

Hyperimmune immunoglobulin for hospitalised patients with COVID-19 (ITAC): a double-blind, placebo-controlled, phase 3, randomised trial

The ITAC (INSIGHT 013) Study Group Lancet 2022; doi.org/10.1016/S0140-6736(22)00101-5

Hyperimmune immunoglobulin for hospitalised patients with COVID-19 (ITAC): a double-blind, placebo-controlled, phase 3, randomised trial



The ITAC (INSIGHT 013) Study Group*

Summary

Background Passive immunotherapy using hyperimmune intravenous immunoglobulin (hIVIG) to SARS-CoV-2, derived from recovered donors, is a potential rapidly available, specific therapy for an outbreak infection such as SARS-CoV-2. Findings from randomised clinical trials of hIVIG for the treatment of COVID-19 are limited.

Methods In this international randomised, double-blind, placebo-controlled trial, hospitalised patients with COVID-19 who had been symptomatic for up to 12 days and did not have acute end-organ failure were randomly assigned (1:1) to receive either hIVIG or an equivalent volume of saline as placebo, in addition to remdesivir, when not contraindicated, and other standard clinical care. Randomisation was stratified by site pharmacy; schedules were prepared using a mass-weighted urn design. Infusions were prepared and masked by trial pharmacists; all other investigators, research staff, and trial participants were masked to group allocation. Follow-up was for 28 days. The primary outcome was measured at day 7 by a seven-category ordinal endpoint that considered pulmonary status and extrapulmonary complications and ranged from no limiting symptoms to death. Deaths and adverse events, including organ failure and serious infections, were used to define composite safety outcomes at days 7 and 28. Prespecified subgroup analyses were carried out for efficacy and safety outcomes by duration of symptoms, the presence of anti-spike neutralising antibodies, and other baseline factors. Analyses were done on a modified intention-to-treat (mITT) population, which included all randomly assigned participants who met eligibility criteria and received all or part of the assigned study product infusion. This study is registered with ClinicalTrials.gov, NCT04546581.

Findings From Oct 8, 2020, to Feb 10, 2021, 593 participants (n=301 hIVIG, n=292 placebo) were enrolled at 63 sites in 11 countries; 579 patients were included in the mITT analysis. Compared with placebo, the hIVIG group did not have significantly greater odds of a more favourable outcome at day 7; the adjusted OR was 1.06 (95% CI 0.77–1.45; p=0.72). Infusions were well tolerated, although infusion reactions were more common in the hIVIG group (18·6% vs 9·5% for placebo; p=0.002). The percentage with the composite safety outcome at day 7 was similar for the hIVIG (24%) and placebo groups (25%; OR 0·98, 95% CI 0·66–1·46; p=0·91). The ORs for the day 7 ordinal outcome did not vary for subgroups considered, but there was evidence of heterogeneity of the treatment effect for the day 7 composite safety outcome: risk was greater for hIVIG compared with placebo for patients who were antibody positive (OR 2·21, 95% CI 1·14–4·29); for patients who were antibody negative, the OR was 0·51 (0·29–0·90; p_{interaction}=0·001).

Interpretation When administered with standard of care including remdesivir, SARS-CoV-2 hIVIG did not demonstrate efficacy among patients hospitalised with COVID-19 without end-organ failure. The safety of hIVIG might vary by the presence of endogenous neutralising antibodies at entry.

Funding US National Institutes of Health.

Copyright © 2022 Published by Elsevier Ltd. All rights reserved.

Introduction

Current effective therapies for individuals hospitalised with COVID-19 target viral replication or pathological elements of the host inflammatory response;^{1,4} however, morbidity and mortality persist, and additional treatments are urgently needed.

