Agafina *et al.*
European Journal of Medical Research (2024) 29:418
https://doi.org/10.1186/s40001-024-02008-x

European Journal of Medical Research

RESEARCH

Open Access

Efficacy and safety of trimodulin in patients with severe COVID-19: results from a randomised, placebo-controlled, double-blind, multicentre, phase II trial (ESsCOVID)

Alina Agafina[1], Valeria Cristina Aguiar[2], Maria Rossovskaya[3], Muriel Sarah Fartoukh[4], Ludhmila Abrahao Hajjar[5], Guillaume Thiéry[6], Jean-François Timsit[7], Ivan Gordeev[8], Denis Protsenko[9], Javier Carbone[10], Rita Pellegrini[11], Claudio Marcel Berdun Stadnik[12†^], Sergey Avdeev[13], Miquel Ferrer[14], Corina C Heinz[15], Thomas Häder[15], Patrick Langohr[15], Iris Bobenhausen[15], Jörg Schüttrumpf[15,16], Alexander Staus[15], Markus Ruehle[15], Sabrina Weissmüller[15], Andrea Wartenburg-Demand[15] and Antoni Torres[17*]

Abstract

Background Trimodulin (human polyvalent immunoglobulin [Ig] M ~ 23%, IgA ~ 21%, IgG ~ 56% preparation) has previously been associated with a lower mortality rate in a subpopulation of patients with severe community-acquired pneumonia on invasive mechanical ventilation (IMV) and with clear signs of inflammation. The hypothesis for the ESsCOVID trial was that trimodulin may prevent inflammation-driven progression of severe coronavirus disease 2019 (COVID-19) to critical disease or even death.

Methods Adults with severe COVID-19 were randomised to receive intravenous infusions of trimodulin or placebo for 5 consecutive days in addition to standard of care. The primary efficacy endpoint was a composite of clinical deterioration (Days 6–29) and 28-day all-cause mortality (Days 1–29).

Results One-hundred-and-sixty-six patients received trimodulin ($n=84$) or placebo ($n=82$). Thirty-three patients died, nine during the treatment phase. Overall, 84.9% and 76.5% of patients completed treatment and follow-up, respectively. The primary efficacy endpoint was reported in 33.3% of patients on trimodulin and 34.1% of patients on placebo ($P=0.912$). No differences were observed in the proportion of patients recovered on Day 29, days of invasive mechanical ventilation, or intensive care unit-free days. Rates of treatment-emergent adverse events were comparable.

A post hoc analysis was conducted in patients with early systemic inflammation by excluding those with high CRP (> 150 mg/L) and/or D-dimer (≥ 3 mg/L) and/or low platelet counts ($< 130 \times 10^9$/L) at baseline. Forty-seven patients in the trimodulin group and 49 in the placebo group met these criteria. A difference of 15.5 percentage points

^Claudio Marcel Berdun Stadnik—deceased prior to approval of final draft.

*Correspondence:
Antoni Torres
ATORRES@clinic.cat
Full list of author information is available at the end of the article

in clinical deterioration and mortality was observed in favour of trimodulin (95% confidence interval: −4.46, 34.78; $P = 0.096$).

Conclusion Although there was no difference in the primary outcome in the overall population, observations in a subgroup of patients with early systemic inflammation suggest that trimodulin may have potential in this setting that warrants further investigation.

ESsCOVID was registered prospectively at ClinicalTrials.gov on October 6, 2020. NCT04576728

Keywords COVID-19, Immunoglobulin, Trimodulin, Early systemic inflammation, Immunomodulation

Background

Coronavirus disease 2019 (COVID-19) has had a substantial impact on day-to-day living over the last 4 years. Although COVID-19 is asymptomatic or results in mild symptoms in most individuals, some patients still require hospitalisation due to development of severe pneumonia [1].

Severity of COVID-19 was defined initially by respiratory parameters [2, 3]. Now additional markers indicating systemic inflammation, such as high C-reactive protein (CRP) levels, and markers indicating dysregulated coagulation, such as elevated D-dimer and fibrinogen, low platelet counts and prolongation of prothrombin time, have been associated with disease severity [4–7]. Markers of dysregulated coagulation may indicate hypercoagulability (also called COVID-19-associated coagulopathy) that may lead to intravascular thrombotic complications. Together with various hyperinflammatory immune responses, these mechanisms lead to immunothrombosis, which is thought to be a major contributor to morbidity and mortality in COVID-19 [8, 9].

Given these links with systemic inflammation, immune-modulating therapies have now become part of the therapeutic pathway in patients hospitalised with COVID-19 [3]. Indeed, hospitalised patients with severe or critical COVID-19 have been shown to benefit from treatment with immunomodulatory drugs, some of which have been granted regulatory approval and are included in COVID-19 treatment guidelines (e.g. dexamethasone, tocilizumab and baricitinib) [10, 11]. For these medications, results from different trials provided evidence of benefit in certain patient subpopulations with COVID-19 [12].

However, despite these developments and the declining rates of severe COVID-19, expansion of treatment approaches for hospitalised COVID-19 patients remains desirable. Currently approved medications may not be available universally, vaccines may not elicit an immune response or may be contraindicated, or new, more virulent variants may appear, against which current antiviral therapies may be less effective or effective vaccines may not yet be available.

Trimodulin is a human plasma-derived native polyvalent antibody preparation in clinical development for respiratory tract infections. In contrast to other intravenous immunoglobulin (Ig) preparations (IVIg), which contain ≥ 95% IgG, trimodulin contains ~ 56% IgG plus relevant amounts of IgM (~ 23%) and IgA (~ 21%). In addition to anti-pathogen activity, polyvalent IgM is immune modulating at the complement level [13–15], and both polyvalent IgM and IgA are immune modulating at the cytokine level [16–18]. Trimodulin is also assumed to contain relevant amounts of natural IgM [19]. Natural IgM is a first-line defence against pathogens but also plays a role in maintenance of tissue homeostasis via the clearance of damaged and apoptotic cells [19–21]. Given these multiple modes of action, use of trimodulin represents a new therapeutic strategy for COVID-19 compared with those that suppress the immune system more broadly or target only a single component of an inflammatory pathway.

In a previous phase II clinical trial, trimodulin improved outcomes of patients with severe community-acquired pneumonia (sCAP) on invasive mechanical ventilation (IMV), evidenced by a significantly lower mortality rate in subpopulations with elevated CRP levels, or with reduced IgM serum concentrations, or both [22]. The hypothesis for the present Escape from severe COVID-19 (ESsCOVID) clinical trial was that trimodulin may prevent inflammation-driven progression of severe COVID-19 to critical disease or even death. Accordingly, the efficacy and safety of trimodulin in adults hospitalised with severe COVID-19 was investigated. An additional post hoc analysis was performed to identify those patients that benefited most from treatment with trimodulin to inform the design of future clinical trials.

Methods

Trial design

ESsCOVID was a phase II, randomised, placebo-controlled, double-blind, multicentre clinical trial (NCT04576728) conducted across 16 centres in Brazil, France, Russia, and Spain. Blinding (investigators, patients, and all personnel involved in the conduct and outcome assessments of the trial) was maintained until

after database lock. The trial was conducted according to the International Council for Harmonisation, Good Clinical Practice standards and the Declaration of Helsinki, and with independent ethics committee approval. Written informed consent from the patient, or legally authorised representative, was obtained in compliance with all local legal requirements.

Sample size calculation

Data from clinical studies conducted at a similar time during the COVID-19 pandemic, reported that ~ 40% of severe patients on non-invasive ventilation or high-flow oxygen deteriorated and of these, approximately 50% died [2, 23–26]. Therefore, a deterioration/mortality rate of 40% of patients was assumed in the placebo group. A previous phase II trial with trimodulin (CIGMA trial [22]) was performed in patients with sCAP caused by any pathogen. In a subgroup with elevated CRP levels, the mortality was reduced by 16.7% and progression to septic shock was reduced by 7.8% [22]. Accordingly, a deterioration/mortality rate of 20% was assumed in the trimodulin group. Based on these assumptions the trial was powered at 80% to detect a difference of 20 percentage-points in the composite primary endpoint (placebo: 40%, trimodulin: 20%) with a sample size of 164 patients. Sample size estimation was performed using nQuery Version 8.5.1.0 and the statistical analysis was performed using SAS® version 9.4.

Patient population

Adult patients (≥ 18 years of age) hospitalised with severe COVID-19 were enrolled. At screening, patients were required to have laboratory-confirmed severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2) infection from a test performed on a respiratory tract sample within the last 5 days and a diagnosis of community-acquired severe COVID-19 within 10 days after hospital admission. Severe COVID-19 was defined as the need for non-invasive ventilation (NIV) and/or high-flow oxygen (HFO; via nasal cannula or mask; score 5 [hospitalised with severe disease] on the 9-category ordinal scale, where 0 is non-hospitalised [discharged/cured] and 8 is death; Additional file 1: Table S1). In addition, patients were required to have at least one of five clinical respiratory parameters (dyspnoea, respiratory frequency ≥ 30 breaths/min, $SpO_2 \leq 93\%$, PaO_2/FiO_2 100–300 mmHg, lung filtrates > 50% within 24 to 48 h). Patients were also required to have at least one measurement of CRP ≥ 50 mg/L within 36 h prior to the start of treatment.

