Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.
Intravenous immunoglobulins in patients with COVID-19-associated moderate-to-severe acute respiratory distress syndrome (ICAR): multicentre, double-blind, placebo-controlled, phase 3 trial

Aurélien Mazeraud, Matthieu Jamme*, Rossella Letizia Mancusi*, Claire Latroche*, Bruno Megarbane, Shidasp Siami, Jonathan Zarka, Guy Moneger, Francesco Santoli, Laurent Argaud, Patrick Chillet, Gregoire Muller, Cedric Bruel, Pierre Asfar, Francois Beloncle, Jean Reignier, Christophe Vinsonneau, Caroline Schimpf, Julien Amour, Cyril Goulonok, Caroline Lemaître, Benjamin Rohaut, Philippe Mateu, Stéphane De Rudnicki, Bruno Mourvillier, Pierre-Louis Declercq, Carole Schwebel, Annabelle Stoclin, Marc Garnier, Benjamin Madeux, Stéphane Gaudry, Karine Bailly, Christian Lamer, Philippe Aegerter, Christine Rieu, Khaoussou Sylla*, Bruno Lucas*, Tarek Sharshar

Summary

Background Acute respiratory distress syndrome (ARDS) is a major complication of COVID-19 and is associated with high mortality and morbidity. We aimed to assess whether intravenous immunoglobulins (IVIG) could improve outcomes by reducing inflammation-mediated lung injury.

Methods In this multicentre, double-blind, placebo-controlled trial, done at 43 centres in France, we randomly assigned patients (1:1) receiving invasive mechanical ventilation for up to 72 h with PCR confirmed COVID-19 and associated moderate-to-severe ARDS to receive either IVIG (2 g/kg over 4 days) or placebo. Random assignment was done with a web-based system and was stratified according to the participating centre and the duration of invasive mechanical ventilation before inclusion in the trial (<12 h, 12–24 h, and >24–72 h), and treatment was administered within the first 96 h of invasive mechanical ventilation. To minimise the risk of adverse events, the IVIG administration was divided into four perfusions of 0.5 g/kg each administered over at least 8 hours. Patients in the placebo group received an equivalent volume of sodium chloride 0.9% (10 mL/kg) over the same period. The primary outcome was the number of ventilation-free days by day 28, assessed according to the intention-to-treat principle. This trial was registered on ClinicalTrials.gov, NCT04350580.

Findings Between April 3, and October 20, 2020, 146 patients (43 [29%] women) were eligible for inclusion and randomly assigned: 69 (47%) patients to the IVIG group and 77 (53%) to the placebo group. The intention-to-treat analysis showed no statistical difference in the median number of ventilation-free days at day 28 between the IVIG group (0.0 [IQR 0.0–8.0]) and the placebo group (0.0 [0.0–6.0]; difference estimate 0.0 [0.0–0.0]; p=0.21). Serious adverse events were more frequent in the IVIG group (47 events in 15 [20%] patients; p=0.089).

Interpretation In patients with COVID-19 who received invasive mechanical ventilation for moderate-to-severe ARDS, IVIG did not improve clinical outcomes at day 28 and tended to be associated with an increased frequency of serious adverse events, although not significant. The effect of IVIGs on earlier disease stages of COVID-19 should be assessed in future trials.

Funding Programme Hospitalier de Recherche Clinique.

Copyright © 2021 Elsevier Ltd. All rights reserved.

