARS-CoV-2 antibodies and the concentrations of IgG, IgA, IgM, and albumin are assessed. The preparation of convalescent plasma obtained from donors entails many processing processes.

(Ali et al. 2021) elucidates the processing of convalescent plasma through the essential phases involved. The initial step in the processing phase entails the precipitation of plasma proteins, excluding immunoglobulins, with the use of caprylic acid. Caprylic acid is utilized for the elimination of encapsulated viruses (Novaretti and Dinardo 2011). Subsequently, ultrafiltration/diafiltration of the supernatant is conducted to eliminate contaminants and concentrate the immunoglobulin (Ali et al. 2021). This is succeeded by protein quantification and purity assessment via the biuret technique. Subsequently, the amounts of IgG, IgM, IgA, and albumin are quantified via immunoturbidimetry, followed by an electrochemiluminescence immunoassay to ascertain the anti-SARS-CoV-2 antibody titer in the final product (Ali et al. 2021). This is subsequently determined by toxicity testing designed to ensure the safety of the final formulation and prevent unpleasant reactions upon ingestion.

The administration of IVIG in clinical settings for the treatment of COVID-19 is guided by existing information regarding dosing, with many research investigating the efficacy of IVIG at differing dosages. (Tzilas et al. 2020) demonstrated the efficacy of IVIG administered at a dosage of 0.5 to 2.0 g/kg, with the predominant regimen being 0.5 g/kg daily for three consecutive days(Cao et al. 2021) employed a high dosage of 2 g/kg body weight administered during two weeks of disease start for the treatment of severe Covid-19 infection. (Rojas et al. 2020) advocate administering a dosage of 3 mL/kg over a two-day period. (Bongomin et al. 2021) advocate a high dosage of 0.1 to 0.5 g/kg/day of IVIG for 15 days, administered alongside normal critical care measures, including antibiotics, steroids, and antiviral medications, for severe COVID-19 cases. In clinical practice, the frequently utilized IVIG pharmaceutical formulations for the treatment of COVID-19 encompass Prevagen and Octagam (Garcia et al. 2021; Herth, Sakoulas, and Haddad 2020; Poremba et al. 2021). Although there is no established dosage for IVIG treatment of COVID-19, it is apparent that a high dosage is predominantly utilized for severe cases of the condition.

Research Evidence of the Effectiveness of IVIG in the Treatment of Covid-19

Research studies have demonstrated the usefulness of IVIG as an adjunctive treatment for COVID-19. Over the past two years, there has been an increasing study emphasis on the effectiveness and efficacy of IVIG in treating COVID-19, with researchers documenting discoveries about its impact on disease progression and prognosis in severe cases of COVID-19. Although findings have been varied, most of the research indicate favorable results associated with the administration of IVIG. Research evidence indicates that IVIG effectively modulates immune inflammation during the initial phase of deterioration in COVID-19 patients. (Flores-Oria et al. 2021) assert that the use of IVIG in the early phase of COVID-19 mitigated illness progression by bolstering the immune system. (Tzilas et al. 2020) report that the use of IVIG during the early phase and initial days of patient admission is associated with a deceleration of illness progression, resulting in favorable patient outcomes. The administration of IVIG in mild and severe COVID-19 significantly affects the duration of hospitalization. (Tzilas et al. 2020) discovered that the prompt administration of IVIG within the initial three days of admission resulted in a markedly reduced duration of stay, ranging from 3 to 14 days, whereas delayed administration was associated with prolonged hospital stays of 8 to 48 days. In a comparable trial, (Flores-Oria et al. 2021) discovered that the prompt administration of IVIG within the initial 48 hours of admission resulted in decreased ventilator utilization and considerably shortened the duration of hospitalization and intensive care unit stay. A study conducted in China by (Shao et al. 2020) revealed that the delivery of IVIG during the initial 48 hours resulted in a reduction in mechanical ventilation utilization, as well as a decrease in both ICU and hospital stay duration. Moreover, Huang et al. (2021) (Huang et al. 2021) discovered that early delivery of IVIG not only shortened hospital stays but also diminished antibiotic usage, including the concurrent use of two or more antibiotics. The effectiveness of IVIG in treating COVID-19 is contingent upon the timing of administration, with optimal results observed when the first dose is given during the initial 2-3 days post-admission.

