Should Intravenous Immunoglobulin G (IVIg) be used in the treatment of COVID-19?

Authors: Gregorio, Germana Emerita
Date of Review: 10 July 2020 (version #2)
Last Updated: 10 July 2020 (version #2)

KEY FINDINGS

There is conflicting evidence on the efficacy of intravenous immunoglobin G in the treatment of COVID 19 patients with severe disease.

- Intravenous immunoglobulin G (IVIg) is a mixture of polyclonal immunoglobulin G (IgG3, IgG4) antibodies as well as variable amounts of proteins; IgA, IgE, and IgM antibodies isolated and pooled from healthy donors. Immunoglobulin G is involved in viral neutralization. It also modulates the induction of anti-inflammatory cytokines and cytokine antagonists such as interleukin (IL)-1b, IL-1 receptor antagonist and tumour necrosis factor (TNF)-a.
- There was a retrospective study (Yun Xie 2020) and several case reports that described recovery of COVID positive patients with severe disease (Wei Cao, 2020; Mohtadi N 2020; Lanza 2020; Zhou ZG 2020). However, a retrospective study also showed that immunoglobulin G with steroids and antivirals did not improve COVID patients with acute respiratory distress syndrome (Liu Y 2020)
- There is conflicting evidence on the efficacy of intravenous immunoglobin G in the treatment of COVID 19 patients with severe disease.. There are several ongoing clinical trials on the use of intravenous immunoglobulin G in COVID 19 patients
- Immediate adverse effects mainly include flu-like syndrome, dermatologic side effects, arrhythmia, hypotension, and transfusion-related acute lung injury (TRALI). Delayed adverse effects can be severe or even lethal and affect less than 1% of patients. These events include thrombotic events, neurological disorders, renal impairment, hematologic disorders, electrolyte disturbance, and transfusion-related infection.
- Surviving sepsis campaign guidelines suggest against the routine use of IVIg in critically ill adults with COVID-19. (Weak recommendation, low-quality evidence) Clinical Practice Guideline for Sepsis and Septic Shock in Adults in the Philippines 2020 also does not recommend the use of standard polyclonal intravenous immunoglobulins in sepsis and septic shock. (Strong recommendation, high quality evidence)

RESULTS

In a retrospective study of 58 COVID positive with severe pneumonia, patients given IVIg <48 hours from admission had significantly shorter length of ICU and hospital stay, required less mechanical ventilation and had increased 28 day survival time as compared to those given IVIg >48 hours. (Yun Xie 2020). In this report, 35 patients survived and 23 died.

There are presently three case series on the use of intravenous IgG in COVID positive patients. The first successfully treated three COVID positive adult patients with severe disease during the early stage of clinical deterioration. (Wei Cao, 2020). Another described the recovery of ten COVID 19 patients who were given short term moderate dose corticosteroids and immunoglobulin G (Zhou ZG 2020). And a third case series administered high dose IVIg in five severely ill COVID positive patients in whom standard treatment has failed (Mohtadi N 2020).

A 42 year old Italian woman was also effectively treated with IVIg for severe COVID pneumonia (Lanza 2020)

In another retrospective study, the survival of 53 COVID positive patients with ARDS was not improved with antivirus, corticosteroids and immunoglobulin G treatment (Liu Y 2020).

CONCLUSION

There is conflicting evidence on the use of Intravenous Immunoglobulin G on COVID 19 patients with severe disease. There are ongoing clinical trials on the use of intravenous immunoglobulin G in severe COVID patients. Result of these trials are needed before any recommendation is made. Surviving sepsis campaign guidelines suggest against the routine use of IVIg in critically ill adults with COVID-19.

Declaration of Conflict of Interest

No conflict of interest

REFERENCES

Alhazzani, W., Møller, M., Arabi, Y., Loeb, M. et al., 2020. Surviving Sepsis Campaign: guidelines on the management of critically ill adults with Coronavirus Disease 2019 (COVID-19). Intensive Care Medicine,.