Augmenting the host humoral immune response to SARS-CoV-2 via passive immunotherapy is one possible therapeutic approach. Development of endogenous neutralising antibody responses to SARS-CoV-2 appears variable and might not be present at the time of hospitalisation.^{5,6}

Approaches using engineered monoclonal antibodies targeting viral elements have shown benefit among outpatients early in the course of COVID-19.^{8,9} Results from two trials of monoclonal antibodies indicate that the clinical benefit and possibly safety of monoclonal antibodies for patients admitted to hospital with COVID-19 might depend on the presence of endogenous neutralising antibodies at the time of randomisation.^{10,11}

Convalescent plasma from recovered donors has been studied in both non-randomised and randomised trials for a variety of infectious diseases. With few

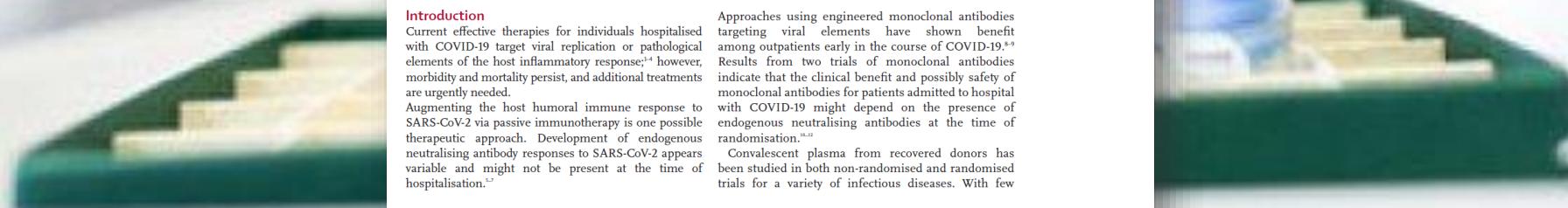
Published Online
January 27, 2022
[https://doi.org/10.1016/S0140-6736\(22\)00101-5](https://doi.org/10.1016/S0140-6736(22)00101-5)

See Online/Comment
[https://doi.org/10.1016/S0140-6736\(22\)00112-X](https://doi.org/10.1016/S0140-6736(22)00112-X)

*A complete list of members of the ITAC Study Group is provided in the appendix p 7

Correspondence to:
Prof Mark N Polizotto, Clinical
Hub for Interventional Research,
The Australian National
University, Canberra, ACT 2600,
Australia
mark.polizotto@anu.edu.au

See Online for appendix



Hintergrund (I)

Hospitalisierte COVID-19-Patienten ziehen offenbar keinen Nutzen aus hyperimmunem intravenösem Immunglobulin (hIgIG) gegen SARS-CoV-2, wenn dieses zusätzlich zu Remdesivir und Standardtherapie zum Einsatz kommt, wie eine randomisiert-kontrollierte Phase-3-Studie im Lancet zeigt

Eine passive Immuntherapie, die hIgIG von genesenen Donoren verwendet, könnte eine rasch verfügbare und spezifische Therapie für Infektionsausbrüche wie SARS-CoV-2 sein

Es wurde untersucht, ob hIgIG gegen SARS-CoV-2 das Risiko des Fortschreitens der Erkrankung verringern kann, wenn es zur Standardbehandlung mit Remdesivir bei hospitalisierten erwachsenen Patienten hinzugefügt wird

Ergebnisse (I)

Das Ergebnis erwies sich allerdings als enttäuschend: Nach 7 Tagen war es den COVID-19-Patienten in der hIIVIG-Gruppe nicht besser ergangen als in der Placebogruppe

In die verblindete Studie waren von Oktober 2020 bis Februar 2021 in 11 Ländern insgesamt 593 Patienten eingeschlossen worden

Von ihnen hatten 301 hIIVIG und 292 Kochsalzlösung als Placebo erhalten, dies jeweils zusätzlich zu Remdesivir und der üblichen Standardtherapie. Die Nachbeobachtung war über 28 Tage gelaufen

Ergebnisse (II)

Der primäre Endpunkt wurde an Tag 7 gemessen, er bestand aus 7 Kategorien, die unter anderem den Lungenstatus und extrapulmonale Komplikationen berücksichtigten

