South African National Department of Health
Brief Report of Rapid Review
Component: COVID-19

TITLE: INTRAVENOUS IMMUNOGLOBULIN FOR COVID-19: EVIDENCE REVIEW OF POTENTIAL BENEFIT AND HARM

Date: 8 April 2020

Key findings

- Effective treatment for hospitalised COVID-19 patients is urgently needed and several potential medicines are being evaluated in the WHO-led SOLIDARITY Clinical Trial, which will include South African participants.
- We conducted a rapid review of available clinical evidence for intravenous immunoglobulin (IVIG), with or without other medicines, for hospitalised COVID-19 patients.
- No relevant systematic reviews or controlled trials were found.
- A single publication reporting on three COVID-19 patients who received IVIG was unidentified; we are thus unable to determine the likely benefit or harm related to the use of IVIG in COVID-19 patients.
- No reports on the use of IVIG in children with COVID-19 were identified.

THERAPEUTIC GUIDELINES SUB-COMMITTEE RECOMMENDATION:

There is currently insufficient evidence to support inclusion of IVIG in treatment guidelines for COVID-19 in South Africa until further data become available.

Eligible patients with COVID-19 in South Africa should be considered for enrolment in relevant therapeutic trials.

Therapeutic Guidelines Sub-Committee of the COVID-19 Management Clinical Guidelines Committee: Andy Parrish, Andy Gray, Tamara Kredo, Gary Maartens, Gary Reubenson, Karen Cohen, Renee De Waal, Marc Blockman, Jeremy Nel, Helen Rees.

Note: Due to the continuous emergence of new evidence, the rapid review will be updated if and when more relevant evidence becomes available.

BACKGROUND

The novel human respiratory coronavirus (SARS-CoV-2), which is the cause of COVID-2019, was declared a pandemic on 11 March 2020. There are currently more than 1,300,000 confirmed COVID-19 cases in about 200 countries and SARs-C0V-2 has caused more than 74,000 deaths (WHO 2020; as at 10am 7 April, 1,348,628 confirmed cases, 74,834 deaths; 285,064 recoveries https://coronavirus.jhu.edu/map.html.)

Effective therapeutic options to manage hospitalised patients with COVID-19 cases need to be urgently identified. Current management is supportive, but respiratory failure has been reported as the leading cause of mortality[1]. Intravenous immunoglobulin (IVIG) has been suggested as a possible treatment for hospitalised COVID-19 patients. Pooled from healthy donors, IVIG mainly consists of IgG with traces of IgA[2] and is indicated for a number of conditions, including idiopathic thrombocytopenic purpura (ITP), Kawasaki disease and Guillain-Barré syndrome[3,4,5].

Excessive cytokine production ('cytokine storm') as part of a hyperinflammatory response has been suggested as a cause of severe COVID-19 disease[6,7,8]. Therapeutic options aimed at ameliorating this response are being evaluated -one of these therapies is IVIG[7]. A motivation for the use of IVIG in patients with severe COVID-19 was received from the Gauteng Provincial Pharmacy and Therapeutics Committee.

Despite potential benefits, IVIG can also cause a number of adverse effects. ADRs following IVIG administration include flu-like syndrome, dermatologic side effects, arrhythmias, hypotension, and transfusion-related acute lung injury (TRALI)[9]. Delayed life-threatening ADRs are uncommon but include thrombotic events[10] and renal impairment[11].

RESEARCH QUESTION: Should IVIG be used for treating hospitalised COVID-19 patients?

METHODS

We conducted a rapid evidence review including systematic searching of two electronic databases (PubMed and the Epistemonikos). Screening of records and data extraction was conducted by one reviewer (TL), with results reviewed and checked by another reviewer (JR). If searching these databases did not produce any records, a google scholar search was performed. Relevant records were extracted in a narrative table of results. No appraisal or meta-analysis was done. The final rapid review was reviewed by a third reviewer (GR). The search strategy is shown in Appendix 1.

Eligibility criteria for review

Population: Patients hospitalised with confirmed COVID-19, no age restriction.

Intervention: Intravenous immunoglobulin either alone or in combination with another medicine. No restriction on dose, frequency, or timing with respect to onset of symptoms/severity of disease.

Comparators: Any (standard of care/placebo or active comparator).

Outcomes: Mortality, duration of hospitalisation, duration of ICU stay, duration of respiratory support, adverse reactions.

Study designs: Systematic review, randomised controlled trials, non-randomised cohorts, case series and case reports in humans.

RESULTS

We searched PubMed and the Epistemonikos electronic databases on 8 April 2020. Details of each search are provided in Appendix 1. One reviewer screened 63 records, but no eligible articles were identified. The second reviewer confirmed these findings. An additional google scholar search idenitifed one potentially relevant article was identified. Data in **Table 1** report the main characteristics and outcomes of this report. **Table 2** describes planned trial(s) found during the searches.

