Philippine COVID-19 Living Clinical Practice Guidelines
Institute of Clinical Epidemiology, National Institutes of Health, UP Manila
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EVIDENCE SUMMARY

Should intravenous immunoglobulin be used in the treatment of COVID-19?

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RECOMMENDATION

We suggest against the use of intravenous immunoglobulin as treatment for moderate to severe COVID-19. (*Very low quality of evidence; Conditional recommendation*)

Consensus Issues

A conditional recommendation was made while waiting for the results of the 31 ongoing trials.

Key Findings

Four RCTs (n=277) that were of low to very low quality found that the use of intravenous immunoglobulin (IVIg) did not significantly reduce mortality or risk of mechanical ventilation among patients with moderate to severe COVID-19. However, one very low quality RCT found higher incidence of virologic clearance as assessed by negative RT PCR with the use of IVIg. There was also no significant increase risk of adverse events with its use in COVID-19.

Introduction

The acute respiratory distress syndrome of COVID-19 has been described as being driven by pro-inflammatory markers. The use of IVIg has been proposed as a treatment for COVID-19 due to its anti-inflammatory and immunomodulatory effects and its wide use in inflammatory and infectious diseases as well.[1] However, observational studies on the use of IVIg for severe COVID-19 show conflicting results. Hence we evaluated randomized control trials investigating the effectiveness of IVIg for COVID-19.

Review Methods

We performed a systematic literature search in online databases such as MEDLINE and CENTRAL. Additional searches in MedRxiv and WHO ICTRP were also done to look for articles awaiting publication and ongoing clinical trials, respectively. We used search terms such as “intravenous immunoglobulin,” “intravenous immune globulin,” “normal human immunoglobulin,” “human normal immunoglobulin,” “IVIg,” and “COVID-19.” References from review articles were also manually searched for additional articles.

Results

The initial search from all the databases retrieved 331 references. After removal of duplicates, letters, commentaries, narrative reviews, and studies not meeting the inclusion criteria, we retrieved four full text articles.

Four RCTs compared the use of IVIg in various doses among 277 patients with moderate to severe COVID-19 (Appendix 1). The study by Gharebaghi et al. [4] compared IVIg against placebo while the three other RCTs [5–7] compared it to standard care. Pooled analysis of these three RCTs found no significant effect on mortality (RR 0.91 [95% CI 0.56, 1.46]) or need for mechanical ventilation (RR 0.79 [95% CI 0.53, 1.18]). However, the use of IVIg was associated with a higher chance of virologic clearance (RR 3.8 [95% CI 2.3, 6.3]). [5] There was also no increase in the risk of adverse events with the use of IVIg. [5,6]

In terms of length of hospital stay, two studies demonstrated a longer duration of hospitalization with the use of IVIg (median duration 2 to 3 days) [4,7] while the study by Raman et al., [5] showed a shorter mean length of hospital stay by 10 days (SD 5). Pooled analysis on the length of hospital stay showed a mean difference of -1.9 days (-2.8 to -0.9) which we considered as inconclusive.

The studies investigating the use of IVIg in COVID-19 were limited by high risk of unclear allocation concealment, and lack of intention to treat analysis. In addition, the studies were of small sample size leading to serious risk of imprecision (see Appendix 2).

Recommendations from Other Groups

The Surviving Sepsis Campaign Guidelines suggest against the routine use of standard IV immunoglobulin in critically-ill adults with COVID-19 (updated March 2021). [8]

Clinical practice guidelines from WHO, IDSA, US NIH, UK NHS, American Thoracic Society/European Respiratory Society, and the Australian Living Guideline made no recommendation on the use of intravenous immunoglobulin as treatment for COVID-19.

The US NIH however, did evaluate the use of SARS-COV2 specific immunoglobulins and found no sufficient evidence to support its use pending results of clinical trials.

Ongoing Studies

There are currently 31 ongoing randomized clinical trials in different phases investigating the effect of various forms of immunoglobulin as treatment for COVID-19 patients (Appendix 3).