Die Kategorien reichten von keinen einschränkenden Symptomen bis hin zum Tod

In die modifizierte Intention-to-treat-Analyse flossen die Daten von 579 Patienten ein. Die Odds Ratio für einen günstigeren Verlauf in der hIIVIG-Gruppe verglichen mit der Placebogruppe betrug 1,06 (95-%-KI 0,77–1,45; p=0,72)

Ergebnisse (III)

Die Infusionen wurden im Allgemeinen gut vertragen

Allerdings waren Infusionsreaktionen in der hIVIG-Gruppe häufiger: Betroffen waren 18,6 % der hIVIG-Patienten und 9,5 % der Placebopatienten ($p=0,002$)

Der aus Tod und Komplikationen wie Organversagen und schweren Infektionen umfassende Sicherheitsendpunkt war an Tag 7 in beiden Gruppen vergleichbar. Unter hIVIG wurde er von 24 % der Patienten erreicht, unter Placebo von 25 % ($p=0,91$).

Ergebnisse (IV)

In Subgruppenanalysen wurden die Wirksamkeits- und Sicherheitsendpunkte nach der Symptomdauer, dem Vorhandensein von neutralisierenden Antikörpern gegen das Spikeprotein von SARS-CoV-2 und anderen Faktoren aufsplittert

Beim primären Endpunkt ließen sich keine Unterschiede zwischen den Subgruppen feststellen

Doch beim Sicherheitsendpunkt gab es Diskrepanzen: Das Risiko, den Sicherheitsendpunkt zu erreichen, war nämlich bei Patienten, die Antikörper-positiv waren, größer (OR 2,21). Für Patienten ohne Antikörper betrug die OR dagegen 0,51 (p für Interaktion = 0,001)

Ergebnisse (V)

Somit zeigte diese Studie – anders als andere Studien zu monoklonalen Antikörpern – keinen Nutzen neutralisierender Antikörper gegen SARS-CoV-2 gezeigt

Allerdings deuten die Ergebnisse darauf hin, dass die Sicherheit von hIgIG und potenziell auch anderer passiver Immuntherapien vom Antikörperstatus der Patienten abhängt

