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Efficacy of IVIG in Post-Acute Sequelae of SARS-CoV-2 Infection: Present Evidence and Future Perspectives

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Immunomodulatory treatment called intravenous immunoglobulin (IVIG) is used to treat several neuroimmune conditions, such as Guillain-Barré Syndrome, chronic inflammatory demyelinating polyneuropathy, multiple sclerosis, and multifocal motor neuropathy. Furthermore, to acute COVID-19 infection, IVIG has been considered for the treatment of post-acute sequelae of SARS-CoV-2 infection (PASC). The administration of IVIG is a providing the receiver with a collection of antibodies, which are capable of regulating the immunity response through a variety of methods. The prompt initiation of IVIG and plasmapheresis in severe cases has the potential to decrease the necessity for mechanical breathing, reduce the duration of ICU and hospital admissions, and diminish mortality rates. In PASC, IVIG has demonstrated efficacy in reducing persistent symptoms among limited patient cohorts. Nevertheless, there are several possible side effects that can occur with IVIG, including anaphylaxis, headaches, thrombosis, elevated liver enzymes, and renal problems. Payers and patients may not want to use IVIG because it costs a lot. This review offers an updated overview of the application of IVIG in PASC, production methods, pricing, and mechanisms of action. Future investigations should focus on finding the best way to dose, time, and select patients for immunoglobulin products in different circumstances, especially in light of the COVID-19 and PASC.

Keywords: Covid-19, IVIG, post-acute sequelae of SARS-CoV-2, , PASC, Long COVID, prolonged COVID, and post-COVID

INTRODUCTION

Intravenous immunoglobulins (IVIG) are a blood product derived from the plasma of several donors who have undergone plasmapheresis to produce a high concentration of immunoglobulins (Ig). IgG is the most prevalent component of IVIG, accounting for more than 95% of the total; however, other Ig fractions may also be present. Commercial IVIG formulations vary in concentration, Ig content (Ig isotypes, IgG, IgM, IgA, and IgE), and other properties (Perez et al., 2017; Schwab & Nimmerjahn, 2013). IVIG contains structurally and functionally complete Ig with half-lives ranging from 18-32 days, similar to natural IgG. It has a typical proportion of subclasses, including 95% monomeric IgG, tiny quantities of dimers, and varying levels of IgA and IgM. IVIG may also contain soluble molecules such as human leukocyte antigen (HLA) and cytokines. They lack high molecular weight immune complexes and pollutants such as vasomotor peptides and endotoxins. IVIG undergoes industrial modification, inactivation, and chemical and physical elimination of germs and viruses. IVIG preparations may have different pharmacological qualities (osmolality, pH, salt content, stabilizer, and IgA content), which might impact safety and acceptability (Seite et al., 2008). IVIG has represents a promising but still investigational therapeutic approach for post-acute sequelae of SARS-CoV-2 infection (PASC), commonly known as Long COVID (Reznik et al., 2022).

Long COVID is a multisystemic illness characterized by severe symptoms after a severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. Globally, at least 65 million people have COVID, with an estimated 10% of infected persons and over 651 million recorded COVID-19 instances (Ballering et al., 2022). However, the number of unregistered cases is expected to be significantly higher. The estimated incidence is 10-30% for non-hospitalized patients, 50-70% for hospitalized cases (Bull-Otterson et al., 2022; Ceban et al., 2022) , and 10-12% for vaccinated cases (Al-Aly et al., 2022; Ayoubkhani et al., 2022).