Introduction

Globally, more than 133 million patients have been infected by SARS-CoV-2, and more than 2.9 million have died from COVID-19.1 Acute respiratory distress syndrome (ARDS) is one of the most severe complications of COVID-19; it is associated with increased mortality, prolonged invasive mechanical ventilation, increased length of stay in an intensive care unit or in hospital,2 and long-term disability.3 COVID-19-associated ARDS results from both the viral infection and its accompanying inflammatory response.4 In cases where antiviral therapies did not have a benefit, some anti-inflammatory treatments have been shown to reduce the severity of COVID-19-associated pneumonia.5 For example, dexamethasone reduced 28-day mortality in patients with COVID-19 receiving invasive mechanical ventilation by 12%, and tocilizumab, an anti-interleukin-6 receptor monoclonal antibody, might have benefits on organ failure.6,7 However, despite these advances, mortality related to COVID-19-associated ARDS remains as high as 30–40%, prompting the assessment of other immunomodulatory approaches.8,9
SARS-CoV-2 replicates in bronchial cells and pneumocytes, inducing a local inflammatory reaction that spreads to the lung and triggers the local recruitment of immune cells and activated lymphocytes during the acute phase immune response. Intravenous immunoglobulins (IVIGs) have various immune modulatory properties that are theoretically relevant in COVID-19. In addition to IVIG scavenging the complement system and cytokines, they also stimulate the proliferation of regulatory T cells and restore their suppressive functions, thereby reducing the activation of innate immune cells and effector T cells. Of note, IVIG are commonly prescribed for post-viral endothelitis, as seen in Kawasaki disease. Furthermore, IVIG have been reported to be safe in patients who are critically ill, with treatment associated with a low rate of acute renal failure and thromboembolism. Retrospective observational studies have suggested that IVIG decrease mortality and duration of invasive mechanical ventilation in COVID-19-associated ARDS. Furthermore, it has been reported in China that about a third of patients with COVID-19 and ARDS have been treated with IVIG, without the specific effect of IVIG being evaluated. However, because of the cost and scarcity of IVIGs, which is currently indicated in various autoimmune and inflammatory diseases, showing the efficacy and safety of IVIG in patients who are critically ill with COVID-19 is needed to explore IVIG therapy as a viable treatment option.

Therefore, we aimed to assess the efficacy, safety, and immunomodulatory effects of IVIG in patients admitted to an intensive care unit for moderate-to-severe ARDS associated with COVID-19.

Methods

Study design and participants

ICAR was a phase 3, double-blind, randomised, multi-centre, placebo-controlled study, done in 43 centres in France (appendix 1 pp 2–4), evaluating the effect of IVIG in patients hospitalised with COVID-19-associated moderate or severe ARDS requiring mechanical ventilation. This investigator-initiated trial was designed in collaboration with the sponsor—Groupe Hospitalier Universitaire Paris Psychiatrie et Neurosciences, Paris, France—and was overseen by an Independent Data Monitoring Committee. The design of ICAR was published in a futility interim analysis study done in August, 2020, on 50 patients by the Independent Data Monitoring Committee defined upon a protocol amendment (protocol amendment 3; June 11, 2020; appendix 2 p 113). Critically ill patients (≥18 years) with COVID-19, confirmed by a positive PCR test, admitted to the intensive care unit were eligible for inclusion if they required invasive mechanical ventilation for moderate-to-severe ARDS, according to the Berlin Definition criteria. Patients had to be enrolled in the study within 72 h after starting invasive mechanical ventilation. Exclusion criteria were acute renal failure at admission, defined as plasma creatinine above 354 μmol/L, an increase in plasma creatinine baseline concentration by three-times or more; a diuresis of less than 0.3 mL/kg over the last 24 h, or anuria over the last 12 h; pregnancy; immunoglobulin A deficiency; allergy to IVIG; and participation in another intervention trial. The patients received standard care according to the policy of each site, particularly regarding the use of corticosteroids and supportive care. Written informed consent, in accordance with local legislation, was obtained from all patients or their surrogates. If written informed consent could not be obtained, patients were included because the study was considered an emergency research by the institutional review board; consent was obtained as soon as the patients were able to provide it.

The trial was centrally approved by the Paris X ethics committee and has been done in accordance with Good Practice in Research involving humans—Responsible Conduct, and the ethical code of the World Medical Association—Declaration of Helsinki.

The trial was centrally approved by the Paris X ethics committee and has been done in accordance with Good
Clinical Practice guidelines and the principles of the Declaration of Helsinki.

