INTRAVENOUS IMMUNOGLOBULIN (IVIG)

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Introduction

Intravenous immunoglobulin (IVIG) is a plasma product consisting primarily of immunoglobulin G (IgG) pooled from more than 10,000 human donors. Although used for immunoglobulin (IgG) replacement for Primary Immunodeficiency Diseases, at higher doses, it has an anti-inflammatory and immunomodulatory effect for various autoimmune or auto-inflammatory conditions.[1]

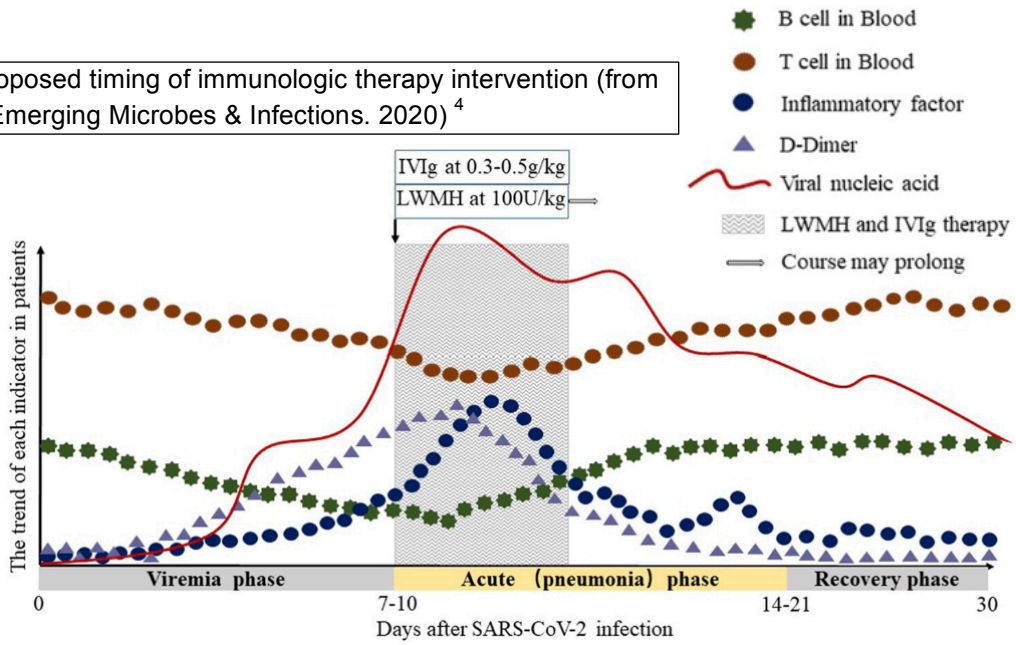
Mechanism of action and effect on COVID-19 infection

The mechanisms for its immunomodulatory effect are complex. These include modulation of antibody receptor expression and functions, interference with complement activation and the cytokine network, provision of anti-idiotypic antibodies, modulation of dendritic cell, T and B cell activation, differentiation, and effector functions. In vivo, a major mechanism by which IVIG exerts its anti-inflammatory effects is through the modulation of TH1 and TH2 cytokine and cytokine antagonist production.[2]

IVIG has been noted to reduce the levels of circulating IL-1β, increases levels of IL-1 receptor antagonists by 1000X and inhibits TNF-α mediated cytotoxicity in patients with other inflammatory conditions; hence it may have a role in controlling the initial phase of the cytokine storm in COVID-19 infection in adjunct with systemic anti-inflammatory agents such as corticosteroids.[3]

It is theorized that IVIG would be best given between day 7 to 14 or during the acute (pneumonia) phase to enhance the immune system (Figure 2)[4] and inhibit the formation of cytokine storm.[5] It is during this critical period that the immune system could be overwhelmed and pushed to a severe disease progression.