Long COVID is most common in non-hospitalized patients with mild acute illness, accounting for the majority of COVID-19 cases. Long COVID affects people of all ages and acute-phase disease severity levels

(Davis et al., 2021). Hundreds of biological studies have been published, with patients suffering from a range of symptoms across multiple organ systems (Davis et al., 2021). Long COVID results in many adverse effects. Type 2 diabetes (Xie & Al-Aly, 2022), myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) (Kedor et al., 2022; Mancini et al., 2021), cardiovascular, cerebrovascular, and thrombotic diseases (Xie et al., 2022), and dysautonomia, including postural orthostatic tachycardia syndrome (POTS) (Larsen et al., 2022), are among the common new-onset diseases. Although IVIG has shown promise in treating a variety of neuroimmune conditions, such as Guillain-Barré syndrome (GBS) and chronic inflammatory demyelinating polyneuropathy (CIDP), there is an insufficient of clinical evidence to support its use in treating PASC (Morse et al., 2025).

Ongoing research efforts, such as the nationwide RECOVER initiative, are rigorously assessing the efficacy of IVIG for treating autonomic dysfunction and various manifestations of Long COVID through the implementation of randomized controlled trials (National Institutes of Health (NIH), 2025b). The therapeutic rationale emphasizes on the immunomodulatory properties of IVIG and its capacity to reduce inflammatory pathways that could be linked to ongoing post-COVID symptoms, although conclusive evidence of its efficacy is still lacking.

Background and Established Uses of IVIG:

IVIG has become a fundamental therapy for numerous autoimmune and inflammatory illnesses, with notable effectiveness in neuroimmunological disorders. The main component of IVIG is polyclonal IgG antibodies, which are derived from the blood of thousands of healthy donors and mostly comprise monomeric IgG1 and IgG2 subclasses with lesser amounts of IgG3 and IgG4 (Lünemann et al., 2016). Studies have shown that IVIG treatment can improve the status of individuals with autoimmune neuropathies like GBS, myasthenia gravis, and CIDP (Lünemann et al., 2015; Morse et al., 2025)

IVIG has demonstrated the benefit of IVIG in neuroimmune disorders, which is proposes significant insight into its potential use in Long COVID patients. In patients with CIDP, IVIG has shown efficacy comparable to plasma exchange therapy, with clinical trials indicating that most patients experience improvements in functional outcomes. The therapeutic mechanisms that contribute to the effectiveness of IVIG in these conditions encompass several pathways, such as the saturation of neonatal Fc receptors (FcRn), modulation of complement activation, and the presence of anti-idiotype antibodies capable of neutralizing pathogenic autoantibodies (Mielke et al., 2019; Reznik et al., 2022)

Ephrem et al. (2005), Galeotti et al. (2017), and Perricone et al. (2020) all point to IVIG's anti-inflammatory and immune-modulating effects in autoimmune disorders, as well as its efficacy as a therapy alternative and in fighting infections. Igs produce antiviral effects via stimulating innate immune cells and complement pathways, as well as by inhibiting cellular penetration (Perricone et al., 2020). Those with impaired immune systems or hypogammaglobulinemia (primary or secondary deficiency) may benefit from intravenous immunoglobulin injection for the treatment or prevention of frequently infections caused by bacteria and viruses (Manaresi & Gallinella, 2019; Mouthon et al., 2005; Mouthon & Lortholary, 2003). The composition of IVIG is influenced by the antibody profiles present within the donor population (Planitzer et al., 2011; Siegel, 2005). However, IVIG usually exhibits potent antiviral effects against a range of viruses, such as polyomavirus BK (Randhawa et al., 2015), respiratory syncytial viral (RSV), hepatitis A virus (HAV), herpes simplex virus (HSV), cytomegalovirus (CMV), parvovirus B19, varicella-zoster virus (VZV), Epstein-Barr virus (EBV), and measles, mumps, rubella (Krause et al., 2002) (fig1). Post-transplant patients with severe or drug-resistant cases of CMV, parvovirus B19, or polyomavirus BK infections may also benefit from intravenous immunoglobulin (IVIG) treatment (Jordan et al., 2009, 2011).