Randomisation and masking
Randomisation was done with a web-based system. Trial group designation was concealed and the randomisation group was electronically sent to the centre’s pharmacy. Patients were assigned (1:1) to receive either IVIG (IVIG group) or placebo (placebo group). Random assignment was stratified according to the participating centre and the duration of invasive mechanical ventilation before inclusion in the trial (<12 h, 12–24 h, and >24–36 h). The protocol was amended to extend the last temporal category to 72 h (protocol amendment 1, May 4, 2020; appendix 2 p 96).

Trial participants, care providers, and outcome assessors were masked to patient assignment. The double-blinding was provided by each hospital pharmacy, using opaque sleeves and tubing to conceal the product administered. To preserve the masking, research nurses supervised the administration and were asked not to disclose whether IVIG or placebo was infused. Masking was removed in the event of an adverse effect that could be attributed to IVIG or placebo and upon the responsible investigator’s approval. The statisticians who analysed the data were masked to group assignment.

Procedures
CLAYRIG (Laboratoire Français du fractionnement et des biotechnologies, Les Ulis, France), a saccharose and maltose free IVIG, was administered for a total dose of 2 g/kg. IVIG infusion had to start before the end of the 96 h after the onset of invasive mechanical ventilation. To minimise the risk of adverse events, IVIG administration was divided into four perfusions of 0·5 g/kg each given over at least 8 h over 4 days. Patients in the placebo group had to receive an equivalent volume of sodium chloride 0·9% (10 mL/kg), over the same period. The protocol was amended to extend the time for starting the IVIG administration from 72 h to 96 h after onset of invasive mechanical ventilation (protocol amendment 1, May 4, 2020; appendix 2 p 96).

Efficacy was evaluated on day 28, and patients were followed for 90 days. Assessments (administered treatments, ventilation parameters PaO₂:FiO₂ ratio, ventilator weaning trials, and sequential organ failure score) were done daily throughout the intensive care unit stay until day 28. If the patient was discharged from the intensive care unit but still in hospital, a visit was scheduled on days 14 and 28, and if the patient left the hospital, a telephone interview was done at day 90 by an investigator to collect primary and secondary outcome data. Baseline characteristics were collected upon admission to the intensive care unit. COVID-19 treatments administered between 7 days before enrolment up and day 2 after randomisation were considered concomitant.

Outcomes
The primary outcome was the number of ventilator-free days at day 28, defined as the number of days between the last extubation day and day 28. In the case of death before day 28, the score was zero. The primary outcome composite components were as time-to-event censored at day 28, within a competing risk framework; therefore, on day 28, the secondary efficacy endpoints of mortality, the proportion of patients who were extubated, and the duration of invasive mechanical ventilation were collected as subcomponents of the primary endpoint, measured according to the intention-to-treat population.

The key secondary outcomes were the sequential organ failure assessment score at day 14 and day 28, the occurrence of grade 3 or 4 adverse events or serious adverse events attributed to IVIG; the time to intensive care unit or hospital discharge; the clinical status at day 28 and day 90 as assessed by the seven-category ordinal scale; 90-day mortality; and lung injury score at day 28. The main exploratory secondary outcomes were occurrence of pulmonary embolism and nosocomial pneumonia within the first 28 days, cytokines concentrations (IL-6, TNF-α, and IL-13), and circulating lymphocytes populations at admission, days 7, 14, and 28. All were measured in the intention-to-treat population.
Adverse events were coded using the MedDRA (version 22) coding dictionary; each adverse event was electronically reported to the sponsor and monitored until its complete resolution. The adverse events considered related to IVIG are included in appendix 1 (p 22). The number of deaths due to an adverse event and study discontinuation due to an adverse event were recorded. The safety analysis included all patients who received at least one dose of the study drug.

### Statistical analysis

At the time of study design and according to previous studies on ARDS before the COVID-19 pandemic, we assumed that the mean number of days without invasive mechanical ventilation would be 10 days (SD 6 days) in the placebo group and 15 days (SD 6 days) in the IVIG group. With an assumed 28-day mortality rate of 50% in the placebo group and 40% in the IVIG group, the mean number of days without invasive mechanical ventilation was expected to be 9 days in the placebo group and 5 days in the IVIG group. A reduction in the mortality rate of 10% and a 5-day period of invasive mechanical ventilation resulting in a 4-day increase of ventilator-free days at day 28 was considered clinically relevant.