Patients were excluded if they deteriorated prior to randomisation, as reflected by, for example, the need for IMV (score > 5 on the 9-category ordinal scale; Additional file 1: Table S1) or improved so they were on low-flow oxygen or no oxygen prior to randomisation (score < 5). Patients were also excluded if they had severe neutropenia (neutrophil count < 500/mm^3), thrombocytopenia (platelet count < 30,000/mm^3) or haemoglobin < 7 g/dL within 24 h of treatment initiation, known haemolysis, or had known thrombosis or thromboembolic events (TEEs) within the previous 3 months. Patients particularly at risk of TEEs for reasons other than COVID-19 were also excluded. In addition, patients on dialysis or with severe renal impairment, estimated glomerular filtration rate < 30 mL/min/1.73 m^2 assessed within 24 h of starting treatment, or patients with end-stage renal disease or known focal segmental glomerulosclerosis were excluded, as were those with known severe lung diseases interfering with COVID-19 treatment, decompensated heart failure, pre-existing hepatic cirrhosis or severe hepatic impairment (Child–Pugh score ≥ 9 points) or hepatocellular carcinoma, and those who had received treatment for thorax, head, neck or haematological malignancies in the previous 12 months.

Randomisation and treatment schedule

Eligible patients were randomised 1:1 on Day 1 to either trimodulin or placebo stratified by centre according to a pre-defined randomisation list generated and implemented by interactive response technology. Trimodulin (BT588; Biotest AG, Dreieich, Germany) or an equal volume of placebo (1% human albumin solution; Biotest AG, Dreieich, Germany) were administered as intravenous infusions on 5 consecutive days (Days 1 to 5). The volume of trimodulin or placebo administered was 3.65 mL/kg body weight/day. This corresponded to doses of 182.6 mg trimodulin/kg body weight/day or 36.5 mg albumin/kg/body weight/day (as used in the previous phase II CIGMA trial). Infusion was started at a rate of 0.1 mL/min and increased by 0.1 mL every 10 min if tolerated up to a maximum infusion rate of 0.5 mL/min. Patients were followed up to Day 29 or up to hospital discharge, whichever occurred first. An end-of-trial telephone interview was conducted on Day 29 for patients discharged or transferred.

Clinical assessments

Each patient was tested for SARS-CoV-2 at screening. Local laboratory assessment of clinical chemistry, haematology and coagulation parameters was performed on Days −1, 1–5 (pre-dose), 7, 14 and 21, and on Day 29/discharge. In addition a physical examination was performed on Days 1 and 29/discharge, with vital signs (including blood gas measurements) assessed on Days −1, 1–7, 9, 14 and 21, and Day 29/discharge. Samples for pharmacokinetic (PK) assessment were taken

pre-dose on Days 1 and 5, post-dose on Day 5 and on Day 29/discharge. Samples for pharmacodynamic (PD) assessment were taken pre-dose on Days 1, 3 and 5, and on Days 9 and 29/discharge.

Hospitalisation and intensive care unit (ICU) dates, as well as oxygen supply type and dates and the daily clinical status of the patients according to the ordinal scale, were recorded.

Standard of care

Standard of care (SoC) included procedures for acute respiratory distress syndrome (ARDS), IMV and extra corporeal membrane oxygenation (ECMO), including prone positioning and weaning. SoC also covered all prior and concomitant medication given due to the COVID-19 infection and the subject's clinical situation, including antivirals, antibiotics, corticosteroids and antithrombotic therapy, according to local guidelines and protocols. Use of other Ig preparations, interferons, blood products (including [convalescent] plasma and albumin), passive immunisations, or active vaccinations and extracorporeal cytokine adsorbing therapy was prohibited within 21 days before entering the trial and during the trial. Use of other antibody-containing products, including immune-modulating monoclonal antibodies and antiviral monoclonal antibody products, was allowed prior to, but was prohibited during the trial. In cases where these types of prohibited medications were administered during the trial (e.g. in an emergency, to avoid further aggravation, or by accident), these patients were excluded from the per-protocol set (PPS), PK and/or PD sets.

Efficacy assessment

The primary endpoint was assessed in the full analysis set (FAS, $n=166$). The primary efficacy endpoint was a composite endpoint of two parameters assessed by using the 9-category ordinal scale (Additional file 1: Table S1): the clinical deterioration rate assessed during the post-treatment follow-up period (between Days 6 and 29) and the 28-day all-cause mortality rate (score = 8) assessed from the first day of treatment (Day 1) up to the end of the follow-up period (Day 29). Deterioration was defined as worsening to requirement for IMV (score = 6) and/or development of additional organ dysfunctions, organ failures, sepsis and/or septic shock (score = 7). The maximum score reached within 28 days was applied.

Secondary efficacy endpoints included, among others, proportion of patients recovered on Day 29 (score ≤ 2 on the ordinal scale), days of IMV and ICU-free days, hospital-free days, and days without oxygen supply.

Safety assessment

Safety was assessed between signing the informed consent form and Day 29 in the safety analysis set (SAF; $n=166$). Adverse events (AE) were classified using the Medical Dictionary for Regulatory Activities (MedDRA) version 17.1 [27]. Treatment-emergent adverse events (TEAEs; defined as an AE that occurred from the time of first dose of study medication until the end of the trial, independent of relation to study medication), vital signs, electrocardiograms and laboratory parameters, including clinical chemistry, haematology, coagulation and urinalysis, were recorded.

Statistical analyses

The composite primary endpoint was evaluated in the FAS (including all patients who received at least one dose of study medication and had at least one primary efficacy post-dose assessment) using a 2-sided chi-square test with a significance level of 5%. As supportive analysis, a logistic regression was performed to adjust for potential risk factors (age, sex, diabetes, history of heart disease, or other comorbidity at time of informed consent). Kaplan–Meier curves were presented for time to deterioration/mortality. A forest plot including odds ratios (OR) and 95% confidence intervals (CI) for the primary composite endpoint (clinical deterioration plus 28-day mortality) was created for different patient populations.

As a sensitivity analysis, efficacy was evaluated in the PPS, which excluded patients from the FAS with major protocol deviations (not meeting eligibility criteria, use of prohibited medication, trial discontinuation prior to Day 6 for any reason other than death). Safety, demographics and baseline characteristics were assessed using the SAF, which included all patients who received at least one dose of study medication.

In the case of missing deterioration/28-day mortality data, the clinical status up to and including Day 29 was imputed (Additional file 1: Handling of missing data).

Pharmacokinetic analysis was performed in the PK set ($n=146$), which included patients who did not receive prohibited medication affecting Ig serum concentrations (e.g. plasma, IVIg or monoclonal antibody therapies) during the trial. For all subjects in the PK set, observed serum concentrations of IgM, IgA, and IgG (g/L) were summarised (mean ± standard deviation [SD], median, interquartile range [IQR]) by visit. Statistical summaries were presented per treatment group, and for survivors versus non-survivors in the two treatment groups.

Pharmacodynamic analysis was performed in the PD set ($n=142$), which included patients who did not receive prohibited medications affecting immune responses (e.g. anti-inflammatory or immunosuppressing treatments)

during the trial. Use of corticosteroids was permitted in the PD set. Patients in the PD set with available baseline levels for CRP, D-dimer AND platelets (n = 132) were subdivided into patients with early systemic inflammation ($n = 80$) or advanced systemic inflammation ($n = 52$).

Post hoc analyses

Exploratory, post hoc analyses driven by data and clinical/disease pathology were performed after unblinding of all data sets, to identify potential patient subgroups that benefitted most from treatment with trimodulin. During the pandemic, threshold levels for inflammatory markers related to increased risk of critical disease or death have been identified. For CRP, a median level of 125 mg/L [28] and an interquartile range (IQR) of 50–150 mg/L [4] or a median of 100.0 (IQR 60.7–179.4) mg/L [29] have been reported for non-survivors. For D-dimer, concentrations > 1 mg/L were found to be the strongest independent predictor of mortality [6], with an IQR of 3.8–8.0 mg/L associated with significant risk of death in critically ill patients [29], a value that is similar to the threshold of > 3.06 mg/L reported by Pan and colleagues [30]. In addition, mortality in COVID-19 has been associated with thrombocytopenia (defined as platelets $\leq 125 \times 10^9$/L [7]). Based on these reported thresholds, the relevance of these markers to disease severity, and on data from the present trial, a data-driven subgroup of patients with early systemic inflammation was defined by excluding patients with CRP > 150 mg/L and/or D-dimer ≥ 3 mg/L and/or platelets $< 130 \times 10^9$/L. Post hoc analyses in this subgroup were conducted in the FAS and PPS.

Results

Patient disposition

Between 6 October 2020 and 29 June 2021, 185 patients were screened, with 166 being randomised to either trimodulin ($n = 84$) or placebo ($n = 82$). All 166 randomised patients were included in the SAF and FAS, irrespective of whether they completed or discontinued treatment. A total of 141 patients were analysed in the PPS (trimodulin, $n = 70$; placebo, $n = 71$). For participant flow and details on different analysis sets, see Additional file 2: Fig. S1. The trial ended after the planned recruitment of at least 82 patients per arm.

Baseline demographics and patient characteristics

Baseline demographics and patient characteristics were generally balanced between groups (Table 1), although more patients in the placebo group had a history of heart disease. In both groups, the majority of patients received NIV or HFO at the time of treatment initiation. Three patients in the trimodulin group deteriorated before ($n = 1$; excluded from PPS) or after ($n = 2$) randomisation and required IMV before/at the start of treatment.

