CURRENT MEDICAL RESEARCH AND OPINION
https://doi.org/10.1080/03007995.2021.1903849
Article ST-0021.R1/1903849

Taylor & Francis
Taylor & Francis Group

EDITORIAL

Adjunctive intravenous immunoglobulins (IVIg) for moderate-severe COVID-19: emerging therapeutic roles

Approximately 1−5% of patients with the coronavirus disease 2019 (COVID-2019), caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) develop severe or critical disease characterized by acute respiratory distress syndrome (ARDS), coagulopathy, sepsis and multiple-organ failure, requiring intensive care support[1,2].

As efficacious COVID-19 vaccines are being rolled out to control the pandemic, their distribution and demand is overwhelming. Moreover, there is no established targeted anti-viral therapy for COVID-19, which makes clinical management extremely difficult. Several candidate therapies, including supportive interventions (supplemental oxygenation, mechanical ventilation and extracorporeal membrane oxygenation), immunomodulatory agents (corticosteroids), antiviral therapy like remdesivir, convalescent plasma, and intravenous immunoglobulins (IVIg) have been tentatively applied in clinical settings based on limited evidence[3,4].

Recent evidence suggests that the cytokine release syndrome (or cytokine storm), a scenario characterized by an exaggerated cytokine release in response to viral infection, underlies severe COVID-19[5]. Overproduction of pro-inflammatory cytokines such as interleukin (IL)-1, IL-6, IL-8, IL-12, chemokine ligand (CCL)-2, and tumor necrosis factor-alpha (TNFα) leads to alveolar and vascular lung damage, presenting as ARDS seen in severe COVID-19[6]. Therefore, therapeutics such as convalescent plasma, IVIg, and monoclonal antibodies targeting the immune response to SARS-CoV-2 have proven some benefit in the management of COVID-19. IVIg are intravenously administered antibody products purified from pooled plasma of thousands of healthy donors. They are a concentration of antibodies classically made up of polyspecific immunoglobulin G (IgG) and trace amounts of IgA or IgM[7].

The major mechanisms of action of IVIg in hyper-inflammatory states include; 1. blockage of intact Fcγ receptors on immune cells to inhibit their activation and subsequent intracellular signaling and cell function, 2. up-regulation of inhibitory Fcγ receptor IIB (CD32B) on various immune cells including B cells, Dendritic cells, Monocytes/macrophages and Basophils, which switches off the intracellular inflammatory cascades; 3. Inhibiting complement-mediated tissue damage, and 4. down-regulating pro-inflammatory cytokines (TNFa, IL-1b, IL-6, IL-12) while up-regulating anti-inflammatory cytokines (IL-10 and transforming growth factor)[8]. IVIg has also been found to suppress inflammation through T-helper 2 biased pathway and may also contain natural antibodies that act against tumors, auto-reactive B-cells, pathogens and altered molecules[9,10]. Various studies and systemic reviews have been done on the effects of these immunoglobulins on coronaviruses like SARS-CoV, SARS-CoV-2, MERS-CoV, and other viruses like H1N1; some of the results were seemingly promising, but many were inconclusive or weak, secondary to concurrent use of other drugs, and other confounding factors[11].