Arabi YM, Arifi A, Balkhy H et al. Clinical Course and Outcomes of Critically Ill Patients With Middle East Respiratory Syndrome Coronavirus Infection. Ann Int Med 2014; 160: 389-97

Clinical Practice Guidelines for Sepsis and Septic Shock Task Force 2020. Clinical Practice Guideline for Sepsis and Septic Shock in Adults in the Philippines 2020. [Unpublished]

Dourmishev LA, Guleva DV, Miteva LG. Intravenous Immunoglobulins: Mode of Action and Indications in Autoimmune and Inflammatory Dermatosis. International Journal of Inflammation 2016, Article ID 3523057, 6 pages http://dx.doi.org/10.1155/2016/3523057

Guo Y, Tian X, Wang X, Xiao Z. Adverse Effects of Immunoglobulin Therapy. Front Immunol. 2018; 8: 1-13

Lanza M, Polistina GE, Imitazione P, Annunziata A, Di Spirito V, Novella C, Fiorentino G.
Version 2. Successful intravenous immunoglobulin treatment in severe COVID-19 pneumonia. IDCases. 2020; 21:e00794

Liu Y, Sun W, Li J, et al. Clinical features and progression of acute respiratory distress syndrome in coronavirus disease 2019. MedRxiv 2020 [cited 2020 Apr 13].

Mohtadi N, Ghaysouri A, Shirazi S, Ansari S, Shafiee E, Bastani E, Kokhazadeh T, Tavan H. Recovery of Severely Ill COVID-19 Patients by Intravenous Immunoglobulin (IVIG) Treatment: A Case Series. Virology 2020 25; 548: 1-5

Wang JT, Sheng WH, Fang CT, et al. Clinical manifestations, laboratory findings, and treatment outcomes of SARS patients. Emerg Infect Dis. 2004;10: 818-24

Wei C, Xiaosheng L, Tao B. High dose inravenous immunoglobulin as a therapeutic option for deteriorating patients with Coronavirus Disease 2019 (accepted for publication)
https://academic.oup.com/ofid/advancearticle/doi/10.1093/ofid/ofaa102/5810740

Yun Xie, Song Cao, Hui Dong, et al. Effect of Regular Intravenous Immunoglobulin Therapy on Prognosis of Severe Pneumonia in Patients With COVID-19. J Infect 2020; S0163-4453(20)30172-9

Zhou, Zhi-Guo & Xie, Shu-Min & Zhang, Jing & Zheng, Fang & Jiang, Di-Xuan & Li, Ke-Yu & Zuo, Qi & Yan, Yu-Sheng & Liu, Ji-Yang & Xie, Yuan-Lin & Peng, Hong & Lei, Zhang. (2020). Short-Term Moderate-Dose Corticosteroid Plus Immunoglobulin Effectively Reverses COVID-19 Patients Who Have Failed Low-Dose Therapy.
https://www.researchgate.net/publication/339743438_Short-Term_Moderate-Dose_Corticosteroid_Plus_Immunoglobulin_Effectively_Reverses_COVID-19_Patients_Who_Have_Failed_Low-Dose_Therapy

A multicenter study in China led by Peking Union Medical College Hospital, Chinese Academy of Medical Sciences to determine if high dose intravenous immunoglobulin G will reverse the worsening course of COVID 19 patients
https://www.trialsitenews.com/chinese-academy-of-medical-sciences-led-study-reveals-high-dose-ivig-improves-severe-covid-19-cases

Comparison between the efficacy of intravenous immunoglobulin and convalescent plasma in improving the condition of patients with COVID-19: A randomized clinical trial. Led by Birjand University of Medical Sciences Iran. https://www.irct.ir/trial/47212

To evaluate the effectiveness of intravenous immunoglobulin (IVIG) for the treatment of COVID-19-induced cytokine storm. Led by Tabriz University of Medical Sciences in Iran. https://www.irct.ir/trial/47014

Evaluation of the efficacy of intravenous immunoglobulin (IVIg) in patients with severe COVID-19 (Before intubation phase) who have not responded to treatment with the standard three-drug protocol (hydroxychloroquine / chloroquine + lupinavir / ritonavir + ribavirin). Led by Mashhad University of Medical Sciences. https://www.irct.ir/trial/46811

Polyvalent Immunoglobulin in COVID-19 Related ARds (ICAR). Led by Centre Hospitalier St Anne Parid, France.
https://clinicaltrials.gov/ct2/show/NCT04350580?id=NCT04264858+OR+NCT04350580+OR+NCT04261426&draw=2&rank=1&load=cart