Most patients (68.1%) received at least one medication that started and stopped prior to the first infusion of trimodulin or placebo. Prior medications specifically given for COVID-19 included corticosteroids for systemic use (including dexamethasone [28.3%], prednisolone [5.4%], others [3.6%]), immunosuppressants (tocilizumab [15.1%], olokizumab [12.0%], hydroxychloroquine [9%], baricitinib [4.2%], levilimab [4.2%], tofacitinib [3.6%] and sarilumab [0.6%]) and antivirals for systemic use (including favipiravir [21.1%], remdesivir [6.0%], and others [7.2%]). All patients had at least one concomitant medication that started before and was ongoing at treatment initiation, or that started on or after treatment initiation but no later than the Day 29 visit (Additional file 2: Table S2). Concomitant medications specifically used to treat COVID-19 in the trimodulin and placebo groups during the trial included corticosteroids for systemic use (76.2% and 72.0%, including dexamethasone [54.8% and 42.7%]), antivirals for systemic use (36.9% and 30.5%, such as remdesivir [7.1% and 3.7%]), and immunosuppressants (16.7% and 13.4%, including tocilizumab [3.6% and 1.2%] and baricitinib [1.2% for both]) (Additional file 2: Table S2).

Pharmacokinetics

In the PK set, mean levels of IgM (1.3 g/L vs 1.2 g/L), IgA (2.9 g/L vs 2.8 g/L) and IgG (10.1 g/L vs 9.9 g/L) were similar between trimodulin ($n = 73$) and placebo ($n = 73$) at baseline and were all well within the normal range (Fig. 1). For patients receiving placebo, the mean concentrations of all three Igs remained close to baseline levels until Day 29. Treatment with trimodulin resulted in a significant increase in all three Igs up to Day 5 end of infusion compared with baseline: for IgM, a mean ± SD concentration of 2.5 ± 0.98 g/L (median: 2.4 g/L; IQR 1.9–2.9 g/L) was achieved ($P < 0.001$), and this value was marginally above the upper limit of the normal (ULN, Fig. 1A). For IgA, a mean concentration of 5.1 ± 1.4 g/L (median: 5.0; IQR 4.1–5.7 g/L) was achieved ($P < 0.001$), and this value was above the ULN (Fig. 1B). For IgG, a mean concentration of 15.9 ± 3.1 g/L (median: 15.3; IQR 14.1–17.6 g/L) was achieved ($P < 0.001$), and this value was close to the ULN (Fig. 1C). For all three Igs, levels had returned to near baseline by Day 29. No difference in PK was observed between survivors and non-survivors (Additional file 2: Table S3).

Efficacy

In the FAS, clinical deterioration/28-day all-cause mortality (composite primary endpoint) was reported in 33.3% of patients in the trimodulin group and 34.1% of

Table 1 Baseline demographics and patient characteristics (SAF)

	Trimodulin (*n* = 84)	Placebo (*n* = 82)	Total (*n* = 166)
Male, n (%)[a]	50 (59.5)	50 (61.0)	100 (60.2)
Age (years), mean ± SD	58.1 ± 12.9	59.0 ± 12.2	58.5 ± 12.6
> 60 years, n (%)[a]	40 (47.6)	40 (48.8)	80 (48.2)
Race, n (%)[a]			
Asian	0	2 (2.4)	2 (1.2)
Black/African American	2 (2.4)	0	2 (1.2)
White/Caucasian	64 (76.2)	63 (76.8)	127 (76.5)
Unknown/not reported/missing	18 (21.4)	17 (20.7)	35 (21.1)
Body mass index (n)	*n* = 82	*n* = 82	*n* = 164
Mean ± SD (kg/m^2)	30.7 ± 4.7	29.4 ± 4.3	30.1 ± 4.5
CAP, n (%)[a]	82 (97.6)	79 (96.3)	161 (97.0)
ARDS, n (%)[a]	33 (39.3)	35 (42.7)	68 (41.0)
Non-invasive ventilation	8 (9.5)	11 (13.4)	19 (11.5)
High-flow oxygen[b]	20 (23.8)	24 (29.3)	44 (26.5)
Both (alternating)	1 (1.2)	0	1 (0.6)
Invasive mechanical ventilation[c]	3 (3.6)	0	3 (1.8)
Non-high-flow oxygen	1 (1.2)	0	1 (0.6)
Category of supplementary oxygen use at time of treatment initiation, n (%)[a]			
Non-invasive ventilation	23 (27.4)	22 (26.8)	45 (27.1)
High-flow oxygen[b]	55 (65.5)	60 (73.2)	115 (69.3)
Invasive mechanical ventilation[c]	3 (3.6)	0	3 (1.8)
Extracorporeal membrane oxygenation	0	0	0
Non-high-flow oxygen	1 (1.2)	0	1 (0.6)
Missing[d]	2 (2.4)	0	2 (1.2)
History of chronic disease, n (%)[a]			
Diabetes	18 (21.4)	18 (22.0)	36 (21.7)
Heart disease	26 (31.0)	35 (42.7)	61 (36.7)
Chronic lung disease	2 (2.4)	5 (6.1)	7 (4.2)
Chronic liver disease	1 (1.2)	2 (2.4)	3 (1.8)
Asthma	4 (4.8)	2 (2.4)	6 (3.6)
Time since hospital admission (days)[e]			
Mean ± SD	4.3 ± 3.0	4.5 ± 3.5	4.4 ± 3.3
Median [Q1–Q3]	3.5 [2.0–6.5]	3.0 [2.0–6.0]	3.0 [2.0–6.0]
Time since ICU admission (days)[e]	*n* = 64	*n* = 62	*n* = 126
Mean ± SD	2.5 ± 2.2	2.6 ± 2.3	2.5 ± 2.2
Median [Q1–Q3]	2.0 [1.0–3.0]	2.0 [1.0–3.0]	2.0 [1.0–3.0]
Time since start of supplementary oxygen (days)[e]			
Mean ± SD	3.0 ± 2.8	3.2 ± 3.1	3.1 ± 2.9
Median [Q1–Q3]	2.0 [1.0–4.0]	2.0 [1.0–4.0]	2.0 [1.0–4.0]

ARDS acute respiratory distress syndrome, *CAP* community-acquired pneumonia, *FAS* full analysis set, *ICU* intensive care unit, *n* number of patients, *PPS* per-protocol set, *Q* quartile, *SD* standard deviation

[a] Percentages are based on the number of patients in the SAF analysis set by treatment group

[b] Via nasal cannula or mask

[c] Three patients in the trimodulin group deteriorated and required invasive mechanical ventilation before the start of treatment. One patient deteriorated before randomisation (constituted a protocol deviation; included in the FAS but excluded from the PPS) and two patients deteriorated shortly after randomisation (included in the FAS and PPS)

[d] For two patients in total, high-flow oxygen supply was documented on the day of first infusion. As time was not recorded, these patients are designated as 'missing'

[e] Time since event (days) was defined as date of treatment start minus date of start of event

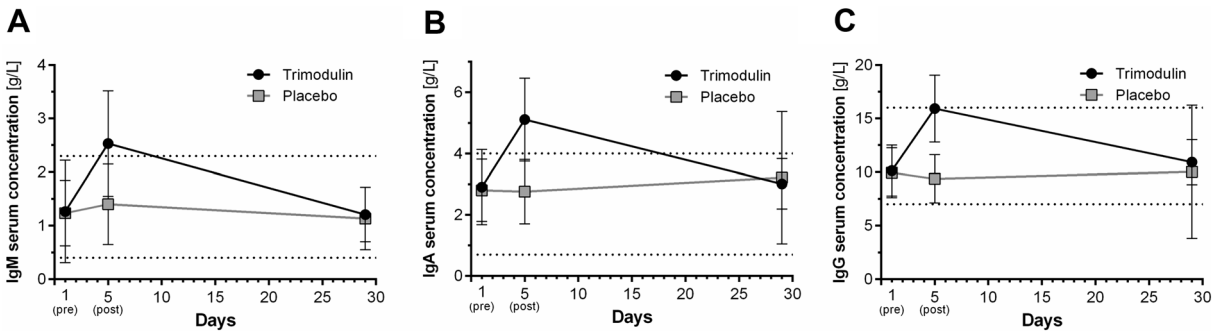

Fig. 1 Pharmacokinetics of IgM, IgA and IgG in COVID-19 patients (PK set). Serum concentrations (mean ± SD) for IgM (**A**), IgA (**B**) and IgG (**C**) were assessed in patients in the PK set. Graphs show PK assessments from samples taken pre-dose on Day 1 (trimodulin, $n = 73$; placebo, $n = 73$) and post-dose on Day 5 (trimodulin, $n = 53$; placebo, $n = 63$) and Day 29 (trimodulin, $n = 7$; placebo, $n = 8$). Dotted line: normal reference ranges [31]. *COVID-19* coronavirus disease 2019, *Ig* immunoglobulin, *PK* pharmacokinetics, *SD* standard deviation

patients in the placebo group (OR 0.96; 95% CI: 0.51, 1.84; $P = 0.912$, Fig. 2A). Supplementary logistic regression analysis to correct for risk factors (covariates: age, sex, diabetes, history of heart disease or other comorbidity) at time of informed consent, determined an OR of 1.07 (95% CI: 0.55, 2.09; $P = 0.836$) (not shown). In line with these results, no difference ($P = 0.84$, log-rank test) in clinical deterioration/28-day all-cause mortality was observed in Kaplan–Meier analysis between the trimodulin and placebo groups in the overall population (Fig. 2B). In the PPS (not shown), clinical deterioration/mortality was 31.4% in the trimodulin group and 35.2% in the placebo group (OR 0.84; 95% CI: 042, 1.70; $P = 0.634$). No difference was observed in any of the evaluated secondary efficacy endpoints for trimodulin vs placebo in the FAS or the PPS (Table 2 and additional file 2: Table S4). For other secondary efficacy endpoints (such as time to clinical deterioration, time to mortality, time to clinical improvement to score = 3 or score = 4), no conclusions could be derived as median time was not reached due to high level of censoring for > 70% of the subjects for various reasons (e.g. no clinical deterioration occurred in > 50% of subjects, worsening occurred before first infusion, death, or other discontinuation before event). Consequently, these data are not shown.