The mechanism by which IVIG demonstrates substantial efficacy upon early administration remains a subject of investigation. The main cause of the disease's progression and bad prognosis, according to data from clinical testing and autopsy results, is inflammation and the immunological response brought on by the virus infection (Shao et al. 2020). It can be hypothesized that early therapy of IVIG halts the advancement of COVID-19, hence mitigating adverse health consequences and enhancing prognosis in patients. The administration of IVIG in the early stages of the disease is crucial, as it has demonstrated the ability to impede disease progression, thereby averting the transition from mild to severe COVID-19 (Huang et al. 2021). Consequently, these findings underscore the necessity for the prompt administration of IVIG to mitigate the occurrences of severe COVID-19 cases. Nevertheless, certain research yield conflicting findings about the effect of IVIG on hospitalization duration. The delivery of IVIG actually extended the period of hospitalization in the IVIG treatment group relative to the control group, according to a 2021 study by Xiang et al (2021). This contradicts the conclusions of

most investigations, indicating a discrepancy that requires additional examination.

A notable advantage of IVIG administration in COVID-19 therapy is the substantial decrease in mortality associated with severe illness. Numerous studies have indicated a decrease in death rates among severe cases of COVID-19. Cao et al. (2021) (Arias-Reyes et al. 2020) discovered that prompt delivery of IVIG in severe cases decreased 28-day mortality and enhanced clinical outcomes in patients. Tzilas et al. (2020) (Tzilas et al. 2020) and Shao et al. (2020) (Shao et al. 2020) similarly showed a notable decrease in 28-day mortality in severe cases. Shao et al. (2020) (Shao et al. 2020) observed no notable enhancement in the 60-day death rate associated with severe COVID-19 illness. Although most research indicate a reduction in 28-day mortality, some show opposing results. A systematic evaluation conducted by Focosi et al. in 2022 (Focosi et al. 2022) revealed that the use of IVIG did not correlate with a substantial decrease in mortality risk. The inconclusive findings about mortality necessitate additional investigation to establish definitive evidence. IVIG has demonstrated efficacy in the management of COVID-19 in patients with neurological problems related to the condition. Mucolli et al. (2021) (Muccioli et al. 2021) administered an IVIG dosage of 0.4 g/kg to COVID-19 patients exhibiting encephalopathy. The researchers reported benefits as early as 3-4 days post-administration, with patients achieving full recovery by 29.8 days (Muccioli et al. 2021). Freire-Alvarez et al. (2021) (Freire-Álvarez et al. 2020) have reported more favourable results in patients with acute demyelinating encephalomyelitis. The clinical efficacy of IVIG in neurological problems connected with COVID-19 is enhanced by its anti-inflammatory properties, linked to its anti-cytokine characteristics (Muccioli et al. 2021). In addition to neurological diseases, the use of IVIG has demonstrated efficacy in the management of COVID-19 individuals afflicted with Guillain-Barre syndrome. In a case presentation by (Garcia et al. 2021), the researchers observed that intravenous immunoglobulin (IVIG) therapy in a pregnant patient with Guillain-Barré Syndrome arrested illness development, resulting in favourable results, with the patient being discharged after 33 days. This singular instance offers encouraging insights into the management of COVID-19 related Guillain-Barre Syndrome within the obstetric demographic. Although the data regarding the clinical efficacy of IVIG in treating COVID-19 are varied, it is clear that the majority of evidence supports its clinical efficacy (Garcia et al. 2021). Therefore, it is essential for healthcare practitioners to consider and employ IVIG therapy to facilitate the effective recovery of COVID-19 patients, while simultaneously alleviating the disease's significant health and economic burdens.

Mortality data across several research are inconclusive. Randomized research by (Gharebaghi et al. 2020) indicated considerably decreased in-hospital mortality in the IVIG group; however, the subsequent randomized ICAR study found no advantage of IVIG treatment (Gharebaghi et al. 2020; Mazeraud et al. 2022).