Because of the uncertainty about the assumption of normality of the distributions, the non-parametric Wilcoxon-Mann-Whitney test (U-test) was used for sample size estimation. Considering a power of 90% and a bilateral two-sided significance level of 0·05, adjusted for the number of primary and secondary outcomes, 159 patients (79 per group) were needed to detect a difference in ventilator-free days of 4 days with a type I error of 5% and a type II error of 10%.

The clustered Wilcoxon rank-sum test (Rosner-Glynn-Lee method) stratified by centre and invasive mechanical ventilation duration was used for the primary analysis of the principal endpoint. The hypothesis of equality of ventilation duration was used for the primary analysis of the Hodges-Lehmann estimator was used to assess the difference in median and relative CI for all quantitative outcomes. Unadjusted and adjusted odds ratios were used to test the risk of in-hospital death at 28 and 90 days.

The log-rank test and Kaplan-Meier plot were used for time-to-event analysis (survival at 28 days and 90 days, intensive care unit stay, and hospital discharge). A non-prespecified analysis of the effect of IVIG on the main outcome in patients who received corticosteroids was done. A subgroup analysis of patients with a BMI of 30 or more or aged 65 years or older of the main and secondary outcomes was done. Finally a sensitivity analysis was done on the per-protocol population. All other statistical analyses were done in the intention-to-treat population using SPSS (version 26.0) and RStudio (version 1.3.1093; appendix 1 p 8). This trial is registered on ClinicalTrials.gov, NCT04350580.

### Role of the funding source

Neither the funder of the study nor the organisation providing the study drug had a role in study design, data analysis, or manuscript writing. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

---

### Table 1: Baseline demographic and disease characteristics

| Demographics and comorbidities | IVIG group (n=69) | Placebo group (n=77) |
|--------------------------------|-------------------|---------------------|
| **Sex**                        |                   |                     |
| Male                           | 49 (71%)          | 54 (70%)            |
| Female                         | 20 (29%)          | 23 (30%)            |
| **Age**                        |                   |                     |
| Age (years)                    |                   |                     |
| Patients 65 years or older     | 65 (1·2)          | 66·5 (1·3)          |
| Patients 65 years or older     | 38 (55%)          | 49 (64%)            |
| Body-mass index (kg/m²)        | 30·9 (5·75)       | 30·2 (6·20)         |
| **COVID-19 course**            |                   |                     |
| Time between symptom onset and initiation of invasive mechanical ventilation in days | 8 (6·0–11·0) | 8 (6·0–12·5) |
| Time between initiation of invasive mechanical ventilation and random assignment | 12 h | 23 (33%) |
| >12 h                          | 23 (33%)          | 23 (30%)            |
| >24–72 h                       | 23 (33%)          | 23 (30%)            |
| Simplified acute physiology score II | 41·0 (32·0–50·0) | 39·0 (31·5–50·0) |
| **Critical illness and acute respiratory distress syndrome severity** | | |
| Sequential organ failure assessment score | 6·4 (0·8–8·0) | 6 (0·8–8·0) |
| Kidney disease improving global outcome score | 0 (0–0) | 0 (0–0) |
| Vasopressor support            | 36 (52%)          | 35 (45%)            |
| Lung injury score              | 3 (2·7–3·3)       | 3 (0·3–3·5)         |
| PaO₂:FiO₂ ratio                | 125 (96–155)      | 110 (80–153)        |
| Lung compliance (ml/cm H₉O)     | 32·5 (29·0–36·0)  | 29·5 (26·0–33·0)    |
| Radiological score (number of quadrant[s] with alveolo-interstitial opacities) | 4 (2–4) | 4 (3–4) |
| **Acute respiratory distress syndrome management** | | |
| Tidal volume (ml/kg of predicted body weight) | 6·2 (5·6–6·7) | 6·2 (5·8–6·6) |
| Positive end expiratory pressure (cm H₂O) | 12 (9·8–14·0) | 12 (10·0–14·0) |
| Inspiratory plateau pressure (cm H₂O) | 24 (23–26) | 25 (24–26) |
| **Laboratory value**           |                   |                     |
| Lymphocyte count (×10⁹/L)      | 0·67 (0·28)       | 0·56 (0·28)         |
| Platelet count (×10⁹/L)        | 292 (136)         | 278 (103)           |
| Plasma C-reactive protein concentration (µg/mL) | 164 (91) | 160 (90) |
| **COVID-19 treatment before and 2 days after random assignment** | | |
| Corticosteroid                 | 49 (71%)          | 55 (71%)            |
| Remdesivir                     | 5 (7%)            | 7 (9%)              |
| Antibiotics                    | 56 (81%)          | 65 (84%)            |