In this issue of the Current Medical Research and Opinion, Esen and colleagues report their findings of a single centre, retrospective study from Turkey on effects of adjunctive IVIg, Octagam, in the treatment of severe COVID-19[12]. In this report, Octagam showed a superior survival time and an anti-inflammatory effect evidenced by the significant decrease in C-reactive protein levels[12]. The team studied 93 patients over a 2-month period in two intensive care units (ICU) of the University hospital of Istanbul, where the patients had random assignation of treatment (although inadvertently): either standard ICU care only or standard ICU care plus Octagam 5%. At baseline, the characteristics measured were age, sex, blood group, Acute Physiology and Chronic Health Evaluation II (APACHE II) and Sequential Organ Failure Assessment (SOFA) scores, plasma troponin, and pro-brain natriuretic peptide (proBNP) concentrations. The clinical outcome measures observed were duration of specific treatment modalities, change in ventilation mode, time to beginning of mechanical ventilation, ICU and hospital discharge and overall survival. However, changes in other inflammation biomarkers were small and insignificant. There were, however, notable imbalances at baseline between the two groups regarding concurrent co-morbidities, age, proBNP and troponin levels (lower in the Octagam group). This could in part explain the large difference observed in ICU survival (Octagam 61% and non-Octagam 38%). It is therefore not surprising that controlling for the APACHE II Score, rendered the difference non-significant. It still calls into question of the reliability of the study results. While survival time was still significantly longer in the intervention group after controlling for the APACHE II score, the results need to be interpreted with caution considering that differences in age and comorbid conditions (established predictors of COVID − 19-related mortality) were not controlled for. Additionally, the small sample size could have prevented the investigators from detecting salient differences in the intervention and control group. Nonetheless, the findings from this study are consistent with previous studies. In these studies, IVIg consistently showed a reduction in mortality, decrease in inflammatory responses and led to improved organ function. Though the results of this study suggests mortality benefit of IVIg, randomized clinical trials are required to confirm these findings.

The mechanism of action of IVIg in COVID-19 is not yet understood but owes to their anti-inflammatory and immunomodulatory properties. Studies suggest that IVIg might prevent superantigen-mediated T cell activation and cytokine release, inhibit innate immune cells and effector T-cells activation, expand on regulatory T-cells and aid in complement scavenging[13]. As well, available IVIg products like Gamunex-C and Flebogamma DIF have been confirmed to contain antibodies that react against SARS-CoV-2 antigens in *in vitro* studies. Though this is a promising finding, more research is needed to prove actual benefits in COVID-19.

In a retrospective, multi-centre study done by Shao and colleagues on 325 individuals with severe COVID-19 from southern China showed improved prognosis of patients receiving early administration (within 7 days of admission) of high dose IVIg (0.1–0.5 g/kg/day) for 5–15 days, coupled with the then standard of intensive care including antibiotics, steroids and antiviral drugs[14]. In an open label randomized clinical trial recruiting 100 participants, adjunctive IVIg therapy was associated with a significantly shorter median time to real-time polymerase chain reaction negativity compared to standard of care (7 vs.18 days)[15]. Additionally, a case series involving 3 patients done in China showed that administering high dose IVIg to COVID-19 patients at an early stage of clinical deterioration led to prevention of disease progression and improved outcome: it should be noted that due to small number of cases and patients having received other drugs, more evidence is needed to confirm these findings[16]. High dose IVIg has also been recommended as early therapy in COVID-19 viral pneumonia alongside an anticoagulant[17].

A retrospective study on 5 cases suggests that IVIg may be safe and effective in treatment of COVID-19-associated encephalopathy[18]. Other studies, mostly retrospective or case studies, also show that when initiated early and in high dose, IVIg can improve oxygen saturation, clinical condition and prevent progression of lung lesions; as well in cases of COVID-19 patients that did not respond to low dose IVIg therapy, a short-term moderate dose corticosteroid accompanying IVIg might show benefit[8,19–22]. One of the retrospective studies showed that though severely ill patients on IVIg had higher incidence of ARDS and myocardial injury, they had less shock and were less likely to require invasive mechanical ventilation; also some improvements were noted with administration of high dose IVIg ($\geq$10 g/day) compared to the regular IVIg dose[23]. Benefits may also occur when IVIg is coupled with corticosteroids like methylprednisolone or the recombinant modified IL-1 receptor antagonist, anakinra, however these benefits are difficult to evaluate[24,25]. Use of IVIg in patients with severe COVID-19 infection who do not respond to initial therapy has also be found to improve clinical outcomes, reducing mortality[26].

Meanwhile, in patients with non-severe COVID-19, IVIg has does not offer additional benefit to standard of care. In a recent retrospective study of 639 non-severe patients with COVID-19, 45 patients received IVIg therapy and 594 received non-IVIg therapy. based on (PSM) was designed. After propensity score matching (1:2 ration), no statistically significant differences were found between IVIg group and control group in the duration of fever, virus clearance time, length of hospital stay, and the use of antibiotics[27]. Moreover, comparable proportions of patients progressed to severe illness or died in either arms.