Notably, the aforementioned randomized research included patients with severe COVID-19, whereas the ICAR study focused on patients with moderate-to-severe ARDS associated with COVID-19 (Gharebaghi et al. 2020; Mazeraud et al. 2022). Additionally, patient populations ranging from 16 to 77 were included in randomized trials (Sakoulas et al. 2020; Gharebaghi et al. 2020; Tabarsi et al. 2021; Mazeraud et al. 2022). Although a second big retrospective trial found no effect in terms of mortality, a major retrospective multicenter investigation revealed a decrease in mortality in the IVIG group (Liu et al. 2021; Shao et al. 2020). A comprehensive randomized study with a substantial patient cohort is essential to conclusively ascertain whether IVIG decreases mortality rates. Nonetheless, certain studies have indicated further advantages of IVIG. It appears from examining the findings of the referenced trials that there is a group of patients with severe or serious COVID-19 who would benefit most from early high-dose IVIG administration. Their possible detection could be aided by immunological and inflammatory indicators. The effectiveness of IVIG may enhance when an increasing proportion of donors develop neutralizing antibodies to SARS-CoV-2 over time (Kwapisz and Bogusławska 2023). To determine if the most recent batches of IVIG will have a higher level of effectiveness, therefore, additional trials are required.

In brief, 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 (Guo et al. 2018; Kwapisz and Bogusławska 2023). Overall, serious adverse events were not statistically significantly more frequently reported in the IVIG arm, based on the mentioned studies.

Reported Adverse Events Associated with the Administration of IVIG in the Treatment of COVID-19

A significant issue in healthcare is the occurrence of adverse medication reactions, particularly in novel diseases lacking established therapy. Given the detrimental effects on health and the possibility of death in certain situations, adverse occurrences in the healthcare system are a serious cause for concern. In addition to health consequences, bad events entail considerable economic and legal ramifications due to negligence by healthcare providers. On the other hand, it

has been demonstrated that the administration of intravenous immunoglobulin for the treatment of COVID-19 does not result in any side events, such as adverse medication reactions. Clinical trials and COVID-19 cases conducted in hospital environments highlight the rarity of adverse reactions to IVIG in the treatment of COVID-19 patients (Muccioli et al. 2021; Ali et al. 2021; Mazeraud et al. 2021; Kolahchi et al. 2021). Medical records and research indicate that IVIG treatment for COVID-19 has been associated with little side effects, such as renal impairment and allergic reactions (Mazeraud et al. 2021). (Kolahchi et al. 2021) note that although adverse events associated with IVIG treatment for COVID-19 are uncommon, they occur in approximately 10% of patients, with rare instances of thromboembolism, necessitating the administration of anticoagulant medications during IVIG therapy to ensure patient hydration. Considering this, even though the overall low number of adverse reactions and drug-related adverse events associated with IVIG therapy for COVID-19 suggests that it is safe and appropriate, healthcare professionals must exercise caution to avoid rare side effects like thromboembolism in COVID-19 infected.

Examining the Challenges Associated with IVIG in COVID-19 Treatment

In along with the safety concerns regarding potential adverse effects associated with IVIG therapy for COVID-19, there are also substantial hurdles related to its application. The foremost fundamental difficulty that significantly burdens patients pertains to the expense of IVIG therapy. The pharmacoeconomic value of IVIG is questionable due to its relatively high cost; the median cost of IVIG in Poremba's treatment group was $27,645, according to (Poremba et al. 2021) . Given the high reliability of IVIG therapy in the immunodeficient patient population, (Kolahchi et al. 2021) ascribe the high cost of IVIG to the increase in demand resulting from its growing use in treating COVID-19. Consequently, since COVID-19 patients increasingly depend on the same medicine, demand has surged, impacting the cost of IVIG and consequently restricting patient access. An additional difficulty regarding cost arises from the supplementary infusion expenses amounting to $100 per gram of IVIG, rendering IVIG therapy an exceedingly costly treatment alternative for numerous individuals (Kolahchi et al. 2013). Considering that the pandemic continues to exert adverse economic effects on the general populace, affording the expense of IVIG treatment has consequently emerged as a significant barrier for an already economically strained society. A second issue associated with the use of IVIG in COVID-19 therapy involves the danger of inducing an inadequate immunization. (Kolahchi et al. 2021) observe that IVIG therapy may decrease the natural antibody response in patients, resulting in poor immunization against COVID-19. This suggests that the administration of IVIG for COVID-19 treatment may attenuate the antibody response, hindering the development of an immunological response against viremia, hence rendering patients susceptible to recurrent reinfections (Pourahmad et al. 2020). This presents a significant health hazard, as COVID-19 has been demonstrated to induce recurrent infections in persons who have already healed. Consequently, it is essential for persons who have undergone IVIG therapy to receive vaccinations after their recovery to mitigate the risk of reinfection. An additional problem associated with IVIG administration in the treatment of COVID-19 is the potential danger of antibody-dependent intensification of infection. (Pourahmad et al. 2020) indicate that this pertains to the complications linked to other infectious diseases during the transfer of blood components or as a consequence of a reaction to serum contents. Antibody-dependent increase of infection occurs when antibodies specifically target one viral serotype while inadequately neutralizing others, a behavior frequently observed with coronaviruses (Pourahmad et al. 2020; Kolahchi et al. 2021). Antibody-dependent increase of infection has long been observed in coronaviruses, but it has become a significant worry because to studies suggesting its potential occurrence in COVID-19 (Wan et al. 2020). Antibody-dependent increase of infection poses a significant problem in COVID-19, since it may exacerbate symptoms and result in adverse health consequences. Considering the findings of antibody-dependent increase of infections in coronaviruses and SARS-CoV-2, it is imperative to address this issue, as it may exacerbate the course of COVID-19 into severe cases (Wan et al. 2020).