Researchers have examined the role of IVIG in the treatment of acute COVID-19 infections; however, the findings have been inconsistent and generally inconclusive. There is not enough data to draw firm clinical recommendations for treating acute infection, despite some trials showing promise in small population subgroups, especially in reducing cytokine storms in severe COVID-19 patients (Luke Halpern, 2024; Morse et al., 2025). The inconclusive evidence regarding acute COVID-19 treatment have led researchers to explore the potential efficacy of IVIG in alleviating the persistent symptoms associated with PASC (Luke Halpern, 2024; Morse et al., 2025; Thompson et al., 2023).

Theoretical Evidence for IVIG in PASC Therapy:

The theoretical model of IVIG application in PASC is founded on numerous critical immunological processes that may target the underlying pathophysiology of prolonged COVID. Long COVID is increasingly recognized as a syndrome potentially influenced by chronic inflammation, autoimmune mechanisms (Arthur et al., 2021; Proal & VanElzakker, 2021; Su et al., 2022; Wallukat et al., 2021), and dysregulated immune responses (Glynne et al., 2022; Klein et al., 2023; Phetsouphanh et al., 2022; Proal & VanElzakker, 2021) subsequent to initial SARS-CoV-2 infection. Considering that IVIG's methods of action address these identical pathogenic processes, researchers have hypothesized that it may successfully mitigate

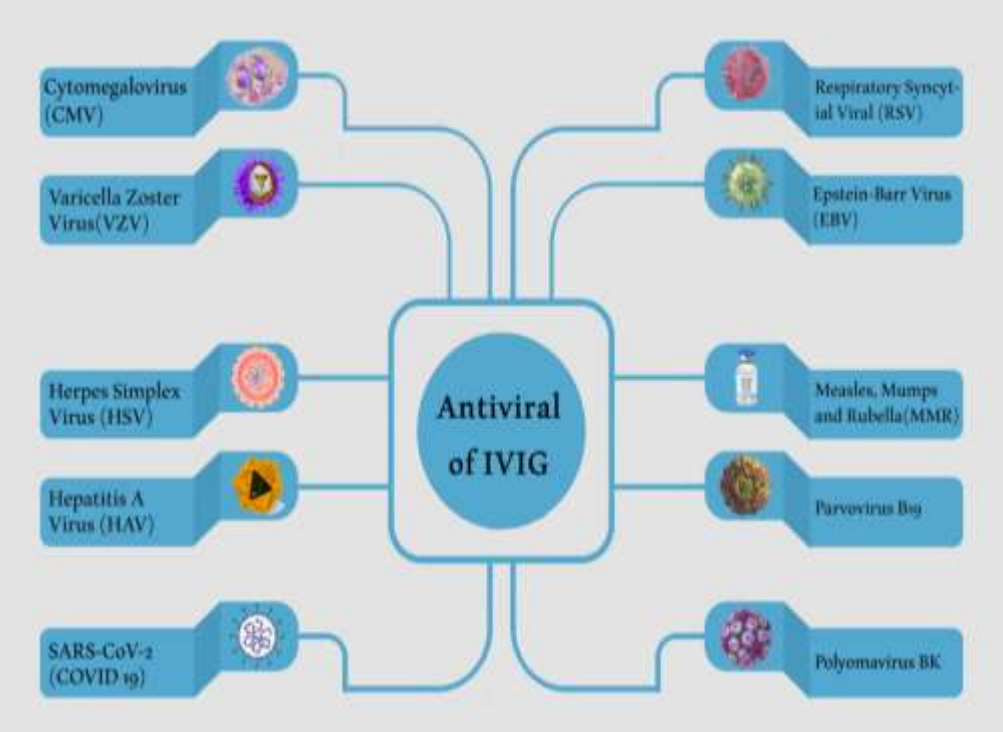

Figure 1: **This diagram has displayed the anti-viral activities of the IVIG**.

symptoms in PASC patients (Reznik et al., 2022).