Data are n (%), median (IQR), or mean (SD). FiO₂=fraction of inspired oxygen. IVIG=intravenous immunoglobulins.

---

**Articles**

Medécine Intensive et Réanimation, Centre Hospitalo-Universitaire de Grenoble Alpe, Grenoble, France (Prof C. Schwobel MD); Service de Réanimation Gustave Roussy, Villejuif, France (A. Stoddon MD);
Baseline demographic and disease characteristics were similar between both groups (table 1; appendix 1 pp 10–13). The mean age was 65·1 years (SD 12·2) in the IVIG group and 66·5 years (9·3) years in the placebo group. The median time between symptom onset and initiation of invasive mechanical ventilation was 8 days (6·0–11·0) in the IVIG group and 8 days (6·0–12·5) in the placebo group. The severity of critical illness and ARDS was similar between the two groups, as indicated by the absence of difference for the simplified acute physiology score II, sequential organ failure assessment score, lung compliance, and PaO₂/FiO₂ ratio upon admission (table 1). The ventilator settings did not differ between the two groups, nor did the use of corticosteroids and tocilizumab (table 1). The median dose of IVIG was 2 g/kg (IQR 1·9–2·0) over 4 days (appendix 1 p 20).

The median number of ventilator-free days at day 28 was 0·0 (IQR 0·0–8·0) in the IVIG group and 0·0 (0·0–6·0) in the placebo group (with a difference estimate between the medians of 0·0 [95% CI 0·0–0·0]; p=0·21; table 2; figure 2). The mortality rate at day 28 did not differ between the two groups (24 [35%] of 69 patients in the IVIG group vs 20 [26%] of 77 patients in the placebo group; unadjusted odds ratio 1·52 [0·75–3·09]; p=0·25; table 2). The proportion of extubated patients at day 28 and the median duration of invasive mechanical ventilation were also similar between the two groups (table 2).

The sequential organ failure assessment and the lung injury scores at day 14 (appendix 1 p 14) and day 28 (table 2) were not statistically different between the two groups, whereas lung compliance was significantly lower in the IVIG group at day 14 (appendix 1 p 14). The day 28 and day 90 seven-category clinical ordinal scale between the IVIG and placebo groups were similar (table 2; appendix 1 pp 16–17) as were the proportion of patients discharged (16 [37%] of 43 patients in the IVIG group vs 19 [37%] of 52 patients in the placebo group) and the median length of intensive care unit and hospital stays (table 2).

The number of adverse events was similar between the two groups (152 events in the IVIG group vs 154 in the placebo group; table 3). There was a non-statistically significantly higher number of serious adverse events in the IVIG group (78 events in the IVIG group vs 47 events in the placebo group; table 3; appendix 1 pp 22–23). 22 (32%) patients in the IVIG group had at least one serious adverse event compared with 15 (20%) patients in the placebo group (p=0·089). Three adverse events led to unmasking in the placebo group. There was no difference in the occurrence of ventilator acquired pneumonia between the two groups. However, ten (15%) patients in the IVIG group had at least one serious adverse event compared with three (4%) in the placebo group. Additionally, four of the ten patients in the IVIG group had pulmonary embolism compared with one patient in the placebo group (table 3; appendix 1 pp 22–23).