Last Updated: 10/July/2020

Table 1. Characteristics of ongoing clinical trials

No.	Clinical Trial ID / Title	Status	Start and estimated primary completion date	Study design	Country	Population	Intervention Group(s)	Comparison Group(s)	Outcomes
1	NCT04261426 A Randomized, Open-label, Controlled, Single-center Study to Evaluate the Efficacy of Intravenous Immunoglobulin Therapy in Patients With Severe 2019- nCoV Pneumonia	Not yet recruiting	February 10,2020 April 30,2020	Randomized Open Label Parallel Controlled Clinical Trial	China	COVID 19	IVIg	Standard Care	Clinical Improvement based on the 7 point scale Lower Murray lung injury score 28 day mortality Duration of mechanical ventilation Duration of hospitalization Proportion of patients with negative RT-PCR results Proportion of patients in each category of the 7 point scale Proportion of patient with normalized inflammation factors Frequency of adverse drug events Frequency of serious adverse drug events
2	**IRCT20200413047056N1** Comparison between the efficacy of intravenous immunoglobulin and convalescent plasma in improving the condition of patients with COVID-19: A randomized clinical trial	Not yet recruiting	April 18, 2020 June 18 2020	Clinical trial with control group-randomized-parallel groups	Iran	COVID 19	IVIg Convalescent plasma treatment g	Convalescent plasma treatment group Control group	Lung involvement in X-ray and CT-scan, Oxygen saturation (pulse oximetry and ABG) Viral load

									Length of hospital stay Duration of mechanical ventilation Blood tests: LDH enzyme, acute phase protein, white blood cell count ESR
3	**IRCT20200317046797N3** **To evaluate the effectiveness of intravenous immunoglobulin (IVIG) for the treatment of COVID-19-induced cytokine storm**	Not yet recruiting	April 18, 2020 July 22 2020	Randomly assigned to intervention and control	Iran	COVID 19	IVIg	Control group	Change of pneumonia severity on CT scanning Decrease hospitalization period Decrease ARDS symptoms Decrease mortality Decrease hospitalization period
4	**IRCT20200325046859N1** **Evaluation of the efficacy of intravenous immunoglobulin (IVIg) in patients with severe COVID-19 (Before intubation phase) who have not responded to treatment with the standard three-drug protocol (hydroxychloroquine / chloroquine + lupinavir / ritonavir + ribavirin)**	Not yet recruiting	April 4, 2020 May 5, 2020	Convenience sampling Clinical trial with no control group, not blinded and not randomized	Iran	COVID 19	IVIg	Standard Treatment	Change in the following before and after treatment Body temperature Respiration rate Pulse rate O2 saturation Labs: WBC; number of lymphocytes; LDH; Signal Recognition Particle (SRP); findings of CT scan
	NCT04350580 **Polyvalent Immunoglobulin in COVID-19 Related ARds (ICAR)**	Recruiting	April 11, 2020 June 2020	Randomized Parallel Assignment	France	COVID 19	Human Immunoglobulin	Placebo	Primary Outcome: Ventilator-free days [Time Frame: 28 days] Sum of the days the patient did not receive VM, but if death

									occurs before D28, the score is zero Secondary Outcome: Mortality [Time Frame: 28 and 90 days] Sequential Organ Failure Assessment Score [Time Frame: Days 1, 3, 7, 14, 21 and 28] P/F ratio [Time Frame: Days 1, 3, 7, 14, 21 and 28] Lung compliance [Time Frame: Days 1, 3, 7, 14, 21 and 28] Radiological score [Time Frame: Days 1, 3, 7, 14, 21 and 28] Severity scoring of lung oedema on the chest radiograph Biological efficacy endpoints \ C-reactive protein [Time Frame: Days 1, 3, 7, 14, 21 and 28] Procalcitonin [Time Frame: Days 1, 3, 7, 14, 21 and 28] Concentration in microgram/L Immunological profile [Time Frame: Up to 28 days] Number of CD4 HLA-DR+ and CD38+, CD8 lymphocytes

									Number of patients using other treatments for COVID-19 related ARDS [Time Frame: Up to 28 days] Use of corticosteroids, antiretroviral, chloroquine Occurrence of deep vein thrombosis or pulmonary embolism [Time Frame: 28 days] Total duration of mechanical ventilation, ventilatory weaning and curarisation [Time Frame: 28 days] Kidney Disease: Improving Global Outcomes (KDIGO) score and need for dialysis [Time Frame: 28 days] Divided in 3 stages, with higher severity of kidney injury in higher stages Occurrence of adverse event related to immunoglobulins [Time Frame: 28 days] Kidney failure, hypersensitivity with cutaneous or hemodynamic manifestations, aseptic meningitis, hemolytic anemia, leuko-neutropenia, transfusion related

									acute lung injury (TRALI) Occurrence of critical illness neuromyopathy [Time Frame: Up to 28 days] Medical research council sum score on awakening Occurrence of ventilator-acquired pneumonia [Time Frame: Up to 28 days] Radiological and clinical context associated with a bacteriological sampling in culture of tracheal secretions, bronchiolar-alveolar lavage or a protected distal sampling