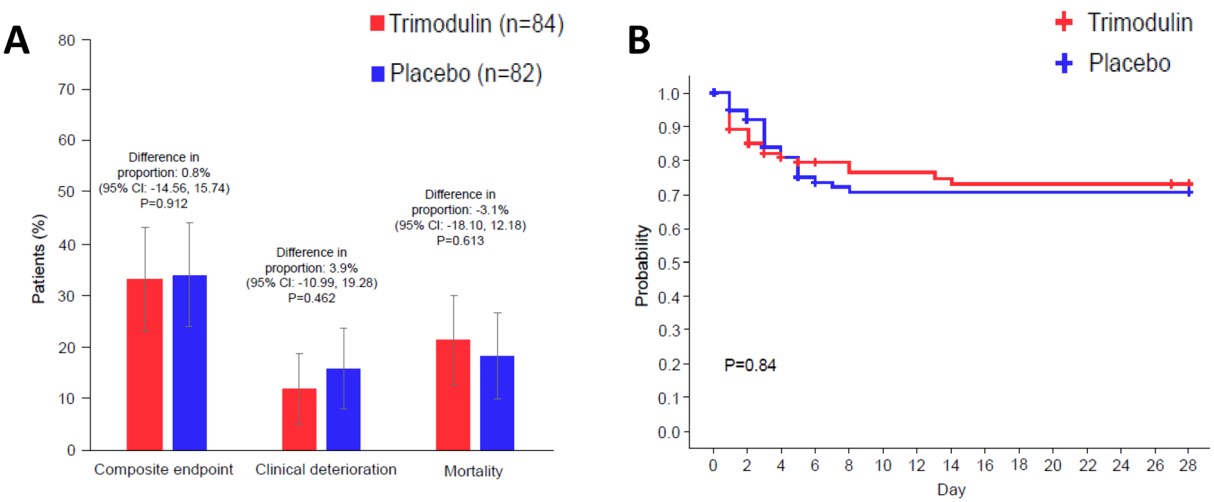

Fig. 2 Impact on clinical deterioration and 28-day mortality (overall population [FAS]). **A** Bar graph represents the proportion of patients achieving the composite endpoint (patients who clinically deteriorated [between Days 6 and 29] plus patients who died [between Days 1 and 29]) and the individual components of this composite endpoint. *P* values calculated by chi-square test. Error bars denote 95% CIs. **B** Kaplan–Meier of probability of survival without an event (defined as deterioration or mortality between Days 1 and 29) in the FAS. *P* value was calculated by log-rank test. *CI* confidence interval, *FAS* full analysis set

Table 2 Primary and secondary* efficacy endpoints (overall trial population [FAS and PPS])

	Overall trial population		
	Trimodulin	**Placebo**	***P* value**
FAS	n = 84	n = 82	
Primary composite endpoint			0.912
Total, n (%)[a]	28 (33.3)	28 (34.1)	
95% CI	23.25, 43.41	23.88, 44.41	
Deterioration, n (%)	10 (11.9)	13 (15.9)	
Mortality, n (%)	18 (21.4)	15 (18.3)	
Days of IMV			0.723
n (%)[a] receiving IMV	17 (20.2)	17 (20.7)	
Mean ± SD	7.6 ± 11.8	7.0 ± 11.1	
Median [Q1, Q3]	0 [0, 21]	0 [0, 19]	
ICU-free days			0.680
Mean ± SD	16.2 ± 11.9	17.0 ± 11.1	
Median [Q1, Q3]	21.5 [0, 26.5]	21.0 [3, 26]	
Proportion of patients recovered (score ≤ 2) by Day 29			0.832
n (%)[a]	54 (64.3)	54 (65.9)	
95% CI	54.04, 74.53	55.59, 76.12	
PPS	n = 70	n = 71	
Primary endpoint			0.634
n (%)[a]	22 (31.4)	25 (35.2)	
95% CI	20.55, 42.30	24.10, 46.32	
Deterioration, n (%)	7 (10)	12 (16.9)	
Mortality, n (%)	15 (21.4)	13 (18.3)	
Days of IMV			0.790
n (%)[a] receiving IMV	14 (20)	16 (22.5)	
Mean ± SD	7.8 ± 12.0	7.3 ± 11.1	
Median [Q1, Q3]	0 [0, 23]	0 [0, 21]	
ICU-free days			0.838
Mean ± SD	16.3 ± 11.9	16.7 ± 11.2	
Median [Q1, Q3]	21.5 [0, 27]	21 [1, 26]	
Proportion of patients recovered (score ≤ 2) by Day 29			0.773
n (%)[a]	47 (67.1)	46 (64.8)	
95% CI	56.09, 78.11	53.69, 75.91	

CI confidence interval, *FAS* full analysis set, *ICU* intensive care unit, *IMV* invasive mechanical ventilation, *n* number of patients, *PPS* per-protocol set, *Q* quartile, *SD* standard deviation

* Data are not presented for secondary endpoints where no conclusions could be derived (e.g. events did not occur in the majority of patients, data were skewed, or medians were not reached due to censoring)

[a] Percentages are based on the number of patients in the FAS or PPS analysis sets by treatment group

Safety

At least one TEAE occurred in 78.6% and 78.0% of patients in the trimodulin and placebo groups, respectively. TEAEs were most commonly (overall incidence > 10% of patients) reported in the following System Organ Classes: investigations (43 [51.2%] and 38 [46.3%] patients for the trimodulin and placebo groups, respectively) and respiratory, thoracic and mediastinal disorders (28 [33.3%] and 30 [36.6%] patients, respectively). The most commonly reported (> 5% of the patients in either group) TEAEs by the MedDRA preferred term are presented in Table 3. The most commonly reported TEAE by preferred term was electrocardiogram QT prolonged. There were no significant differences in the rate of any TEAEs between the two treatment groups.

Post hoc analysis

As knowledge on COVID-19 and its disease stages increased during the pandemic and trial conduct, and due to the good safety profile of trimodulin, exploratory

Table 3 TEAEs by MedDRA preferred term (frequency of > 5% in either treatment group[a]) (SAF)

	Trimodulin (N = 84), n(%)[b]	Placebo (N = 82), n(%)[b]	*P* value[c]
Patients with at least one TEAE	66 (78.6)	64 (78.0)	0.935
Preferred term			
Electrocardiogram QT prolonged	19 (22.6)	19 (23.2)	0.933
Lymphopenia	14 (16.7)	11 (13.4)	0.558
Fibrin D-dimer increased	11 (13.1)	11 (13.4)	0.952
Respiratory failure	11 (13.1)	9 (11.0)	0.675
Lymphocyte count decreased	12 (14.3)	6 (7.3)	0.149
Acute respiratory distress syndrome	7 (8.3)	9 (11.0)	0.564
Alanine aminotransferase increased	7 (8.3)	9 (11.0)	0.564
Aspartate aminotransferase increased	6 (7.1)	7 (8.5)	0.738
Pulmonary embolism	4 (4.8)	8 (9.8)	0.245
Acute kidney injury	4 (4.8)	7 (8.5)	0.367
Hyperglycaemia	5 (6.0)	5 (6.1)	0.969
Hypertension	4 (4.8)	5 (6.1)	0.745
Anaemia	3 (3.6)	5 (6.1)	0.493
Multiple organ dysfunction syndrome	5 (6.0)	3 (3.7)	0.720
Hypoalbuminaemia	5 (6.0)	1 (1.2)	0.210

MedDRA Medical dictionary for regulatory activities, *n* number of patients, *SAF* safety analysis set, *TEAE* treatment-emergent adverse event

[a] TEAEs affecting > 5% (> 4 patients) of either of the treatment groups in the overall analysis

[b] Percentages are based on the number of patients in the SAF by treatment group

[c] *P* values were calculated post hoc using the Chi-square test whenever applicable, or Fisher's exact test alternatively

post hoc analyses were performed. A relevant proportion of the ESsCOVID trial population was found to have baseline levels of CRP, D-dimer and/or platelets in line with those reported in the literature to be related to progression to critical disease and associated with mortality. The hypothesis was that trimodulin cannot prevent deterioration or mortality in patients with advanced systemic inflammation (Additional file 2: Fig. S2) but may be of benefit earlier in the disease course. Therefore a subpopulation of patients (early systemic inflammation subgroup) was identified to test this hypothesis. These patients had elevated CRP, elevated D-dimer and low platelets, but had not yet reached thresholds indicating advanced inflammation (defined by CRP > 150 mg/L, and/or D-dimer ≥ 3 mg/L and/or platelet counts < 130×10^9/L at baseline).

A total of 47 patients in the trimodulin group and 49 patients in the placebo group met these criteria for early systemic inflammation. Demographics and baseline characteristics of the subgroup were in line with those of the overall population and were balanced between the two treatment groups (Additional file 2: Table S5). However, in the trimodulin group a smaller proportion of patients had a history of heart disease, a smaller proportion were aged > 60 years (although median age was comparable [59.0 years in the trimodulin group vs 61.0 in the placebo group]) and a higher proportion were male. A total of 40 (85.1%) patients in the trimodulin group and 35 (71.4%) in the placebo group received corticosteroids (not shown). In addition to CRP, D-dimer and platelet counts, baseline levels of other inflammatory markers among patients in this subgroup were generally consistent with early systemic inflammation (Additional file 2: Table S6).