Theoretically, symptoms of PASC may be relieved by the immunomodulatory effects of IVIG, which work through various complementary pathways. Interactions between the idiotypic determinants on pathogenic autoantibodies and the antibodies contained in IVIG result in the production of anti-idiotype antibodies. These antibodies can then inhibit the activation of Fc receptors (FcRn) on immune cells and diminish complement activation (Reznik et al., 2022). This mechanism may be especially important in PASC if the condition includes autoimmune mechanism, as suggested by some research (Ramasamy et al., 2023).

Although IgG has a protective role, there are several clinical diseases associated to IgG autoantibodies. Consequently, there are a number of FcRn-blocking methods that are being developed for therapeutic usage, and they represent a new and successful approach to lowering circulating levels of harmful IgG autoantibodies and preventing IgG-mediated illnesses (Pyzik et al., 2023). High-dose administration of IVIG saturates FcRn receptors, inhibiting the binding of endogenous pathogenic IgG antibodies and enhancing their elimination from the system (Junghans & Anderson, 1996). This mechanism may assist in the clearance of autoantibodies that could be implicated in the persistence of Long COVID symptoms.

Current Clinical Evidence and Ongoing Trials:

Initial Case Reports and Evidence

The clinical data supporting the efficacy of IVIG in PASC predominantly comprises case reports and small-scale investigations, yielding limited although promising preliminary findings. A significant case report details a 12-year-old girl who experienced severe Long COVID symptoms, including burning sensations, weakness, slurred speech, and cognitive impairment, ultimately resulting in a bedbound condition. The patient exhibited notable neurological symptoms, including tetraparesis, sensory deficits, and areflexia, accompanied by autonomic dysfunction characterized by symptomatic hypotension and reflex tachycardia (Younger, 2021).

The patient underwent monthly IVIG treatments at a dose of 2 g/kg/month from October 2020 to February 2021 after a thorough evaluation that showed reduced epidermal nerve fiber densities, mixed chronic distal demyelinating and axonal changes on electrodiagnosis, and brain imaging demonstrating widespread hypometabolism (Younger, 2021). The case report reveals that the patient exhibited overall clinical enhancement during this therapy period, implying possible therapeutic advantage. The possibility of IVIG in severe PASC cases is

encouraging, despite the fact that this is only one case report and cannot prove efficacy (Younger, 2021). A clinical presentation of the patient exhibited involvement across multiple systems indicatives of severe PASC. This included central nervous system (CNS) dysfunction, as evidenced by abnormalities in brain imaging, peripheral neuropathy shown through nerve conduction studies, and autonomic dysfunction validated by diagnostic procedures. The comprehensive neurological assessment eliminated other possible causes, such as autoimmune encephalitis, thereby reinforcing the argument for PASC as the main diagnosis (Younger, 2021).

The RECOVER Initiative and Systematic Clinical Investigation

The RECOVER initiative represents a major advancement in the evaluation of IVIG for PASC. This extensive research program, established by the United States National Institutes of Health, aims to explore treatment options for Long COVID. In this nationwide initiative, IVIG is one of the first therapeutic agents to be thoroughly researched, demonstrating the scientific community's understanding of its potential therapeutic significance. The RECOVER-AUTONOMIC trial examines autonomic dysfunction associated with Long COVID, providing a focused investigation into the efficacy of IVIG in addressing a significant component of PASC (ClinicalTrials.gov Identifier: NCT06305780). This study is a prospective, multi-center, multi-arm, randomized, controlled platform trial assessing the efficacy of IVIG compared to placebo, alongside non-pharmacologic coordinated care versus usual care, in patients with autonomic dysfunction symptoms, including cardiovascular complications and POTS (National Institutes of Health (NIH), 2023a). The trial design is extensive, with a research period of March 2024 to July 2026 and an expected sample size of 200 patients in the IVIG arm (ClinicalTrials.gov Identifier: NCT06305793). The main objective is to assess the impact of IVIG compared to control on orthostatic intolerance. Secondary objectives include the evaluation of symptom-specific outcomes, performance-based measures, quality of life, and safety and tolerability. A comprehensive evaluation of IVIG's possible therapeutic influence is provided by the exploratory aims, which also involve assessing effects on autonomic function tests and relevant biomarkers (ClinicalTrials.gov Identifier: NCT06305793).