The prespecified subgroup analyses (according to time to randomisation, age, and body-mass index) were
consistent with the main result and did not show any beneficial effect of IVIG (figure 3; appendix 1 p 18). A post-hoc analysis of mortality showed no statistically significant interaction between the IVIG and corticosteroid administration or body-mass index for the unadjusted mortality odds ratios at day 28 and day 90 (appendix 1 pp 18, 31–32). The sensitivity analysis done on the per-protocol population for both the primary outcome and competing events confirmed the non-significant treatment effect shown by the intention-to-treat analysis (appendix 1 p 19).
patients receiving corticosteroids, which was not prespecified in the initial protocol. BMI = body-mass index.

Mean difference is reported for the main outcome of ventilation-free days at day 28 for all the patients and for

the per-protocol population. All subgroup analyses were prespecified except the analysis of

invasive mechanical ventilation time at randomisation, age, survival at day 7, body-mass index, corticosteroid

dose, and in the per-protocol population. BMI = body-mass index.

Discussion

In this multicentre, randomised, placebo-controlled, phase 3, clinical trial, IVIG did not significantly reduce

ventilator-free days at day 28 in patients admitted to the intensive care unit for COVID-19-associated moderate-to-

severe ARDS. Across the whole population—including patients older than 65 years, patients who were obese

(body-mass index ≥ 30 kg/m²), and those who had received corticosteroid—IVIG had no effect on the

duration of invasive mechanical ventilation and mortality, the two components of the primary endpoint.

Both duration of invasive mechanical ventilation and mortality rate were lower than expected on the basis of available data at the time of the ICAR design (end of March, 2020), which could have lowered the power of this study. However, the decrease in invasive mechanical ventilation duration and mortality indicates that the efficiency of care for patients with COVID-19-associated ARDS has dramatically improved since the start of the pandemic, highlighting the commitment of the participating centres to seek the most up to date treatments. The administration of corticosteroids probably had a beneficial effect on clinical outcomes, including contributing to a reduction in invasive mechanical ventilation duration and overall mortality. Our data

demonstrate that IVIG and corticosteroids do not produce any

synergistic effects in COVID-19-associated ARDS. However, one can argue that our study was underpowered and a 4-day reduction in ventilator-free days was too ambitious, suggesting that a benefit from IVIG could not definitively be ruled out.

We hypothesised a reduction in invasive mechanical ventilation duration of 5 days and a 10% mortality rate; we

expected a treatment benefit that would legitimise the large-scale use of IVIG considering their cost and shortage. Despite the results showing the absence of benefits of IVIG in patients with COVID-19-associated ARDS, our data might have an effect on public health: IVIG use should be reserved for inflammatory or autoimmune diseases, such as Kawasaki or chronic polyneuropathy. Of note, it has been reported that up to 30% of patients with COVID-19 have been treated with IVIG.

The limitations of IVIG administration in terms of clinical benefits cannot be ascribed to differences in

the placebo cohort on day 7 (2.7 pg/mL [IQR 1.7 to 3.7]; median difference −4.4 [−6.1 to −2.6]), whereas both IL-6

and TNF-α concentrations were similar between the two groups at all timepoints (appendix 1 p 24). On day 28, the

proportion of circulating CD4 T cells that were regulatory T lymphocytes was higher in patients treated in the IVIG
group (6% [IQR 5 to 7]) compared with patients in the placebo group (4% [3 to 5]; median difference 2

[IQR 1 to 4]; appendix 1 p 25). Additionally, the proportion of circulating memory T CD4 cells at day 28 was higher

in the IVIG group (62% [IQR 60 to 78]) than in the placebo group (41% [33 to 53]; median difference 24

[IQR 7 to 35]; appendix 1 p 25).