Post hoc efficacy analysis

In the subgroup with early systemic inflammation analysed in the FAS, the deterioration/mortality rate was 21.3% (10/47) in the trimodulin group and 36.7% (18/49) in the placebo group (Table 4), a difference of 15.5 percentage points (95% CI: − 4.46, 34.78; $P = 0.096$) in favour of trimodulin (Fig. 3A). A treatment difference was seen for both the clinical deterioration and mortality components, and probability of event-free survival was higher with trimodulin ($P = 0.017$) (Fig. 3B).

For analysed secondary efficacy endpoints, no significant difference was observed in the early systemic inflammation subgroup (FAS) with respect to the mean number of days on IMV, the mean number of ICU-free days, or the proportion of patients recovered on Day 29 (Table 4). Results of primary and secondary efficacy endpoints were aligned but were more pronounced in favour of trimodulin in the PPS (Table 4).

A stacked probability analysis demonstrated that, compared with placebo, more patients in the trimodulin

Table 4 Primary and secondary efficacy endpoints (early systemic inflammation subgroup [FAS and PPS])

	Early systemic inflammation subgroup		
	Trimodulin	**Placebo**	***P* value**
FAS	*N* = 47	*N* = 49	
Primary composite endpoint			0.096
Total, n (%)[a]	10 (21.3)	18 (36.7)	
95% CI	9.58, 32.98	23.24, 50.23	
Deterioration, n (%)	3 (6.4)	8 (16.3)	
Mortality, n (%)	7 (14.9)	10 (20.4)	
Days of IMV			0.197
Mean ± SD	4.3 ± 9.8	7.1 ± 11.0	
Median [Q1, Q3]	0 [0, 0]	0 [0, 21]	
ICU-free days			0.429
Mean ± SD	18.7 ± 11.3	16.9 ± 10.9	
Median [Q1, Q3]	23 [6, 29]	21 [7, 26]	
Proportion of patients that recovered (score ≤ 2) on Day 29			0.326
n (%)[a]	35 (74.5)	32 (65.3)	
95% CI	62.04, 86.96	51.97, 78.63	
PPS	*N* = 37	*N* = 41	
Primary composite endpoint			0.025
n (%)[a]	6 (16.2)	16 (39.0)	
95% CI	4.34, 28.09	24.09, 53.96	
Days of IMV			0.087
Mean ± SD	3.7 ± 9.6	7.8 ± 11.3	
Median [Q1, Q3]	0 [0, 0]	0 [0, 23]	
ICU-free days			0.130
Mean ± SD	20 ± 10.9	16.2 ± 11.0	
Median [Q1, Q3]	23 [17, 29]	20 [3, 25]	
Proportion of patients that recovered (score ≤ 2) on Day 29			0.083
n (%)[a]	30 (81.1)	26 (63.4)	
95% CI	68.48, 93.72	48.66, 78.14	

CI confidence interval, *FAS* full analysis set, *ICU* intensive care unit, *IMV* invasive mechanical ventilation, *n* number of patients, *PPS* per-protocol set, *Q* quartile, *SD* standard deviation

[a] Percentages are based on the number of patients in the early systemic inflammation FAS or PPS analysis sets by treatment group

group were discharged and fewer patients were in hospital at Day 29. Furthermore, fewer patients deteriorated or died, most markedly between Days 5 and 10, with trimodulin compared with placebo (Additional file 2: Fig. S3). The differences between trimodulin and placebo were more pronounced in the PPS compared with the FAS.

The impact of additional parameters (e.g. corticosteroid use, duration of hospitalisation ≤ 10 days before treatment start, HFO at treatment start) on the composite primary endpoint in the different subgroups is shown as a forest plot (Additional file 2: Fig. S4). Results for all subgroups confirm the impact of trimodulin in the 'early' FAS and PPS populations.

Post hoc safety analysis

TEAEs occurred numerically more frequently in patients with early systemic inflammation receiving placebo (83.7%) than in those receiving trimodulin (68.1%) (Additional file 2: Table S7).

Discussion

To prepare for future pandemics, efforts should still be made to identify and understand the mechanisms of action of new effective treatments that target symptoms in hospitalised COVID-19 patients. This includes identifying the characteristics of patients who responded or did not respond to a specific treatment. In the ESsCOVID phase II clinical trial, there was no difference between trimodulin and placebo for the proportion of patients meeting the composite primary endpoint of clinical deterioration and 28-day all-cause mortality and no differences with respect to pre-planned secondary endpoints. However, rates of deterioration and mortality were markedly lower with trimodulin in a subgroup of patients with early systemic inflammation in which patients were excluded with high CRP (> 150 mg/L) and/or D-dimer (≥ 3 mg/L) and/or low platelet counts ($< 130 \times 10^9$/L) at baseline.

The ESsCOVID patient cohort received oxygen supplementation and showed signs of inflammation indicated by elevated CRP and the rationale for investigating trimodulin in these patients was based on its postulated modes of action, including the modulation of dysregulated inflammatory processes to prevent further tissue damage [32, 33]. Trimodulin has multiple immunomodulatory activities through IgM, IgA and IgG, including balancing the complement system, modulating cytokine secretion and modulating monocyte and lymphocyte responses [13, 16–18, 32, 33]. By targeting multiple pathways, trimodulin may have broader host – immune supporting functions against COVID-19 than currently approved treatments targeting a single deregulated pathway. This is supported by preclinical studies demonstrating stronger immune modulation on immune cells and complement by trimodulin compared with IVIg, suggesting that the interplay between IgM, IgA, IgG and the immune system may promote more extensive beneficial effects in the body [13, 17, 18].

In addition, trimodulin could be beneficial in patients with COVID-19 who develop secondary infections. Previous studies in severe bacterial infectious diseases have shown that targeting the pathogen with antibiotics alone

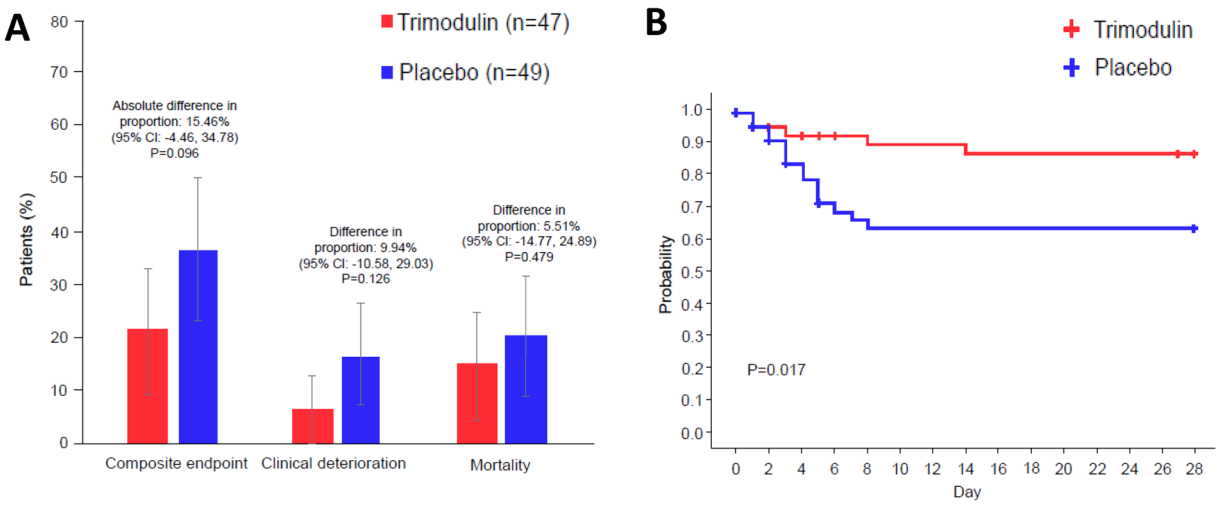

Fig. 3 Impact on clinical deterioration and 28-day mortality (early systemic inflammation subgroup [FAS]). Post hoc analysis of the primary endpoint in the subgroup of patients with early systemic inflammation who had not yet reached the advanced-stage thresholds (C-reactive protein > 150 mg/L and/or D-dimer ≥ 3 mg/L and/or platelet count < 130×10^9/L). **A** Bar graph represents the proportion of patients that clinically deteriorated (between Days 6 and 29) plus those that died (between Days 1 and 29) and the individual components of this endpoint. *P* values calculated by chi-square test. Error bars denote 95% CI. **B** Kaplan–Meier plot showing the probability of survival with an event (defined as deterioration or mortality between Days 1 and 29). *P* value was calculated by log-rank test. *CI* confidence interval, *FAS* full analysis set, *n* number of patients

is not always sufficient (particularly in the case of multi-drug resistant germs or immune compromised patients) and that immunoglobulins provide an additive effect [34–38]. Thus, the additional targeting of pathogens with the IgM/IgA-enriched Ig preparation trimodulin may improve outcomes in patients with such infections [22, 39–41].

As discussed above, identifying which patients did not benefit, and understanding why, is important for further development of trimodulin and to identify new effective treatments. In this trial, COVID-19 was largely defined as 'severe' based on need for oxygen supplementation via NIV or HFO. The aim was to exclude patients in whom infection- and inflammation-related lung damage had progressed too far. Based on its modes of action, trimodulin may prevent tissue damage but is not expected to be of benefit if disease is too far advanced. It was assumed that such an advanced disease stage would primarily apply to patients already requiring IMV. However, despite exclusion of patients on IMV, approximately one-third of patients had advanced systemic inflammation at baseline (CRP > 150 mg/L, and/or D-dimer ≥ 3 mg/L, and/or platelet count < 130×10^9/L) and elevated levels of other immunological parameters (e.g. ferritin, interleukin [IL]-6 and IL-10). The neutrophil to lymphocyte ratio (NLR) was high, consistent with that shown previously to be associated with poor outcomes in COVID-19 patients [42–47]. Patients were thus likely to have progressed beyond the stage of disease where Igs could be expected to have a positive effect. This could indicate that systemic processes like inflammation, vasculitis and coagulopathy had progressed, although patients were not (yet) receiving IMV (Additional file 2: Fig. S2).