In summary, IVIg may have an adjunctive role in the treatment of severe COVID-19, especially in combination with other drugs like corticosteroids or antivirals. However, the current level of evidence requires evaluation in larger, well-designed randomized, controlled, clinical trials. Several of these trials are in progress and we await their findings.

Transparency

Declaration of funding

No funding was received.

Declaration of financial/other relationships

FB is a Makerere University Non-Communicable Diseases (MakNCD) Master's Fellow partially supported by the Forgarty International Centre of the National Institutes of Health under Award Number D43 TW011401. Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

Author contributions

All authors have contributed to the drafting of the manuscript. All have read and approved the final manuscript and agree to be accountable for all aspects of the work.

Acknowledgements

The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

ORCID

Felix Bongomin http://orcid.org/0000-0003-4515-8517
Lucy Grace Asio http://orcid.org/0000-0001-5328-9184
Kenneth Ssebambulidde http://orcid.org/0000-0002-8125-0698
Joseph Baruch Baluku http://orcid.org/0000-0002-5852-9674

References

[1] Zhang W, Zhao Y, Zhang F, et al. The use of anti-inflammatory drugs in the treatment of people with severe coronavirus disease 2019 (COVID-19): the perspectives of clinical immunologists from China. Clin Immunol. 2020;214:108393.
[2] Woldometer. COVID-19 coronavirus pandemic [Internet]; 2021. Available from: https://www.worldometers.info/coronavirus/.
[3] Zheng C, Wang J, Guo H, Anhui Medical Team Members of National Aid to prevent and treat novel coronavirus pneumonia in Wuhan, et al. Risk-adapted treatment strategy for COVID-19 patients. Int J Infect Dis. 2020;94:74–77.
[4] Valk SJ, Piechotta V, Chai KL, et al. Convalescent plasma or hyperimmune immunoglobulin for people with COVID-19: a rapid review. Cochrane Database Syst Rev [Internet]. 2020. DOI:10.1002/14651858.CD013600
[5] Bikdeli B, Madhavan MV, Jimenez D, et al. COVID-19 and thrombotic or thromboembolic disease: implications for prevention,