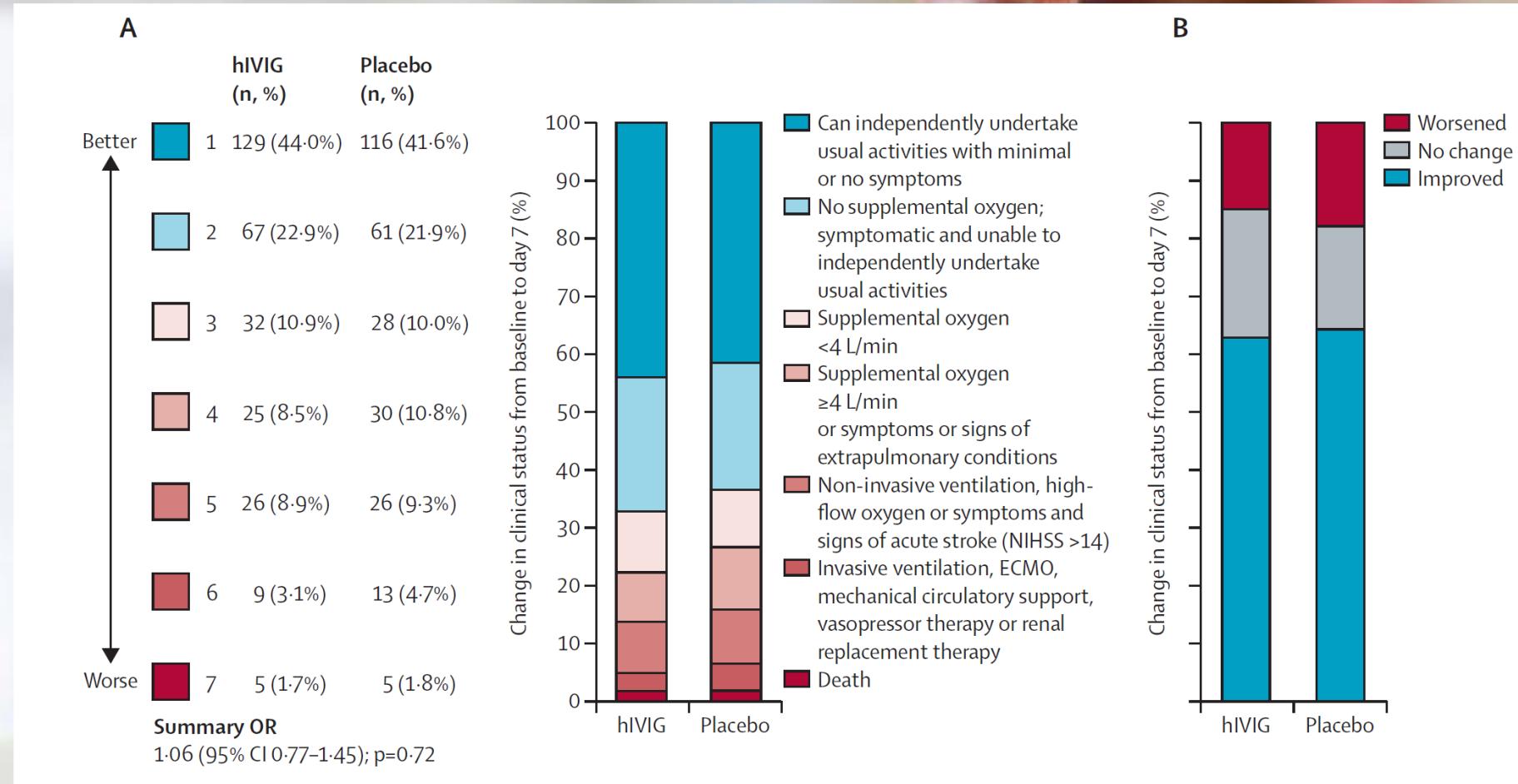
Trotz der nicht vorhandenen Wirksamkeit bei hospitalisierten Patienten, könnte hIgIG möglicherweise in früheren Krankheitsstadien eine Rolle spielen. In der Studie hatten die Patienten im Schnitt seit 12 Tagen Symptome gehabt

Ergebnisse (VI)