References

[1] Yaqinuddin A, Ambia AR, Elgazzar TA, AlSaud M bint M, Kashir J. Application of intravenous immunoglobulin (IVIG) to modulate inflammation in critical COVID-19 – A theoretical perspective. *Med Hypotheses*. 2021;151(January):110592. doi:10.1016/j.mehy.2021.110592

[2] Liu J, Chen Y, Li R, et al. Intravenous immunoglobulin treatment for patients with severe COVID-19: a retrospective multi-center study. *Clin Microbiol Infect*. 2021;(January):19-20. doi:10.1016/j.cmi.2021.05.012

[3] 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(10):1-10. doi:10.1002/cti2.1192

[4] Gharebaghi N, Nejadrahim R, Mousavi SJ, Sadat-Ebrahimi S-R, Hajizadeh R. The use of intravenous immunoglobulin gamma for the treatment of severe coronavirus disease 2019: a randomized placebo-controlled double-blind clinical trial. *BMC Infect Dis*. 2020;20(1):786. doi:10.1186/s12879-020-05507-4

[5] Raman RS, Bhagwan Barge V, Anil Kumar D, et al. A Phase II Safety and Efficacy Study on Prognosis of Moderate Pneumonia in Coronavirus Disease 2019 Patients With Regular Intravenous Immunoglobulin Therapy. *J Infect Dis*. February 2021. doi:10.1093/infdis/jiab098

[6] Sakoulas G, Geriak M, Kullar R, et al. Intravenous Immunoglobulin (IVIG) Significantly Reduces Respiratory Morbidity in COVID-19 Pneumonia: A Prospective Randomized Trial. *medRxiv*. January 2020:2020.07.20.20157891. doi:10.1101/2020.07.20.20157891

[7] Tabarsi P, Barati S, Jamaati H, et al. Evaluating the effects of Intravenous Immunoglobulin (IVIg) on the management of severe COVID-19 cases: A randomized controlled trial. *Int Immunopharmacol*. 2021;90(January):107205. doi:10.1016/j.intimp.2020.107205

[8] Alhazzani W, Møller MH, Arabi YM, et al. Surviving Sepsis Campaign : Guidelines on the Management of Critically Ill Adults with Coronavirus Disease 2019 (COVID-19). 2019;2019.

Appendix 1: Characteristics of Included Studies

Title/Author	Study design	Sample Size	Population	Intervention Group(s)	Control	Outcomes
Gharebaghi et al 2020	RCT	59	patients with severe COVID-19 who did not respond to initial treat-ments, ARDS	4 vials of 5g IVIg x 3 days	placebo	In-hospital mortality
Tabarsi et al	RCT	84	Severely ill COVID-19 pstients	400 mg/Kg daily for three doses	Standard of care	invasive mechanical ventilation and oxygenation, the need for admission to the Intensive Care Unit (ICU), and the mortality rate
Sakoulas et al	RCT, open label	34	Moderate to severe COVID-19	500 mg/kg daily for 3 days	Standard of care	Need for mechanical ventilation, length of hospital stay, length of ICU stay
Raman et al 2021	RCT open label	100	Moderate COVID-19	400 mg/kg daily for 5 days	Standard of care	Number of days hospitalized, time to clinical improvement, duration of mechanical ventilation, 28-day mortality, proportion of patients with negative RT PCR (day 14, 28)

Appendix 2: GRADE Evidence Profile

Author(s): Macalalad-Josue, Faltado
Question: Intravenous immunoglobulin compared to placebo or standard of care for COVID-19
Setting:
Bibliography:

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	intravenous immunoglobulin	placebo or standard of care	Relative (95% CI)	Absolute (95% CI)		
mortality (follow up: 30 days)												
3	randomised trials	very serious [a,b,c]	serious [d,e]	not serious	not serious	none	31/149 (20.8%)	32/128 (25.0%)	**RR 0.91** (0.56 to 1.46)	**22 fewer per 1,000** (from 110 fewer to 115 more)	⨁◯◯◯ VERY LOW	CRITICAL
need for mechanical ventilation												
3	randomised trials	serious [a,b]	serious [e,f]	not serious	serious [g]	none	35/118 (29.7%)	36/99 (36.4%)	**RR 0.79** (0.53 to 1.18)	**76 fewer per 1,000** (from 171 fewer to 65 more)	⨁◯◯◯ VERY LOW	CRITICAL
length of hospital stay (follow up: 28 days; assessed with: number of days; Scale from: 1 to 28)												
3	randomised trials	serious [a,b]	very serious [h]	not serious	serious [g]	none	132	111	-	MD **1.9 days lower** (2.83 lower to 0.94 higher)	⨁◯◯◯ VERY LOW	IMPORTANT
incidence of virologic clearance (assessed with: negative RT PCR)												
1	randomised trials	serious [a,b,c]	not serious	not serious	very serious [g,i]	none	46/50 (92.0%)	12/50 (24.0%)	**RR 3.83** (2.33 to 6.32)	**679 more per 1,000** (from 319 more to 1,000 more)	⨁◯◯◯ VERY LOW	IMPORTANT
Adverse events												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	intravenous immunoglobulin	placebo or standard of care	Relative (95% CI)	Absolute (95% CI)		
2	randomised trials	serious [a,b]	serious [e]	not serious	serious [g]	none	15/67 (22.4%)	12/67 (17.9%)	**RR 1.25** (0.65 to 2.39)	**45 more per 1,000** (from 63 fewer to 249 more)	⨁◯◯◯ VERY LOW	CRITICAL