Despite lack of efficacy in the overall population, the overall safety profile of trimodulin in this trial was good and consistent with the previously known potential and identified risks of trimodulin in other trials [22] and with other IVIgs, as reported in the summaries of product characteristics. It is interesting to note the higher incidence of pulmonary embolism and acute kidney injury in patients treated with placebo vs trimodulin, given the vigilance around these effects in patients treated with Igs [48]. The development of lymphopenia in both groups was not surprising and can be explained by the underlying COVID-19 infection, presence of concomitant diseases, or by the use of certain comedications. Rates were not significantly different between groups and were not considered by the investigators to be treatment related. All events (except one moderate event in the placebo group) were mild in severity. The degree of lymphopenia has previously been shown to correlate with clinical severity of COVID-19 [49, 50]. In line with this, in the present study, fewer patients (12.5% [12/96]) in the early systemic inflammation group than in the more advanced inflammation group (18.6% [13/70]) had lymphopenia.

The good safety profile, together with the observation that a large proportion of patients were already in an advanced disease stage, provided the rationale for

the post hoc analysis. The observed reduction in rates of deterioration/mortality is in accordance with data from studies with another IgM/IgA-enriched preparation, Pentaglobin (12% IgM, 12% IgA and 76% IgG), in patients with severe COVID-19 [51–53]. For example, in a retrospective cohort study in severe and critically ill COVID-19 patients receiving ≥15 g Pentaglobin for at least 3 days, a subgroup of less advanced patients, not yet receiving IMV, showed most benefit from this treatment [53]. Although data regarding use of IVIg in COVID-19 have been controversial, this has aided identification of the critical parameters for IVIg treatment in COVID-19: timing (selecting disease stage) and dose. From the different analyses it became increasingly clear that patients benefited most if treatment was started early, before IMV, and a high dose was administered [54–59]. One meta-analysis performed in non-severe, severe, and critical subgroups based on WHO definitions as used in our trial, have supported the idea that the efficacy of IVIg seems to be associated with the severity of COVID-19 [60]. However, this result was not confirmed in other more recent meta-analyses including more studies [61, 62], suggesting that the dose and type of Ig may well play a role.

Thus, if administered in a timely manner, trimodulin may interfere with several pathological processes that could otherwise lead to respiratory failure, sepsis, multi-organ failure and death. The lower rate of TEAEs observed with trimodulin compared with placebo in patients with early systemic inflammation seems to support this idea. The higher rate of TEAEs observed in the placebo group could largely be the result of disease progression or respiratory sequelae, which was prevented in patients receiving trimodulin.

This trial had some limitations. Firstly, the inflammatory markers defining early systemic inflammation and their corresponding cut-off levels in the post hoc analysis were not pre-specified in the clinical trial protocol, and measurements were not conducted in a central laboratory. Measurement of D-dimer is known to differ between institutions [63] and this could have led to differences in designating patients as having early systemic inflammation, although deterioration/mortality rates in the early systemic inflammation subgroup did not differ much if a threshold of 2, 3 or 4 mg/L D-dimer was used. Secondly, SoC for severe COVID-19 differed between participating sites in the various countries. Since SoC was required to be in line with local guidelines and recommendations, and guidelines changed as the therapeutic landscape for the management of COVID-19 evolved, patients received a range of different therapeutic agents throughout the trial (between October 2020 and June 2021). These medications could have had different effects on patient outcomes and thus may have had an impact on the outcome of this trial. Nevertheless, the aim of the trial was to investigate the use of trimodulin as an adjunct to SoC, and as SoC also differs between countries in routine practice, these results are a close representation of the real-world situation.

Conclusions

In this trial, treatment with trimodulin plus SoC did not result in a significantly lower rate of deterioration/mortality compared with placebo plus SoC in the overall population of patients with severe COVID-19 receiving NIV or HFO. However, the favourable effects observed for trimodulin in a subgroup of hospitalised patients with early systemic inflammation warrant further investigation. Indeed, these findings have informed the design of the ongoing phase III trial of trimodulin in patients with community-acquired pneumonia including COVID-19 pneumonia (TRICOVID trial, NCT05531149). Whereas trimodulin used in this trial was prepared from healthy donors with no exposure to SARS-CoV-2, batches for the phase III trial were developed from donors with an increased anti-SARS-CoV-2 titre. It would therefore be reasonable to predict that treatment with trimodulin would result in lower rates of clinical deterioration/mortality than reported in the current study due to additional anti-SARS-CoV-2 activity. If corroborated, targeted therapy with trimodulin for hospitalised COVID-19 patients based on defined thresholds for markers of inflammation and coagulation may offer a new treatment option.

Abbreviations

AE	Adverse event
ARDS	Acute respiratory distress syndrome
CAP	Community-acquired pneumonia
CI	Confidence interval
COVID-19	Coronavirus disease 2019
CRP	C-reactive protein
ECMO	Extra corporeal membrane oxygenation
ESsCOVID	Escape from severe COVID-19
FAS	Full analysis set
HFO	High-flow oxygen
ICU	Intensive care unit
IL	Interleukin
IMV	Invasive mechanical ventilation
Ig	Immunoglobulin
IQR	Interquartile range
IVIg	Intravenous immunoglobulin G preparation
MedDRA	Medical Dictionary for Regulatory Activities
N/n	Number of patients
NLR	Neutrophil to lymphocyte ratio
NIV	Non-invasive ventilation
OR	Odds ratio
PaO_2/FiO_2	Arterial oxygen partial pressure/fractional inspired oxygen
PD	Pharmacodynamics
PK	Pharmacokinetics
PPS	Per-protocol set
Q	Quartile
SAF	Safety analysis set
SARS-CoV-2	Severe acute respiratory syndrome coronavirus type 2
sCAP	Severe community-acquired pneumonia
SD	Standard deviation

SoC	Standard of care
SpO_2	Blood oxygen saturation
TEEs	Thromboembolic events
TEAEs	Treatment-emergent adverse events
TNF	Tumour necrosis factor
ULN	Upper limit of the normal
WHO	World Health Organization

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s40001-024-02008-x.

Additional file 1. Supplementary methods

Additional file 2. Supplementary results

Acknowledgements
The authors would like to thank Ulrike Wippermann (Biotest) for critical reading of the manuscript, Ksenia Jakubczyk (Biotest) for data analysis and quality control and Lijie Shi for selected extraction of data from the database. The authors thank all patients involved in this study as well as clinical colleagues from Spain (Marisa di Natale, Maria Alejandra Mejia, Alba Alarcon, Marian Escobar [Hospital General Universitario Gregorio Marañon, Madrid]), Brazil, France (Guillaume Voiriot, MD, PhD and Cyrielle Desnos, MD [Assistance Publique-Hôpitaux de Paris, Sorbonne Université, DMU APPROCHES, Service de Médecine Intensive Réanimation, Hôpital Tenon, Paris]) and Russia (Elena Nurmukhametova [Infectious Clinical Hospital, Moscow], Grigory Rodoman [City Clinical Hospital, Moscow], Natalia Tsareva, MD, PhD, and Andrey Yaroshetskiy, MD, PhD [Pulmonology Department, Sechenov First Moscow State Medical University]). We also thank SGS Laboratory, Munich, Germany for sample analysis.

Author contributions
CCH, TH, PL, IB, JS, AS, MR, SW and AW-D contributed to the conceptualisation, methodology and formal analysis of the trial. Data were collected by AA, VCA, MR, MSF, LAH, GT, G-FT, IG, DP, JC, RP, CMBS, SA, MF and AT. CCH, TH, PL, IB, JS, AS, MR, SW, AW-D and AT prepared the first draft of the manuscript. All authors commented on subsequent versions of the manuscript. All authors read and approved the final manuscript.

Funding
The study was funded by Biotest AG.

Availability of data and materials
The data supporting the conclusions of this article are available in the European clinical trials repository, EudraCT, via link: EudraCT Number 2020-002345-42—Clinical trial results—EU Clinical Trials Register.

Declarations

Ethics approval and consent to participate
The trial was conducted according to the International Council for Harmonisation, Good Clinical Practice standards and the Declaration of Helsinki, and with independent ethics committee approval. Written informed consent from the patient, or legally authorised representative, was obtained in compliance with all local legal requirements.

Consent for publication
Not applicable.

Competing interests
MSF reports grant support from BioMérieux, speaker fees from BioMérieux and Fisher & Paykel, and consultancy fees from Pfizer (all outside the submitted work); J-FT reports grant support from MSD, Pfizer and Thermo Fisher, consultancy fees from Becton Dickinson, Gilead Sciences, MSD, and Pfizer, speaker fees from MSD, Pfizer and Shionogi, and Chairmanship of the Critical Care section of the European Congress of Clinical Microbiology and Infectious Diseases; JC reports grant support from Biotest and Grifols, and consultancy fees and speaker fees from LFB; SA reports consultancy fees from AstraZeneca and Boehringer Ingelheim, speaker fees from AstraZeneca, Boehringer Ingelheim, Chiesi, Novartis and Sandoz, and support for meeting attendance from AstraZeneca and Boehringer Ingelheim (all outside the submitted work); AT reports consultancy fees and speaker fees from Biotest AG, Janssen, MSD and Pfizer. CCH, TH, PL, IB, AS, MR, and SW are employees of Biotest AG. AW-D was an employee of Biotest AG during trial conduct and the writing of this manuscript. JS is an employee of Grifols SA, as well as an executive board member of Biotest AG, which has received a German Government Grant (Bundesministerium für Bildung und Forschung [BMBF]). AA, VCA, MR, LAH, GT, MF, IG, DP, and RP have no competing interests to declare.