Figure 2. Proposed timing of immunologic therapy intervention (from Lin L, et al. Emerging Microbes & Infections. 2020) [4]



Efficacy Studies of IVIG in COVID-19 Infections (Appendix 3)

There is limited evidence of IVIG for COVID-19. Present evidence points to some benefit of IVIG if given on the first sign of respiratory deterioration; however, these findings were based on expert opinion and low-quality evidence (case reports and case series).[6,7,8,9,10] A multi-center retrospective cohort study done in China found no significant difference in the 28-day and 60-day mortality between the IVIG and non-IVIG groups. But in its subgroup analyses, patients with critical type illness had significant reduction in the 28-day mortality but not the 60-day mortality. There was also significant reduction in the 28-day and 60-day mortality with IVIG dose >15 g/day (*P*=0.872 and *P*=0.222, respectively). Sixty-day mortality was reduced by using IVIG in the early stage (≤7 days from admission) (*P*=0.008).[11] Another retrospective study showed that the ≤48 h group compared to the >48 h group had significantly shorter length of stay in the hospital (11.50 ± 1.030 vs 16.96 ± 1.620 days, *P*=0.0055), significantly lower proportion of patients requiring mechanical ventilation (6.67% vs 32.14%, *P*=0.016), and significantly longer 28-day survival time (*P*=0.0215).[12] A prospective cohort study by Zhou et al. involving 10 COVID-19 patients showed improvement in [APACHE score (9.10±6.15 vs 5.50±9.01, P<0.05), body temperature (37.59±1.16 vs 36.46±0.25, P<0.05), lymphocyte count (0.59±0.18 vs 1.36±0.51, P<0.05), lactate dehydrogenase (419.24±251.31 vs 257.40±177.88, P<0.05), and C-reactive protein (49.94±26.21 vs 14.58±15.25, P<0.05)] after giving moderate-dose corticosteroid and IVIG treatment.[13]

As of August 16, 2020, there have been 32 case reports, and 12 case series done on IVIG. There are 7 randomized controlled trials listed on clinicaltrials.gov. Three of these researches are recruiting already, the other 4 have not yet started.

Dose and Timing of Administration

1. IV Immunoglobulin (IVIG) for is given as adjunctive treatment in COVID-19 patients at the first sign of respiratory deterioration:
    a. Dyspnea; or
    b. RR > 30/min; or
    c. SpO2 < 93%; or
    d. PaO2/FiO2 < 300; or
    e. Progression of lung infiltrates > 50% within 24-48 hours.[14]
2. Suggested IVIG dose is: 0.3-0.5 g/kg/day for 5 consecutive days. Start infusion at 30 ml/hr (0.5 ml/kg/hr), doubling rate every 15 minutes up to a maximum rate of 100 ml/hr. Consider rate and dose adjustments based on renal and cardiac status.[14]

Adverse Reactions

Adverse reactions to IVIG are reported to occur in up to 5% to 15 % of all IVIG infusions and to affect 20% to 50% of individuals receiving IVIG.[15] Most of these reactions are mild, transient and reversible (flu-like symptoms, flushing, nausea, fatigue, fever, chills, malaise, and lethargy) and always occur within the first hour of infusion. Potentially serious reactions occur in 2% to 6% of patients and are rare such as anaphylaxis (in IgA-deficient patients), thromboembolic events, renal impairment, or severe hemolysis.

The majority of these symptoms are associated with rapid infusion and develop during the initial period of infusion which may be addressed by slowing down or stopping the infusion. Premedication is not a requirement for IVIG infusion; however, in some patients, acetaminophen, diphenhydramine or alternatively a non-sedating antihistamine and/or hydrocortisone one hour before the infusion may be given. Patients at increased risk of thromboembolic complications, or who have had prior thromboembolic complications, may benefit from additional preventive measures including pre-infusion hydration, low molecular weight heparin and use of low osmolality products. Rarely, acute kidney injury may occur with sucrose-containing products and careful evaluation and monitoring of renal function maybe necessary.[15] Routine serum IgA level testing in individuals without specific risk factor for IgA deficiency is not recommended. Importantly, IgA deficiency is not a contraindication to IVIG administration.[16-17]

Conclusion:

The use of IVIG may be beneficial when used early in the course of illness but this needs to be validated through clinical trials. The decision to use IVIG for

COVID-19 must take into consideration the risks mentioned above versus the benefit of this agent, as well as the cost of treatment.

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