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

Explanations

a. unclear allocation concealment
b. lack of blinding
c. reporting bias (lack of intention-to-treat analysis)
d. different comparator
e. different doses
f. heterogeneity I2=58%
g. small sample size
h. heterogeneity I2=99%
i. wide confidence interval

Appendix 3: Characteristics of Ongoing Studies

TrialID	Scientific title	Countries	Condition	Intervention	Control	Primary outcome
ACTRN12620001249943	Intravenous immunoglobulin rich in neutralising antibodies to SARS-CoV-2 as a passive immunity modality in healthy individuals : an open label, active control Phase 1/2 Study to investigate the safety profile and to characterise the pharmacokinetics of COVID-19 complementary plasma and hyperimmune intravenous immunoglobulin G specific to SARS-CoV-2.	Australia	healthy adults	Hyperimmune intravenous immunoglobulin G specific to SARS-CoV-2		safety, tolerability and pharmacokinetic (PK) profile
ChiCTR2000030841	Treatment of Acute Severe COVID-19 With Immunoglobulin From Cured COVID-19 Patients	China	COVID-19	Experimental group:Immunoglobulin of cured patients	gamma-Globulin;	Time to Clinical Improvement (TTCI);
CTRI/2020/06/026222	A Phase II Safety and Efficacy Study on prognosis of Moderate Pneumonia in COVID-19 patients with Regular Intravenous Immunoglobulin Therapy	India	healthy adults	Immunoglobulin and standard of care	Azithromycin ,lopinavir/ritonavir, piperacillin-tazobactam	Number of days to clinical improvement. It is defined as no. of days from initiation of treatment day to discharge day on a six-category ordinal scale Timepoint: 0-28 days
CTRI/2020/11/028779	A phase I, open label, parallel, randomised trial to assess the safety and efficacy of SARS-CoV-2 Equine Antiserum Immunoglobulin (Purified F(ab)2 fragment) in hospitalised COVID-19 patients with moderate disease in addition to standard of care. - None	India	healthy adults	SARS-CoV-2 Antiserum Immunoglobulins (Purified F(ab)2 fragment	Standard care	Proportion of patients with treatment-emergent adverse events including infusion related reactionsTimepoint: Day 0 Through Day 28
CTRI/2021/01/030824	An Open-Label, Randomized, Controlled, Multicenter Study to evaluate the Efficacy and Safety of COVID-19 Hyperimmunoglobulin in Patients with COVID-19	India	COVID-19	Hyperimmunoglobulin 50 mg/kg	Standard care	Mean change in 8 point ordinal scale in clinical improvement from baseline to day 8Timepoint: Day 8
EUCTR2020-001570-30-FR	Interest of early treatment with polyvalent immunoglobulins in the management of respiratory distress syndrome associated with SARS-CoV-2 infections_COVID-19 - ICAR (IgIV in Covid-related ARds)	France	COVID-19	ClairYg 50mg/ml	Placebo	Survival without invasive ventilatory assistance
EUCTR2020-001768-27-FR	"Study Of The Efficiency Of Normal Human Immunoglobulins (Ivig) In Patients Aged 75 Years And Over Covid-19 With Severe Acute Respiratory Failure"	France	elderly patients with moderate to severe COVID-19	Immunoglobulines Humaines Normales	Standard care	Mortality
EUCTR2020-002542-16-GB NCT04546581	An International Multicenter, Adaptive, Randomized Double-Blind, Placebo-Controlled Trial of the Safety, Tolerability and Efficacy of Anti-Coronavirus Hyperimmune	United States; Portugal; Nigeria; Greece;	COVID-19	Anti-COVID-19 Hyperimmune Globulin (Human)	Placebo	All-cause mortality through Day 28.Change in National Early Warning Score