Author details
[1]City Hospital, St Petersburg, Russia. [2]Science Valley Research Institute, São Paulo, Brazil. [3]City Clinical Hospital, Moscow, Russia. [4]Assistance Publique-Hôpitaux de Paris, Service de Médecine Intensive Réanimation, Hôpital Tenon, and DMU APPROCHES, Sorbonne Université, Paris, France. [5]Instituto Do Coração InCor, Hospital das Clínicas HCFMUSP, Faculdade de Medicina, Universidade de São Paulo, São Paulo, Brazil. [6]CHU Saint-Etienne, Saint-Priest-en-Jarez, France. [7]Medical and Infectious Diseases ICU (M12) APHP, Hôpital Bichat—Claude Bernard, Paris, France. [8]City Clinical Hospital #15, Moscow, Russia. [9]City Clinical Hospital #40, Moscow, Russia. [10]Hospital General Universitario Gregorio Marañon, Madrid, Spain. [11]Pesquisare, Santo André, Brazil. [12]Santa Casa de Misericórdia de Porto Alegre, Porto Alegre, Brazil. [13]First Moscow State Medical University, Moscow, Russia. [14]Hospital Clinic of Barcelona, IDIBAPS, CibeRes (CB06/06/0028) University of Barcelona, Barcelona, Spain. [15]Biotest AG, Dreieich, Germany. [16]Grifols SA, Barcelona, Spain. [17]Respiratory and Intensive Care Unit, Hospital Clinic of Barcelona, IDIBAPS, CibeRes (CB06/06/0028), University of Barcelona, Barcelona, Spain.

Received: 15 April 2024 Accepted: 1 August 2024
Published online: 13 August 2024

References

1. Camporota L, Cronin JN, Busana M, Gattinoni L, Formenti F. Pathophysiology of coronavirus-19 disease acute lung injury. Curr Opin Crit Care. 2022;28:9–16.
2. WHO. Report of the WHO-China joint mission on coronavirus disease. 2019. https://www.who.int/docs/default-source/coronaviruse/who-china-joint-mission-on-covid-19-final-report.pdf. Accessed 29 Jan 2024.
3. National Institutes of Health (NIH). COVID-19 treatment guidelines panel. coronavirus disease 2019 (COVID-19) treatment guidelines. https://www.covid19treatmentguidelines.nih.gov/. Accessed 29 Jan 2024.
4. Ruan Q, Yang K, Wang W, Jiang L, Song J. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. Intensiv Care Med. 2020;46:846–8.
5. Velavan TP, Meyer CG. Mild versus severe COVID-19: laboratory markers. Int J Infect Dis. 2020;95:304–7.
6. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, Xiang J, Wang Y, Song B, Gu X, Guan L, Wei Y, Li H, Wu X, Xu J, Tu S, Zhang Y, Chen H, Cao B. 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.
7. Zhu Y, Zhang J, Li Y, Liu F, Zhou Q, Peng Z. Association between thrombocytopenia and 180-day prognosis of COVID-19 patients in intensive care units: a two-center observational study. PLoS ONE. 2021;16: e0248671.
8. Tomerak S, Khan S, Almasri M, Hussein R, Abdelati A, Aly A, Salameh MA, Aldien AS, Naveed H, Elshazly MB, Zakaria D. Systemic inflammation in COVID-19 patients may induce various types of venous and arterial thrombosis: a systematic review. Scand J Immunol. 2021;94(5): e13097.
9. Conway EM, Mackman N, Warren RQ, Wolberg AS, Mosnier LO, Campbell RA, Gralinski LE, Rondina MT, van de Veerdonk FL, Hoffmeister KM, Griffin JH, Nugent D, Moon K, Morrissey JH. Understanding COVID-19-associated coagulopathy. Nat Rev Immunol. 2022;22(10):639–49.
10. Yuan Y, Jiao B, Qu L, Yang D, Liu R. The development of COVID-19 treatment. Front Immunol. 2023;14:1125246.
11. Li G, Hilgenfeld R, Whitley R, De Clercq E. Therapeutic strategies for COVID-19: progress and lessons learned. Nat Rev Drug Discov. 2023;22:449–75.