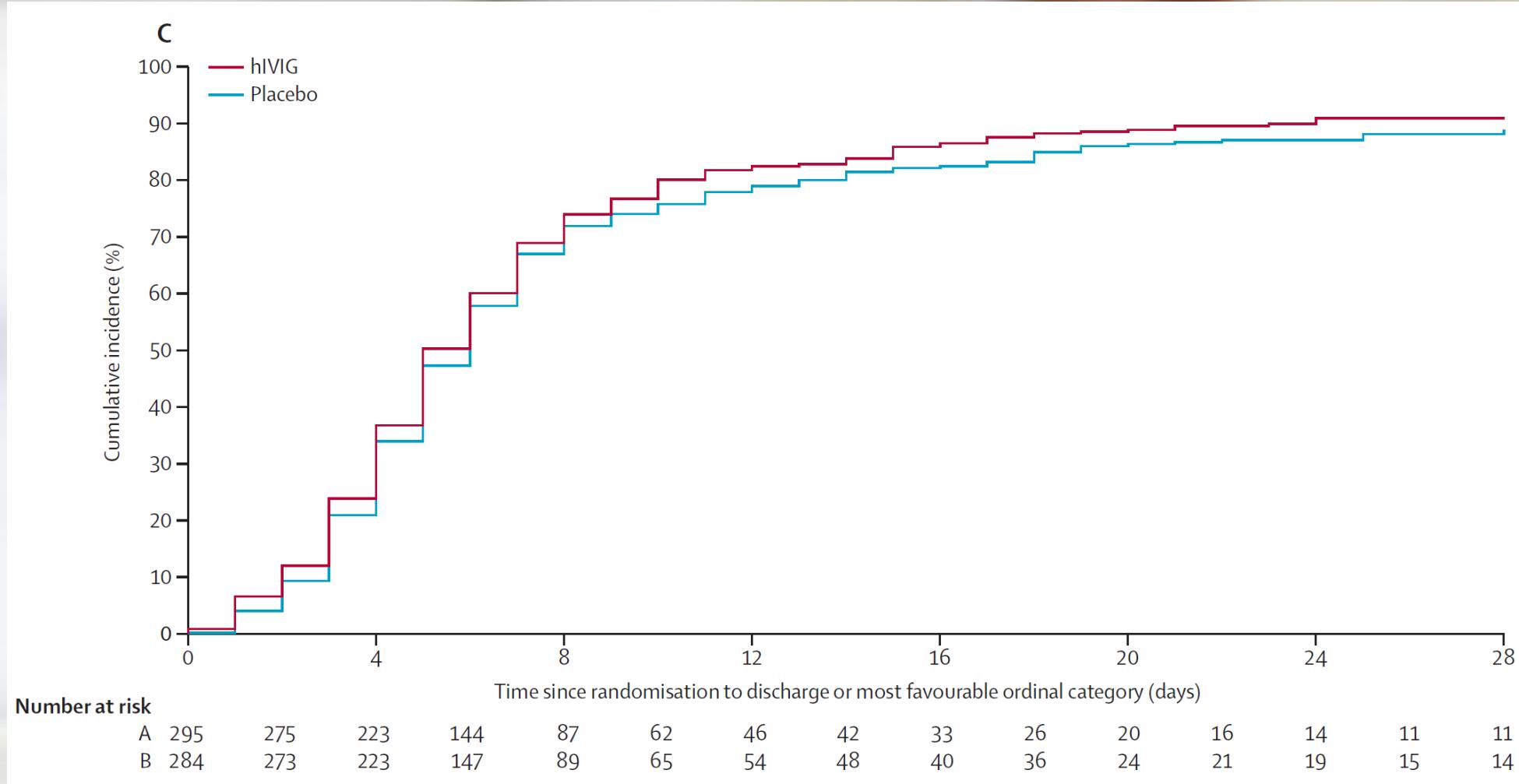
Es ist möglich, dass eine sehr früh behandelte Patientenpopulation einen Nutzen aus der Therapie ziehen könnte

Gelten könnte dies auch für Patientengruppen, die keine eigene humorale Immunantwort aufbauen

Klinischer Status Tag 7 (A) und Veränderung vom Beginn der Studie bis Tag 7 (B)



Kaplan Meier Kurve



Weitere Informationen und Ergebnisse

The ITAC (INSIGHT 013) Study Group Lancet 2022; doi.org/10.1016/S0140-6736(22)00101-5

Hyperimmune immunoglobulin for hospitalised patients with COVID-19 (ITAC): a double-blind, placebo-controlled, phase 3, randomised trial



The ITAC (INSIGHT 013) Study Group*

Summary

Background Passive immunotherapy using hyperimmune intravenous immunoglobulin (hIgIV) to SARS-CoV-2, derived from recovered donors, is a potential rapidly available, specific therapy for an outbreak infection such as SARS-CoV-2. Findings from randomised clinical trials of hIgIV for the treatment of COVID-19 are limited.