	Intravenous Immunoglobulin for the Treatment of Adult Hospitalized Patients at Onset of Clinical Progression of COVID-19 - Inpatient Treatment with Anti-Coronavirus Immunoglobulin (ITAC)	Thailand; Spain; Israel; United Kingdom;France; Mexico; Argentina; Belgium; Poland; Denmark; Peru; Germany; Japan				(NEWS) from baseline at Day 3
EUCTR2020-005410-18-PL	Multicentre, randomized, double-blind, placebo-controlled, non-commercial clinical trial to evaluate the efficacy and safety of specific anti-SARS-CoV-2 immunoglobulin in the treatment of COVID-19	Poland	COVID-19	anti SARS-CoV-2 immunoglobulin	Placebo	No oxygen supplementation required on Day 7 and 14 from the start of the therapy
IRCT20151227025726N20	Evaluating the efficacy and safety of intravenous immunoglobulin (IVIG) in COVID-19 patients	Iran (Islamic Republic of)	COVID-19	IVIG (Biotest) 400 mg/Kg for 3 doses + hydroxychloroquine 200 mg twice daily + Lopinavir/Ritonavir 200-50 mg 2 Tab twice daily for 7 days	hydroxychloroquine 200 mg twice daily + Lopinavir/Ritonavir 200-50 mg 2 Tab twice daily for 7 days.	Need for mechanical ventilation.
IRCT20200310046736N1	Comparison of The Therapeutic Effect of Convalescent Plasma and Plasma-derived Immunoglobulin-enriched solution on COVID-19 Patients: A Clinical Trial Study	Iran (Islamic Republic of)	critical COVID-19	Plasma-derived Immunoglobulin-enriched solution {IV, 0.2 _0.4 g/kg/day	routine care	complete remission of clinical signs of disease
IRCT20200317046797N3	To evaluate the effectiveness of intravenous immunoglobulin (IVIG) for the treatment of COVID-19-induced cytokine storm	Iran (Islamic Republic of)	moderate to severe COVID-19	IVIG for 2 days (100-200 mg twice a day)	HCQ, Kaletra	Mortality rate.;Need for intubation
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)	Iran (Islamic Republic of)	COVID-19	0.4-0.5/g/kg/day of IVIg in 3-5 doses	Standard care	fever, heart rate, respiratory rate, Chest CT scan, WBC
IRCT20200413047056N1	Comparison between the efficacy of intravenous immunoglobulin and convalescent plasma in improving the condition of patients with COVID-19: A randomized clinical trial	Iran (Islamic Republic of)	COVID-19	IVIg (400mg/kg/d)	Standard care	Lung involvement in X-ray and CT-scan
IRCT20200418047116N1	Effect of Intravenous immunoglobulin (IVIG) versus Kaletra (lopinavir and ritonavir) tablets in patients with acute respiratory infection (COVID-19): A clinical trial studies	Iran (Islamic Republic of)	COVID-19	IVIg 400 mg/kg/day in 3 doses	Lopinavir/ritonavir	Pulmonary manifestations (Chest CT)
KCT0005649	A prospective, open-label, randomized, multi-center, phase 2a study to evaluate the dose response, efficacy and safety of Hyper-Ig (Hyper-immunoglobulin) GC5131 in Patients with COVID-19	Korea, Republic of	COVID-19	Hyper-immunoglobulin GC5131	Standard care	Percentage of subjects whose scores decreased by 2 points or reach level 1 or 2 by 9-ordinal scale