Current Evidence: Challenges and Limitations:

The current state of evidence for IVIG in PASC treatment is marked by several notable challenges and limitations, despite the theoretical rationale and ongoing clinical investigations. A major shortcoming is the absence of conclusive proof of effectiveness from completed randomized controlled studies. The RECOVER-AUTONOMIC trial signifies a significant advancement; however, the absence of available results restricts clinicians and patients to a narrow scope of evidence-based guidance (ClinicalTrials.gov Identifier: NCT06305780, NCT06305793)

Evaluation of the effectiveness of IVIG is further complicated by the fact that PASC presentations potentially differ greatly from patient to another. Long COVID presents a diverse array of symptoms that impact various organ systems, such as neurological, cardiovascular, pulmonary, and cognitive functions (Kenny et al., 2023). The variation in patient populations presents challenges in determining which patient may derive the greatest benefit from IVIG therapy, therefore complicating the design of clinical trials with relevant endpoints.

The use of IVIG as a treatment to PASC is also significantly limited by safety concerns. IVIG is not without hazards and contraindications, despite being generally well tolerated in established indications. The therapy should not be administered to patients who have a history of severe anaphylactic reactions to IVIG, as well as to individuals with IgA deficiency who possess anti-IgA antibodies (Burks et al., 1986; Rachid et al., 2011). Furthermore, IVIG products have the potential to modify immune responses to live viral vaccines (Goddard, 2008), a factor that may hold significant importance in the framework of current COVID-19 vaccination initiatives.

Practical limitations related to cost and accessibility may hinder the utility of IVIG, even in cases where its efficacy is confirmed (Justiz-Vaillant et al., 2025). The high cost and complexity of IVIG therapy may has prevented many Long COVID patients from receiving this life-saving treatment. As clinical data grows, significant concerns regarding cost-effectiveness will need to be addressed because to the resource-intensive nature of IVIG treatment and can cause adverse effects like headaches and allergic reactions (Kaur et al., 2022). Moreover, measures are required to reduce IVIG use, especially in the event of imminent shortages (Kaur et al., 2022).

Furthermore, it is difficult to compare results across studies and case reports due to the absence of defined outcome measures and diagnostic criteria for PASC in the present evidence base. In addition to establishing therapy success, this standardization challenge also involves figuring out the best IVIG dosage schedules and treatment durations for Long COVID patients. Regarding the longer than 12-week period of ongoing symptoms that define Long COVID, there are fewer accounts of IVIG being used to treat the different symptoms that happen during this time. Significant impairments such as cognitive dysfunction and fatigue persist, and a rise in severe dysautonomia has been documented (Gavrilova et al., 2022; Montalvo et al.,

2022; Parker et al., 2021; Rodriguez et al., 2021).

Multimodal Treatment Approaches and Clinical Considerations:

Due to the fact that the multi-system complexity of PASC have affects many different systems, researchers have advocated for more than just single therapeutic methods in PASC treatment plans. According to current recommendations, IVIG treatment ought to be incorporated into multidisciplinary treatment plans that take into account the various ways that Long COVID manifests itself, provided that it is shown to be successful. These all-encompassing strategies include strength and balance training, aerobic exercise, psychological counseling, and specialist treatments that address cardiac, respiratory, and neuromuscular symptoms (Reznik et al., 2022).

Recognizing that each patient's presentation of Long COVID is unique and may necessitate individualized treatment plans, it is advised that a multiprofessional and interdisciplinary team approach be used to optimize therapeutic results (Castanares-Zapatero et al., 2022). As an alternative delivery strategy, subcutaneous injection of immune globulins should be taken into consideration for patients who are unable to receive them via the intravenous route because of access issues or other contraindications. For suitable Long COVID patients, this flexibility in administration routes may increase access to immunoglobulin therapy (Overton et al., 2021).