antithrombotic therapy, and follow-up: JACC state-of-the-art review. J. Am. Coll. Cardiol. 2020;75(23):2950–2973.
[6] Ortolani C, Pastorello EA. Hydroxychloroquine and dexamethasone in COVID-19: who won and who lost? Clin Mol Allergy. 2020;18:17.
[7] Ballow M. Mechanisms of immune regulation by IVIG. Curr Opin Allergy Clin Immunol. 2014;14(6):509–515.
[8] Mohtadi N, Ghaysouri A, Shirazi S, et al. Recovery of severely ill COVID-19 patients by intravenous immunoglobulin (IVIG) treatment: a case series. Virology. 2020;548:1–5.
[9] Anthony RM, Kobayashi T, Wermeling F, et al. Intravenous gammaglobulin suppresses inflammation through a novel T(H)2 pathway. Nature. 2011;475(7354):110–113.
[10] Kivity S, Katz U, Daniel N, et al. Evidence for the use of intravenous immunoglobulins-a review of the literature. Clin Rev Allergy Immunol. 2010;38(2–3):201–269.
[11] Arabi Y, Hajeer A, Luke T, et al. Feasibility of using convalescent plasma immunotherapy for MERS-CoV infection, Saudi Arabia. Emerg Infect Dis. 2016;22(9):1554–1561.
[12] Esen F, Özcan PE, Orhun G, et al. Effects of adjunct treatment with intravenous Octagam on the course of severe COVID-19: results from a retrospective cohort study. Curr Med Res Opin. 2020. DOI:10.1080/03007995.2020.1856058
[13] Galeotti C, Kaveri SV, Bayry J. Intravenous immunoglobulin immunotherapy for coronavirus disease-19 (COVID-19). Clin Transl Immunology. 2020;9(10):e1198.
[14] Shao Z, Feng Y, Zhong L, et al. Clinical efficacy of intravenous immunoglobulin therapy in critical ill patients with COVID-19: a multicenter retrospective cohort study. Clin Transl Immunol. 2020;9:e1192.
[15] R SR, Barge VB, Darivenula AK, et al. A phase II safety and efficacy study on prognosis of moderate pneumonia in COVID-19 patients with regular intravenous immunoglobulin therapy. J Infect Dis. 2021;jiab098.
[16] Cao W, Liu X, Bai T, et al. High-dose intravenous immunoglobulin as a therapeutic option for deteriorating patients with coronavirus disease 2019. Open Forum Infect Dis. 2020;7(3):ofaa102.
[17] Scoppetta C, Gennaro GDI, Polverino F. Editorial – High dose intravenous immunoglobulins as a therapeutic option for COVID-19 patients. Eur Rev Med Pharmacol Sci. 2020;24(9):5178–5179.
[18] Muccioli L, Pensato U, Bernabè G, et al. Intravenous immunoglobulin therapy in COVID-19 - related encephalopathy. J Neurol. 2020. DOI:10.1007/s00415-020-10248-0
[19] Lanza M, Emanuele G, Imitazione P, et al. IDCases successful intravenous immunoglobulin treatment in severe COVID-19 pneumonia. IDCases. 2020;21:e00794.
[20] Xie Y, Cao S, Dong H, et al. Effect of regular intravenous immunoglobulin therapy on prognosis of severe pneumonia in patients with COVID-19. J Infect. 2020;81(2):318–356.
[21] Zhou Z-G, Xie S, Zhang J, et al. Short-term moderate-dose corticosteroid plus immunoglobulin effectively reverses Covid-19 patients who have failed low-dose therapy. Research Square. 2020. DOI:10.20944/preprints202003.0065.v1
[22] Zavattaro E, Cammarata E, Tarantino V, et al. Successful treatment of a bullous vasculitis with intravenous immunoglobulins in a COVID-19 patient. Dermatol Ther. 2021. DOI:10.1111/dth.14853
[23] Liu J, Chen Y, Li R, et al. Intravenous immunoglobulin treatment for patients with severe COVID-19: a retrospective multi-center study. Research Square. 2020. DOI:10.21203/rs.3.rs-52428/v1
[24] Sakoulas G, Geriak M, Kullar R, et al. Intravenous immunoglobulin (IVIG) significantly reduces respiratory morbidity in COVID-19 pneumonia: a prospective randomized trial. medRxiv. 2020. DOI:10.1101/2020.07.20.20157891
[25] Zantah M, Dominguez Castillo E, Gangemi AJ, et al. Anakinra and Intravenous IgG versus tocilizumab in the treatment of COVID-19 pneumonia. medRxiv. 2020. DOI:10.1101/2020.09.11.20192401
[26] Gharebaghi N, Nejadrahim R, Mousavi SJ. The use of intravenous immunoglobulin gamma for the treatment of severe coronavirus disease 2019: a randomized placebo-controlled double-blind clinical trial. 2020;20(1):786.
[27] Huang C, Fei L, Li W, et al. Efficacy evaluation of intravenous immunoglobulin in non-severe patients with COVID-19: a retrospective cohort study based on propensity score matching. Int J Infect Dis. 2021. DOI:10.1016/j.ijid.2021.01.009

Felix Bongomin* and Lucy Grace Asio*
Department of Medical Microbiology & Immunology, Faculty of Medicine, Gulu University, P.O. BOX, 166, Gulu, Uganda
drbongomin@gmail.com

Kenneth Ssebambulidde
College of Health Sciences, Infectious Diseases Institute, Makerere University, Kampala, Uganda

Joseph Baruch Baluku
Division of Pulmonology, Kiruddu National Referral Hospital, Kampala, Uganda
Directorate of Programs, Mildmay Uganda, Wakiso, Uganda

*Joint first authors.

Received 9 January 2021; revised 25 February 2021; accepted 11 March 2021