Table 3: Adverse events in the safety population

| Any adverse events | IVIG group (n=68) | Placebo group (n=76) |
|--------------------|------------------|---------------------|
| Patients with at least one adverse event | 51 (75%) | 54 (71%) |
| Any serious adverse event | 78 | 47 |
| Patients with at least one serious adverse event | 22 (32%) | 15 (20%) |

Patients with adverse events of special interest

- Ventilator-associated pneumonia
- Catheter-related infection
- Other infection
- Septic shock
- Acute kidney injury
- Renal replacement therapy
- Deep vein thrombosis or pulmonary embolism
- Other

Mean difference

Invasive mechanical ventilation time at randomisation

| <12 h | 54 | 0.0 (0.0 to 0.0) |
| 12–24 h | 45 | 0.0 (0.0 to 0.0) |
| >24–72 h | 44 | 0.0 (0.0 to 5.0) |

Age (years)

| <65 | 57 | 0.0 (0.0 to 6.0) |
| ≥65 | 86 | 0.0 (0.0 to 0.0) |

Patients alive at day 7

| Yes | 102 | 0.0 (0.0 to 0.0) |
| No | 39 | 0.0 (0.0 to 0.0) |

BMI

| BMI (kg/m²) ≥ 30 | 68 | 0.0 (0.0 to 5.0) |
| BMI (kg/m²) < 30 | 66 | 0.0 (0.0 to 1.0) |

Per-protocol population

| 86 | 0.0 (0.0 to 0.0) |

All patients

| 146 | 0.0 (0.0 to 0.0) |
ARDS severity or management between the two therapeutic groups, including ventilator setting and use of corticosteroids, neuromuscular blocking drugs, prone position, and nitric oxide. Therefore, the absence of an effect of IVIG might result from some detrimental immunological effects. We found that IVIG increased the plasma concentration of IL-13, which has been reported to contribute to lung fibrosis by promoting bronchial epithelium inflammation and inadequate repair processes in primitive lung fibrosis. We also found that IVIGs were associated with a non-significant trend towards more frequent serious adverse events, of note thrombotic events that have been mainly reported to the IVIG-induced hyperproteinenaemia. The administration of IVIG in four infusions of at least 8 h probably resulted in hyperviscosity, accounting for the higher number of patients reporting thrombosis in the IVIG group.

We have only included patients with COVID-19-associated ARDS who needed invasive mechanical ventilation. However, the criteria for invasive mechanical ventilation changed during the 6-month study period (ie, from April to October, 2020). In this time, non-invasive mechanical ventilation and high-flow nasal oxygen became increasingly used to avoid or delay invasive mechanical ventilation. Therefore, our results can be extended to the population of patients with COVID-19 who require non-invasive mechanical ventilation or high-flow nasal oxygen for moderate-to-severe ARDS. Of note, the median time to initiate invasive mechanical ventilation was 8 days (IQR 6–11–0) in the ICAR trial, which is similar to the delay reported in other studies. In terms of COVID-19 course and ARDS severity and management, the ICAR cohort is representative of the general population of patients with COVID-19 who developed ARDS, as shown in large observational studies and clinical trials.

Another possible schedule for administration of IVIG is for it to be administered at different timepoints over the course of COVID-19-associated respiratory failure. We cannot rule out the possibility that IVIG could prevent progression to ARDS if given earlier (eg, in patients with COVID-19-associated pneumonia). Conversely, we found that IVIG induced an increase in circulating regulatory and memory CD4 T lymphocytes at day 28 that could promote the tissue repair processes through a type 2 immune response. This finding suggests that IVIG might be beneficial at the recovery phase of ARDS.

Our study shows that IVIG did not significantly improve outcomes and tended to be associated with more adverse events in patients with COVID-19-associated moderate-to-severe ARDS receiving invasive mechanical ventilation. Therefore, IVIG should not be used in this population but reserved for other diseases. The benefit of IVIGs at an earlier stage of COVID-19 related pneumonia should be addressed in future studies.