The assessment of IVIG in specific populations requires careful examination. In cases where pregnant women are facing severe PASC symptoms, the use of IVIG may be an option, as it falls under FDA pregnancy category C and is typically regarded as safe during pregnancy, with a history of application in managing various fetal and neonatal conditions (Alsaleem, 2020; Leslie J. Vaughan, 2014). However, it is essential to thoroughly assess the risk-benefit profile in every unique case. (Geriak et al., 2022; Reznik et al., 2022).

Future Directions and Research Priorities:

The advancement of IVIG as a treatment for PASC is heavily reliant on the successful conclusion of current randomized controlled trials, especially the RECOVER-AUTONOMIC studies (ClinicalTrials.gov Identifier: NCT06305793, NCT06305806, NCT06305780). The results of these trials will be the first comprehensive look at IVIG's effectiveness, ideal dosage schedules, therapy duration, and criteria for patient selection. Additionally, these studies outcomes will likely influence the decision on whether IVIG is adopted as a standard treatment for Long COVID or continues to be considered an investigational therapy (ClinicalTrials.gov Identifier: NCT06305793, NCT06305806, NCT06305780).

One important area for future research is the identification of biomarkers that can help determine which PASC patients will benefit the most from intravenous immunoglobulin therapy (Kerr et al., 2014; Ogawa, 2014). This tailored approach to medicine has the potential to enhance treatment selection, minimizing the risk and costs associated with IVIG therapy for patients who are unlikely to benefit (Arumugham & Rayi, 2023; Burnouf et al., 2022; Perez et al., 2017). Current trial exploratory goals, such as evaluating pertinent biomarkers and autonomic function tests, are a significant step in this approach.

Studies with long-term follow-up will be necessary to determine how long any therapeutic benefits from IVIG treatment will last. IVIG's experience with various neuroimmune disorders indicates that while some patients may benefit from a brief course of treatment, others may need continuous maintenance medication (Dalakas, 2021). Developing evidence-based treatment procedures for Long COVID patients will require a thorough understanding of these patterns (Ewing et al., 2025). Another crucial research objective that will support upcoming clinical trials and comparative effectiveness studies is the creation of standardized diagnostic criteria and outcome measures for Long COVID (McDuff et al., 2025). The ongoing initiatives to create consensus definitions and validated assessment tools will improve the capacity to perform significant clinical research and facilitate the comparison of results across various studies and treatment centers.

CONCLUSIONS

IVIG has a solid theoretical foundation based on proven mechanisms of action in comparable neuroimmune disorders, making it a potential but still experimental therapy option for PASC. Preliminary case reports indicate a possible clinical benefit, and the therapy's involvement in significant national research initiatives such as RECOVER reflects a degree of scientific optimism; however, conclusive evidence of its efficacy is still absent. The ongoing RECOVER-AUTONOMIC trial is set to yield significant evidence concerning the effectiveness of IVIG, especially in relation to the autonomic dysfunction manifestations associated with Long COVID.

As a single therapy, IVIG may not be sufficient to address the complexity and heterogeneity of PASC presentations; instead, it should be considered as part of a complete, multidisciplinary treatment approach. Future research should concentrate on pinpointing the patient populations that stand to gain the most from IVIG treatment, determining the ideal dosing and duration protocols, and formulating cost-effective treatment strategies.

Medical professionals are still trying to figure out the long-term effects of the COVID-19 pandemic. IVIG is one of many treatment options being carefully studied for

PASC. Current evidence suggests a degree of cautious optimism; however, it is essential for patients and clinicians to await the outcomes of ongoing randomized controlled trials before IVIG can be regarded as a treatment option for Long COVID based on solid evidence. The findings from these studies are expected to have a considerable impact on the future framework of PASC treatment, potentially offering essential therapeutic alternatives for the millions affected by persistent post-COVID symptoms.

Supplementary materials
Not applicable.

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