The single relevant article[12] describes three cases, all from China: all three patients had severe COVID-19 disease and recovered. Their treatment included IVIG, at a dose of 0.3-0.5 g/kg/day for 5 days. The authors suggest administration during the early phase of the disease as, "*Patients might not receive much benefit when overall systemic damage has already taken place"*.

Quality appraisal of this case series was not done. Available evidence is preliminary and hypothesis-generating for further controlled studies and therefore cannot sufficiently inform the assessment of efficacy or safety of IVIG in the treatment of COVID-19.

A randomised clinical trial is currently underway to determine the effectiveness and timing of high dose intravenous immunoglobulin in cases of severe COVID-19 disease (NCT 04261426 RCT) [13] – as of 8 April 2020, patient enrolment does not seem to have commenced.

CONCLUSION

There is currently insufficient evidence to support inclusion of IVIG in treatment guidelines for COVID-19 in South Africa. Eligible patients in South Africa should be considered for enrolment in randomised clinical trials of potential therapies for COVID-19, so that robust data on efficacy and safety of interventions can be generated to inform treatment policies going forward. Judicious use of IVIG is encouraged to ensure supply challenges are not experienced for patients with established indications for IVIG.

Reviewers: Trudy Leong, Jane Riddin, Gary Reubenson

Declaration of interests: TL (National Department of Health, Affordable Medicines – Essential Drugs Programme, South Africa), JR (National Department of Health, Affordable Medicines – Essential Drugs Programme, South Africa), GR (Rahima Moosa Mother & Child Hospital, Johannesburg) have no applicable interests to declare in respect of IVIG therapy for COVID-19.

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Table 1. Characteristics of included studies

Citation	Study design	Population (n)	Treatment	Main findings
Published, peer reviewed Cao W, Liu X, Bai T et al, Open Forum Infectious Diseases, Volume 7, Issue 3, March 2020, ofaa102,[12] https://doi.org/10.1093/ofid/ofaa102	Case series Period: Jan 22 to Jan 29 2020	Setting: Jin Yintan Hospital, Wuhan, China All three patients progressed to severe COVID-19 disease in hospital Case 1: 56-year-old man, progressed to severe disease within 7 days of admission. Case 2: 34-year-old man with comorbid hypertension, progressed to severe disease within 2 days of admission. Case 3: 35-year-old woman, progressed to severe disease within 5 days of admission. On admission all patients had elevated inflammatory markers (ESR and CRP). All patients had chest CT scans showing progressive infiltrations of both lungs	On diagnosis of severe COVID-19 disease, all patients received high dose intravenous immunoglobulin, at a dose of 0.3-0.5 g/kg/day for 5 days. Case 1 received concomitant azithromycin Case 3 received concomitant methylprednisolone and lopinavir/ritonavir	Unable to determine efficacy or safety of IVIG from this small case series. All patients were discharged when PCR testing for SARS-CoV-2 was negative with lung radiographic resolution on CT scan.

Table 2. Characteristics of planned and ongoing studies

Citation	Study design	Population (n)	Treatment
Li T. The Efficacy of Intravenous Immunoglobulin Therapy for Severe 2019-nCoV Infected Pneumonia. clinicaltrialsgov. 2020.[13] https://clinicaltrials.gov/ct2/show/NCT04261426 Entry last updated 7 February 2020 At that time enrolment estimated to start 10 February 2020 and be completed by 30 April 2020 – current enrolment status unclear.	Single-center, randomized, open-label, controlled study	Patients with severe or critically ill 2019-nCoV respiratory disease.	Intervention: Intravenous Immunoglobulin Other: Standard care

Appendix 1: Search strategy

PubMed

(("immunoglobulins"[MeSH Terms] OR "immunoglobulins"[All Fields] OR "immunoglobulin"[All Fields]) AND ("COVID-19"[All Fields] OR "COVID-2019"[All Fields] OR "severe acute respiratory syndrome coronavirus 2"[Supplementary Concept] OR "severe acute respiratory syndrome coronavirus 2"[All Fields] OR "2019-nCoV"[All Fields] OR "SARS-CoV-2"[All Fields] OR "2019nCoV"[All Fields] OR (("Wuhan"[All Fields] AND ("coronavirus"[MeSH Terms] OR "coronavirus"[All Fields])) AND (2019/12[PDAT] OR 2020[PDAT])))) AND "humans"[MeSH Terms]

Output 22 records, all excluded as not relevant to PICO question

Epistemonikos

(title:((title:(intravenous immunoglobulin) OR abstract:(intravenous immunoglobulin)) AND (title:(respiratory) OR abstract:(respiratory))) OR abstract:((title:(intravenous immunoglobulin) OR abstract:(intravenous immunoglobulin)) AND (title:(respiratory) OR abstract:(respiratory))))

Output 41 records, all excluded as not relevant to PICO question