(Kolahchi et al. 2021) identify additional obstacles in managing COVID-19 with IVIG therapy, notably the absence of anti-SARS-CoV-2 antibodies in sera from the general population, which diminishes its efficacy in treating the disease. Additionally, there exists the risk of pathogen transmission, serum sickness, and transfusion-related acute lung injury associated with IVIG. These hazards may restrict the application of IVIG in the treatment of COVID-19, hence necessitating meticulous oversight in plasma collection and the comprehensive industrial processing to guarantee the safety of the final pharmaceutical product for public use.

IVIG therapy for COVID-19: Possible Research Topics

At the start of 2020, SARS-CoV-2 was considered a novel virus, with the lack of research evidence and understanding of the virus posing a challenge on therapeutic strategies to be used. With time, however, researchers and scholars have extensively focused on understanding the virus, leading to the identification of potential therapeutic approaches, including IVIG. While this is so, it is important to note that COVID-19 virus has undergone several mutations since its onset. So far, the main variants that have led to significant health concerns include the Delta and the more recent Omicron variant (Centers for Disease Control and Prevention, 2021).

There is need for research to examine IVIG clinical efficacy variations against the different SARS-CoV-2 variants. Further, existing evidence on the clinical efficacy of IVIG therapy is based on findings from clinical trials that use a relatively small sample size. Some of the studies such as that carry out by (Lanza et al. 2020) and (Garcia et al. 2021) are based on findings recorded from the management of a single patient. While such studies provide a solid argument for the effectiveness and clinical efficacy of IVIG in the treatment of COVID-19, (Kolahchi et al. 2021) underscores the need for further randomized controlled studies to provide more evidence. Most importantly, future studies should utilize large sample sizes to quantify IVIG clinical efficacy in the treatment of COVID-19, thus facilitating the development of evidence-based standardized guidelines on the use of IVIG as an effective treatment strategy for COVID-19. Following the administration of two or more vaccine doses to a diverse population, the variations in vaccine types may contribute to an increase in the potency and efficiency of IVIG for treating COVID-19 and its variants. This could be achieved through the manufacturing of serum derived from vaccinated individuals into new batches of IVIG.

CONCLUSIONS

The ongoing COVID-19 pandemic has since its onset caused significant negative health and economic implications in the healthcare sector. In mitigating this and the lack of a cure, there has been a burgeoning focus on the identification of therapeutic strategies that will effectively halt disease progression and improve the prognosis in severe cases. Notably, evidence from clinical trials highlights IVIG therapy as a suitable adjuvant therapy in COVID-19, with its clinical efficacy attributed to its immunomodulatory and anti-inflammatory effects. While this is so, there exists a need for further research on the clinical efficacy of IVIG, given the use of relatively small sample sizes in the clinical trials conducted so far. Further, other challenges that limit the use of IVIG therapy in COVID-19 include issues of cost and safety concerns that need to be addressed. With further evidence on the clinical efficacy of IVIG, policymakers in the healthcare setting will be able to make substantive conclusions on its effectiveness, thus facilitating the wide adoption of IVIG therapy in mitigating the ongoing COVID-19 burden.

Supplementary materials

Not applicable.

Author contributions

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