NCT04261426	A Randomized, Open-label, Controlled, Single-center Study to Evaluate the Efficacy of Intravenous Immunoglobulin Therapy in Patients With Severe 2019- nCoV Pneumonia		COVID-19	Intravenous Immunoglobulin	Standard care	Clinical improvement based on the 7-point scale;Lower Murray lung injury score;Lower Murray lung injury score
NCT04264858	An Exploratory Clinical Study on the Treatment of Acute Severe 2019-nCoV Pneumonia With Immunoglobulin From Cured 2019-nCoV Pneumonia Patients	China	COVID-19	Intravenous Immunoglobulin of cured patients	gamma-globulin	Time to Clinical Improvement (TTCI)
NCT04350580	Value of Early Treatment With Polyvalent Immunoglobulin in the Management of Acute Respiratory Distress Syndrome Associated With SARS-CoV-2 Infections	France, Mexico	Acute Respiratory Distress Syndrome; COVID-19	Intravenous Immunoglobulin	Placebo	Ventilator-free days
NCT04395170	A Randomized, Multicenter Clinical Trial to Evaluate the Efficacy and Safety of the Use of Convalescent Plasma (PC) and Human Intravenous Anti COVID-19 Immunoglobulin (IV Anti COVID-19 IgG) in Patients Hospitalized for COVID-19.	Colombia	COVID-19	Anti-COVID-19 human immunoglobulin	Standard care	Admission to ICU and/or mechanical ventilation
NCT04403269	"Study Of The Efficiency Of Normal Human Immunoglobulins (Ivig) In Patients Aged 75 Years And Over Covid-19 With Severe Acute Respiratory Failure" Geronimo 19	France	elderly with severe COVID-19	IVIg (0.8 g / kg by IV infusion)		Mortality
NCT04411667	Randomized Open Label Study of Standard of Care Plus Intravenous Immunoglobulin (IVIG) Compared to Standard of Care Alone in the Treatment of COVID-19 Infection	United States	COVID-19	IVIG (Octagam) 0.5g/kg IVPB actual body weight daily x 3 days	Standard care	Mechanical Ventilation
NCT04500067	An Open-label Multicenter Randomized Trial to Evaluate the Efficacy of Bioven, Manufactured by Biopharma Plasma, LLC, in Complex Therapy of Patients With Pneumonia Induced by COVID-19 / SARS-CoV-2	Ukraine	COVID-19	IVIG 0,8-1,0 g/kg once a day for 2 days	Standard care	Period duration (in days) to clinical improvement
NCT04514302	Pilot Study to Evaluate Safety and Efficacy of Anti-SARS-CoV-2 Equine Immunoglobulin F(ab')2 Fragments (INOSARS) in Hospitalized Patients With COVID-19	Mexico	COVID-19	Anti-SARS-CoV-2 equine immunoglobulin fragments (INOSARS)	Placebo	Proportion of patients with improvement in clinical status
NCT04521309	Severe Acute Respiratory Syndrome Corona Virus 2 (SARS-CoV-2) Antibodies Based Intravenous Immunoglobulin (IVIG) Therapy for Severe and Critically Ill COVID-19 Patients	Pakistan	severe COVID-19	SARS-CoV-2 antibody based IVIG therapy	Standard care	28 Days mortality
NCT04548557	Intravenous Immunoglobulins for the Treatment of Covid-19 Patients: a Clinical Trial	Pakistan	Covid19	Biological: intravenous immunoglobulin therapy		In hospital days;14 day mortality
NCT04555148	A Prospective, Open-label, Randomized, Multi-center, Phase 2a Study to Evaluation the Dose Response, Efficacy and Safety of Hyper-Ig (Hyper-immunoglobulin) GC5131 in Patients With COVID-19	Korea, Republic of	Covid19	hyperimmunoglobulin GC5131	Placebo	Ordinal scale outcome
NCT04573855	Treatment With Anti-Sars-Cov-2 Immunoglobulin In Patients With Covid-19: A Phase I / Ii Study	Covid19		Anti-SARS-CoV-2 immunoglobulin	Standard care	Clearence of viral RNA evaluated by RT-PCR;Rate of adverse events.

NCT04661839	A Phase 1, Double-blind, Randomized, Placebo-controlled Study to Evaluate Safety and Pharmacokinetics of Anti-SARS-CoV-2 Immunoglobulin Intravenous (Human) Investigational Product (COVID-HIGIV) Administered as a Single Dose or a Repeat Dose Regimen to Healthy Adults	United States	healthy adults	COVID-HIGIV	Placebo	adverse events
NL9379	A Phase I-II study of virus neutralizing antibodies against SARS-CoV-2. A focus on convalescent plasma and hyperimmune anti-SARS-CoV2 immunoglobulines	The Netherlands	COVID-19	Nanogam plus (IVIG-therapy containing anti-SARS-CoV-2 antibodies)		Pharmacokinetics