12. Paules CI, Wang J, Tomashek KM, Bonnett T, Singh K, Marconi VC, Davey RT Jr, Lye DC, Dodd LE, Yang OO, Benson CA, Deye GA, Doernberg SB, Hynes NA, Grossberg R, Wolfe CR, Nayak SU, Short WR, Voell J, Potter GE, Rapaka RR. A risk profile using simple hematologic parameters to assess benefits from baricitinib in patients hospitalized with COVID-19: a post hoc analysis of the adaptive COVID-19 Treatment trial-2. Ann Intern Med. 2024. https://doi.org/10.7326/M23-2593.
13. Schmidt C, Weißmüller S, Bohländer F, Germer M, König M, Staus A, Wartenberg-Demand A, Heinz CC, Schüttrumpf J. The dual role of a polyvalent IgM/IgA-enriched immunoglobulin preparation in activating and inhibiting the complement system. Biomedicines. 2021;9:817.
14. Rieben R, Roos A, Muizert Y, Tinguely C, Gerritsen AF, Daha MR. Immunoglobulin M-enriched human intravenous immunoglobulin prevents complement activation in vitro and in vivo in a rat model of acute inflammation. Blood. 1999;93:942–51.
15. Roos A, Rieben R, Faber-Krol MC, Daha MR. IgM-enriched human intravenous immunoglobulin strongly inhibits complement-dependent porcine cell cytotoxicity mediated by human xenoreactive antibodies. Xenotransplantation. 2003;10:596–605.
16. Duerr C, Bacher A, de Martin A, Sachet M, Sadeghi K, Baumann S, Heinz C, Spittler A. The novel polyclonal Ab preparation trimodulin attenuates ex vivo endotoxin-induced immune reactions in early hyperinflammation. Innate Immun. 2019;25:374–88.
17. Bohländer F, Riehl D, Weißmüller S, Gutscher M, Schüttrumpf J, Faust S. Immunomodulation: immunoglobulin preparations suppress hyperinflammation in a COVID-19 model via FcγRIIA and FcαRI. Front Immunol. 2021;12: 700429.
18. Bohländer F, Weißmüller S, Riehl D, Gutscher M, Schüttrumpf J, Faust S. The functional role of IgA in the IgM/IgA-enriched immunoglobulin preparation trimodulin. Biomedicines. 2021;9:1828.
19. Kaveri SV, Silverman GJ, Bayry J. Natural IgM in immune equilibrium and harnessing their therapeutic potential. J Immunol. 2012;188:939–45.
20. Notley CA, Brown MA, Wright GP, Ehrenstein MR. Natural IgM is required for suppression of inflammatory arthritis by apoptotic cells. J Immunol. 2011;186:4967–72.
21. Obermayer G, Afonyushkin T, Göderle L, Puhm F, Schrottmaier W, Taqi S, Schwameis M, Ay C, Pabinger I, Jilma B, Assinger A, Mackman N, Binder CJ. Natural IgM antibodies inhibit microvesicle-driven coagulation and thrombosis. Blood. 2021;137:1406–15.
22. Welte T, Dellinger RP, Ebelt H, Ferrer M, Opal SM, Singer M, et al. Efficacy and safety of trimodulin, a novel polyclonal antibody preparation, in patients with severe community-acquired pneumonia: a randomized, placebo-controlled, double-blind, multicenter, phase II trial (CIGMA study). Intensive Care Med. 2018;44:438–48.
23. Guan W, Ni Z, Hu Y, Liang W, Ou C, He J, et al. Clinical characteristics of coronavirus disease 2019 in China. New Engl J Med. 2020;382:1708–20.
24. Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72 314 cases from the Chinese center for disease control and prevention. JAMA. 2020;323:1239–42.
25. Gold JAW, Wong KK, Szablewski CM, Patel PR, Rossow J, da Silva J, et al. Characteristics and clinical outcomes of adult patients hospitalized with COVID-19 — Georgia, March 2020. MMWR Morb Mortal Wkly Rep. 2020;69:545–50.
26. Li L, Zhang W, Hu Y, Tong X, Zheng S, Yang J, et al. Effect of convalescent plasma therapy on time to clinical improvement in patients with severe and life-threatening COVID-19: a randomized clinical trial. JAMA. 2020;324:1–11.
27. MedDRA version 17.1. https://www.meddra.org/how-to-use/support-documentation/english. Accessed 9 Jan 2024.
28. Velavan TP, Kuk S, Linh LTK, Calle CL, Lalremruata A, Pallerla SR, et al. Longitudinal monitoring of laboratory markers characterizes hospitalized and ambulatory COVID-19 patients. Sci Rep. 2021;11:14471.
29. Luo X, Zhou W, Yan X, Guo T, Wang B, Xia H, Ye L, Xiong J, Jiang Z, Liu Y, Zhang B, Yang W. Prognostic value of C-reactive protein in patients with coronavirus 2019. Clin Infect Dis. 2020;71:2174–9.
30. Pan F, Yang L, Li Y, Liang B, Li L, Ye T, et al. Factors associated with death outcome in patients with severe coronavirus disease-19 (COVID-19): a case-control study. Int J Med Sci. 2020;17:1281–92.
31. Dati F, Schumann G, Thomas L, Aguzzi F, Baudner S, Bienvenu J, Blaabjerg O, Blirup-Jensen S, Carlström A, Petersen PH, Johnson AM, Milford-Ward A, Ritchie RF, Svendsen PJ, Whicher J. Consensus of a group of professional societies and diagnostic companies on guidelines for interim reference ranges for 14 proteins in serum based on the standardization against the IFCC/BCR/CAP reference material (CRM 470). Eur J Clin Chem Clin Biochem. 1996;34:517–20.
32. Schmidt C, Weißmüller S, Heinz CC. Multifaceted tissue protective functions of polyvalent immunoglobulin preparations in severe infections - interactions with neutrophils, complement, and coagulation pathways. Biomedicines. 2023;11:3022.
33. Singer M, Torres A, Heinz CC, Weißmüller S, Staus A, Kistner S, Jakubczyk K, Häder T, Langohr P, Wartenberg-Demand A, Schüttrumpf J, Vincent J-L, Welte T. The immunomodulating activity of trimodulin (polyvalent IgM, IgA, IgG solution): a post hoc analysis of the phase II CIGMA trial. Crit Care. 2023;27:436.
34. Busani S, Serafini G, Mantovani E, Venturelli C, Giannella M, Viale P, et al. Mortality in patients with septic shock by multidrug resistant bacteria. J Intensive Care Med. 2019;34:48–54.
35. Giamarellos-Bourboulis EJ, Tziolos N, Routsi C, Katsenos C, Tsangaris I, Pneumatikos I, et al. Improving outcomes of severe infections by multidrug-resistant pathogens with polyclonal IgM-enriched immunoglobulins. Clin Microbiol Infect. 2016;22:499–506.
36. Busani S, Roat E, Serafini G, Mantovani E, Biagioni E, Girardis M. The role of adjunctive therapies in septic shock by Gram negative MDR/XDR infections. Can J Infect Dis Med Microbiol. 2017;2017:2808203.
37. Robak OH, Heimesaat MM, Kruglov AA, Prepens S, Ninnemann J, Gutbier B, et al. Antibiotic treatment-induced secondary IgA deficiency enhances susceptibility to *Pseudomonas aeruginosa* Pneumonia. J Clin Invest. 2018;128:3535–45.
38. Matsuo H, Itoh H, Kitamura N, Kamikubo Y, Higuchi T, Shiga S, et al. Intravenous immunoglobulin enhances the killing activity and autophagy of neutrophils isolated from immunocompromised patients against multidrug-resistant bacteria. Biochem Biophys Res Commun. 2015;464:94–9.
39. Rodriguez A, Rello J, Neira J, Maskin B, Ceraso D, Vasta L, Palizas F. Effects of high-dose of intravenous immunoglobulin and antibiotics on survival for severe sepsis undergoing surgery. Shock. 2005;23:298–304.
40. Nierhaus A, Berlot G, Kindgen-Milles D, Müller E, Girardis M. Best-practice IgM- and IgA-enriched immunoglobulin use in patients with sepsis. Ann Intensive Care. 2020;10:132.
41. Jarczak D, Kluge S, Nierhaus A. Use of intravenous immunoglobulins in sepsis therapy—a clinical view. Int J Mol Sci. 2020;21:5543.
42. Dahan S, Segal G, Katz I, Hellou T, Tietel M, Bryk G, Amital H, Shoenfeld Y, Dagan A. Ferritin as a marker of severity in COVID-19 patients: a fatal correlation. Isr Med Assoc J. 2020;22:494–500.
43. Kaushal K, Kaur H, Sarma P, Bhattacharyya A, Sharma DJ, Prajapat M, Pathak M, Kothari A, Kumar S, Rana S, Kaur M, Prakash A, Mirza AA, Panda PK, Vivekanandan S, Omar BJ, Medhi B, Naithani M. Serum ferritin as a predictive biomarker in COVID-19. A systematic review, meta-analysis and meta-regression analysis. J Crit Care. 2022;67:172–81.
44. Han H, Ma Q, Li C, Liu R, Zhao L, Wang W, Zhang P, Liu X, Gao G, Liu F, Jiang Y, Cheng X, Zhu C, Xia Y. Profiling serum cytokines in COVID-19 patients reveals IL-6 and IL-10 are disease severity predictors. Emerg Microbes Infect. 2020;9:1123–30.
45. Yang L, Liu S, Liu J, Zhang Z, Wan X, Huang B, Chen Y, Zhang Y. COVID-19: immunopathogenesis and immunotherapeutics. Signal Transduct Target Ther. 2020;5:128.
46. Li J, Rong L, Cui R, Feng J, Jin Y, Chen X, Xu R. Dynamic changes in serum IL-6, IL-8, and IL-10 predict the outcome of ICU patients with severe COVID-19. Ann Palliat Med. 2021;10:3706–14.
47. Li Y, Hou H, Diao J, Wang J, Yang H. Neutrophil-to-lymphocyte ratio is independently associated with COVID-19 severity: an updated meta-analysis based on adjusted effect estimates. Int J Lab Hematol. 2021;43:e254–60.
48. Ramirez E, Romero-Garrido JA, Lopez-Granados E, Borobia AM, Perez T, Medrano N, Rueda C, Tong HY, Herrero A, Frías J. Symptomatic thromboembolic events in patients treated with intravenous-immunoglobulins: results from a retrospective cohort study. Thromb Res. 2014;133:1045–51.
49. Lee J, Park SS, Kim TY, Lee DG, Kim DW. Lymphopenia as a biological predictor of outcomes in COVID-19 patients: a nationwide cohort study. Cancers (Basel). 2021;13:471.

50. Qin C, Zhou L, Hu Z, Zhang S, Yang S, Tao Y, et al. Dysregulation of immune response in patients with coronavirus 2019 (COVID-19) in Wuhan, China. Clin Infect Dis. 2020;71:762–8.
51. Corona A, Richini G, Simoncini S, Zangrandi M, Biasini M, Russo G, Pasqua M, Santorsola C, Gregorini C, Giordano C. Treating critically ill patients experiencing SARS-CoV-2 severe infection with Ig-M and Ig-A enriched Ig-G infusion. Antibiotics. 2021;10:930.
52. Tabarsi P, Hashemian SMR, Bauhofer A, Savadkoohi AA, Ghadimi S, Haseli S, Dastan F. IgM-enriched immunoglobulin in COVID-19: case series of 15 severely ill SARS-CoV-2-infected patients. Int Immunopharmacol. 2021;99: 107998.
53. Rahmel T, Kraft F, Haberl H, Achtzehn U, Brandenburger T, Neb H, et al. Intravenous IgM-enriched immunoglobulins in critical COVID-19: a multicentre propensity-weighted cohort study. Crit Care. 2022;26:204.
54. Shao Z, Feng Y, Zhong L, Xie Q, Lei M, Liu Z, et al. Clinical efficacy of intravenous immunoglobulin therapy in critical patients with COVID-19: a multicenter retrospective cohort study. Clin Transl Immunol. 2020;9: e1192.
55. Sakoulas G, Geriak M, Kullar R, Greenwood KL, Habib M, Vyas A, Ghafourian M, Dintyala VNK, Haddad F. Intravenous immunoglobulin plus methylprednisolone mitigate respiratory morbidity in coronavirus disease 2019. Crit Care Explor. 2020;2: e0280.
56. 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;20:786.
57. Mohtadi N, Ghaysouri A, Shirazi S, Ansari S, Shafiee E, Bastani E, Kokhazadeh T, Tavan H. Recovery of severely ill COVID-19 patients by intravenous immunoglobulin (IVIG) treatment: a case series. Virology. 2020;548:1–5.
58. Cao W, Liu X, Hong K, Ma Z, Zhang Y, Lin L, Han Y, Xiong Y, Liu Z, Ruan L, Li T. High-dose intravenous immunoglobulin in severe coronavirus disease 2019: a multicenter retrospective study in China. Front Immunol. 2021;12: 627844.
59. The ITAC (INSIGHT 013) Study group. Hyperimmune immunoglobulin for hospitalised patients with COVID-19 (ITAC): a double-blind, placebo-controlled, phase 3, randomised trial. Lancet. 2022;399:530–40.
60. Xiang H-R, Cheng X, Li Y, Luo W-W, Zhang Q-Z, Peng W-X. Efficacy of IVIG (intravenous immunoglobulin) for corona virus disease 2019 (COVID-19): a meta-analysis. Int Immunopharmacol. 2021;96: 107732.
61. Li MX, Li YF, Xing X, Niu JQ, Yao L, Lu MY, Guo K, Ma MN, Wu XT, Ma N, Li D, Li ZJ, Guan L, Wang XM, Pan B, Shang WR, Ji J, Song ZY, Zhang ZM, Wang YF, Yang KH. Intravenous immunoglobulin for treatment of hospitalized COVID-19 patients: an evidence mapping and meta-analysis. Inflammopharmacology. 2023. https://doi.org/10.1007/s10787-023-01398-4.
62. Marcec R, Dodig VM, Radanovic I, Likic R. Intravenous immunoglobulin (IVIg) therapy in hospitalised adult COVID-19 patients: a systematic review and meta-analysis. Rev Med Virol. 2022;12: e2397.
63. Thachil J, Longstaff C, Favaloro EJ, Lippi G, Urano T, Kim PY. SSC subcommittee on fibrinolysis of the international society on thrombosis and haemostasis the need for accurate D-dimer reporting in COVID-19: communication from the ISTH SSC on fibrinolysis. J Thromb Haemostat. 2020;18:2408–11.

Publisher's Note