References
1. WHO. WHO coronavirus disease (COVID-19) dashboard. 2021. https://covid19.who.int (accessed Feb 19, 2021).
2. COVID-ICU Group. Clinical characteristics and day-90 outcomes of 4244 critically ill adults with COVID-19: a prospective cohort study. Intensive Care Med 2021; 47: 60–73.
3. Herridge MS, Tansey CM, Matté A, et al. Functional disability 5 years after acute respiratory distress syndrome. N Engl J Med 2011; 364: 1293–304.
4. Tay MZ, Poh CM, Rénia L, MacAry PA, Ng LFP. The trinity of COVID-19: immunity, inflammation and intervention. Nat Rev Immunol 2020; 20: 363–74.
5. WHO Solidarity Trial Consortium. Repurposed antiviral drugs for Covid-19. N Engl J Med 2021; 384: 497–511.
6. Horby P, Lim WS,emberson JR, et al. Dexamethasone in hospitalized patients with Covid-19. N Engl J Med 2021; 384: 693–704.
7. Shankar-Hari M, Vale CI, Godolphin PJ, et al. Association between administration of IL-6 antagonists and mortality among patients hospitalized for COVID-19: a meta-analysis. JAMA 2021; 326: 499–518.
8. Gordon AC, Mouncey PR, Al-Beidh F, et al. Interleukin-6 receptor antagonists in critically ill patients with Covid-19. N Engl J Med 2021; 384: 1491–502.
20. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 2020; 395: 1054–62.

21. Yang X, Yu Y, Xu J, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective observational study. Lancet Respir Med 2020; 8: 675–81.

22. Guan W, Ni Z, Hu Y, et al. Clinical characteristics of coronavirus disease 2019 in China. J Emerg Med 2020; 58: 711–12.

23. Boyle JG. COVID-19 and the Threat to Immunoglobulin Availability. 2020. https://primaryimmune.org/news/covid-19-and-threat-immunoglobulin-availability (accessed May 21, 2021)

24. Mazeraud A, Gonçalves B, Aegerter P, et al. Effect of early treatment with polyvalent immunoglobulin on acute respiratory distress syndrome associated with SARS-CoV-2 infections (ICAR trial): study protocol for a randomized controlled trial. Trials 2021; 22: 170.

25. Ranieri VM, Rubenfeld GD, Thompson BT, et al. Acute respiratory distress syndrome: the Berlin Definition. JAMA 2012; 307: 2526–33.

26. WHO Working Group on the Clinical Characterisation and Management of COVID-19 infection. A minimal common outcome measure set for COVID-19 clinical research. Lancet Infect Dis 2020; 20: e192–97.

27. Bellani G, Laffey JG, Pham T, et al. Epidemiology, patterns of care, and mortality for patients with acute respiratory distress syndrome in intensive care units in 50 countries. JAMA 2016; 315: 788–800.

28. Papazian L, Forel J-M, Gacouin A, et al. Neuromuscular blockers in early acute respiratory distress syndrome. N Engl J Med 2010; 363: 1107–16.

29. Rosner B, Glynn RJ, Lee M-LT. Incorporation of clustering effects for the Wilcoxon rank sum test: a large-sample approach. Biometrics 2003; 59: 1089–98.

30. Tjon ASW, van Gent R, Jaalder H, et al. Intravenous immunoglobulin treatment in humans suppresses dendritic cell function via stimulation of IL-4 and IL-13 production. J Immunol 2014; 192: 5625–34.

31. Zhu Z, Homer R, Wang Z, et al. Pulmonary expression of interleukin-13 causes inflammation, mucus hypersecretion, subepithelial fibrosis, physiologic abnormalities, and ectasis production. J Clin Invest 1999; 103: 779–88.

32. Botta M, Tomas AM, Pillay J, et al. Ventilation management and clinical outcomes in invasively ventilated patients with COVID-19 (PROVENT-COVID): a national, multicentre, observational cohort study. Lancet Respir Med 2021; 9: 139–48.

33. Lloyd CM, Snelgrove RJ. Type 2 immunity: Expanding our view. Sci Immunol 2018; 3: eaat1604.

34. Gieseck RL 3rd, Wilson MS, Wynn TA. Type 2 immunity in tissue repair and fibrosis. Nat Rev Immunol 2018; 18: 62–76.