Methods In this international randomised, double-blind, placebo-controlled trial, hospitalised patients with COVID-19 who had been symptomatic for up to 12 days and did not have acute end-organ failure were randomly assigned (1:1) to receive either hIgIV or an equivalent volume of saline as placebo, in addition to remdesivir, when not contraindicated, and other standard clinical care. Randomisation was stratified by site pharmacy; schedules were prepared using a mass-weighted urn design. Infusions were prepared and masked by trial pharmacists; all other investigators, research staff, and trial participants were masked to group allocation. Follow-up was for 28 days. The primary outcome was measured at day 7 by a seven-category ordinal endpoint that considered pulmonary status and extrapulmonary complications and ranged from no limiting symptoms to death. Deaths and adverse events, including organ failure and serious infections, were used to define composite safety outcomes at days 7 and 28. Prespecified subgroup analyses were carried out for efficacy and safety outcomes by duration of symptoms, the presence of anti-spike neutralising antibodies, and other baseline factors. Analyses were done on a modified intention-to-treat (mITT) population, which included all randomly assigned participants who met eligibility criteria and received all or part of the assigned study product infusion. This study is registered with ClinicalTrials.gov, NCT04546581.

Findings From Oct 8, 2020, to Feb 10, 2021, 593 participants (n=301 hIgIV, n=292 placebo) were enrolled at 63 sites in 11 countries; 579 patients were included in the mITT analysis. Compared with placebo, the hIgIV group did not have significantly greater odds of a more favourable outcome at day 7; the adjusted OR was 1.06 (95% CI 0.77–1.45; p=0.72). Infusions were well tolerated, although infusion reactions were more common in the hIgIV group (18·6% vs 9·5% for placebo; p=0.002). The percentage with the composite safety outcome at day 7 was similar for the hIgIV (24%) and placebo groups (25%; OR 0·98, 95% CI 0·66–1·46; p=0·91). The ORs for the day 7 ordinal outcome did not vary for subgroups considered, but there was evidence of heterogeneity of the treatment effect for the day 7 composite safety outcome: risk was greater for hIgIV compared with placebo for patients who were antibody positive (OR 2·21, 95% CI 1·14–4·29); for patients who were antibody negative, the OR was 0·51 (0·29–0·90; p_{interaction}=0·001).

Interpretation When administered with standard of care including remdesivir, SARS-CoV-2 hIgIV did not demonstrate efficacy among patients hospitalised with COVID-19 without end-organ failure. The safety of hIgIV might vary by the presence of endogenous neutralising antibodies at entry.

Funding US National Institutes of Health.

Copyright © 2022 Published by Elsevier Ltd. All rights reserved.

Introduction

Current effective therapies for individuals hospitalised with COVID-19 target viral replication or pathological elements of the host inflammatory response;^{1,4} however, morbidity and mortality persist, and additional treatments are urgently needed.

Augmenting the host humoral immune response to SARS-CoV-2 via passive immunotherapy is one possible therapeutic approach. Development of endogenous neutralising antibody responses to SARS-CoV-2 appears variable and might not be present at the time of hospitalisation.^{5,6}

Approaches using engineered monoclonal antibodies targeting viral elements have shown benefit among outpatients early in the course of COVID-19.^{8,9} Results from two trials of monoclonal antibodies indicate that the clinical benefit and possibly safety of monoclonal antibodies for patients admitted to hospital with COVID-19 might depend on the presence of endogenous neutralising antibodies at the time of randomisation.^{10,11}

Convalescent plasma from recovered donors has been studied in both non-randomised and randomised trials for a variety of infectious diseases. With few

Published Online
January 27, 2022
[https://doi.org/10.1016/S0140-6736\(22\)00101-5](https://doi.org/10.1016/S0140-6736(22)00101-5)

See Online/Comment
[https://doi.org/10.1016/S0140-6736\(22\)00112-X](https://doi.org/10.1016/S0140-6736(22)00112-X)

*A complete list of members of the ITAC Study Group is provided in the appendix p 7

Correspondence to:
Prof Mark N Polizzotto, Clinical
Hub for Interventional Research,
The Australian National
University, Canberra, ACT 2600,
Australia
mark.polizzotto@anu.edu.au

See Online for appendix

