Prolonged higher dose methylprednisolone *versus* conventional dexamethasone in COVID-19 pneumonia: a randomised controlled trial (MEDEAS)

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Shareable abstract (@ERSpublications)
Infusive methylprednisolone did not show major advantages over conventional dexamethasone in severe COVID-19 pneumonia, confirming the favourable drug class effect of prolonged, low-dose glucocorticoids postulated by current guidelines https://bit.ly/3zxSwMn

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Abstract

Background Dysregulated systemic inflammation is the primary driver of mortality in severe coronavirus disease 2019 (COVID-19) pneumonia. Current guidelines favour a 7–10-day course of any glucocorticoid equivalent to dexamethasone 6 mg daily. A comparative randomised controlled trial (RCT) with a higher dose and a longer duration of intervention was lacking.

Methods We conducted a multicentre, open-label RCT to investigate methylprednisolone 80 mg as a continuous daily infusion for 8 days followed by slow tapering *versus* dexamethasone 6 mg once daily for up to 10 days in adult patients with COVID-19 pneumonia requiring oxygen or noninvasive respiratory support. The primary outcome was reduction in 28-day mortality. Secondary outcomes were mechanical ventilation-free days at 28 days, need for intensive care unit (ICU) referral, length of hospitalisation, need for tracheostomy, and changes in C-reactive protein (CRP) levels, arterial oxygen tension/inspiratory oxygen fraction (P_{aO_2}/F_{IO_2}) ratio and World Health Organization Clinical Progression Scale at days 3, 7 and 14.

Results 677 randomised patients were included. Findings are reported as methylprednisolone (n=337) *versus* dexamethasone (n=340). By day 28, there were no significant differences in mortality (35 (10.4%) *versus* 41 (12.1%); p=0.49) nor in median mechanical ventilation-free days (median (interquartile range (IQR)) 23 (14) *versus* 24 (16) days; p=0.49). ICU referral was necessary in 41 (12.2%) *versus* 45 (13.2%) (p=0.68) and tracheostomy in 8 (2.4%) *versus* 9 (2.6%) (p=0.82). Survivors in the methylprednisolone group required a longer median (IQR) hospitalisation (15 (11) *versus* 14 (11) days; p=0.005) and experienced an improvement in CRP levels, but not in P_{aO_2}/F_{IO_2} ratio, at days 7 and 14. There were no differences in disease progression at the prespecified time-points.

Conclusion Prolonged, higher dose methylprednisolone did not reduce mortality at 28 days compared with conventional dexamethasone in COVID-19 pneumonia.

Introduction

A substantial percentage of coronavirus disease 2019 (COVID-19) cases experience severe pneumonia associated with an acute respiratory decompensation requiring supplemental oxygen and mechanical ventilation. The overall fatality rate approximates 40% in patients undergoing invasive mechanical ventilation (IMV) [1]. Glucocorticoid treatment is the intervention associated with the highest mortality reduction in COVID-19 pneumonia [2]. The RECOVERY randomised controlled trial (RCT) first demonstrated the efficacy of dexamethasone once daily for up to 10 days, with a greater impact in those receiving mechanical ventilation (−36%) than oxygen alone (−18%) [1]. Several other RCTs confirmed the rationale for the use of glucocorticoids in severe COVID-19 pneumonia [3]. Current guidelines favour a 7–10-day course of any glucocorticoid equivalent to dexamethasone 6 mg daily (*e.g.* hydrocortisone 50 mg every 8 h) in severe COVID-19 [4, 5]. However, the lack of detailed indications about a preferable glucocorticoid molecule and administration schedule led to heterogeneous treatment protocols and misinterpretation of findings [3].

Glucocorticoids exert their effects binding to the glucocorticoid receptor α (GRα), but different compounds have different pharmacological properties [6]. Clinical efficacy in acute respiratory distress syndrome depends on the magnitude and duration of exposure to glucocorticoid, including genomic and nongenomic effects [7, 8]. Theoretically, optimal results are achievable with an initial bolus to reach close-to-maximal GRα saturation, followed by a prolonged low-dose infusion to maintain high levels of response and a dose-tapering period to favour recovery of the physiological hypothalamic–pituitary–adrenal axis [8]. According to these principles, the 2017 Society of Critical Care Medicine/European Society of Intensive Care Medicine consensus for the diagnosis and management of critical illness-related corticosteroid insufficiency proposed a protocol involving a bolus followed by a continuous infusion of 80 mg methylprednisolone [9]. The same protocol has proven safe and effective in reducing both mortality and duration of IMV among patients affected by severe COVID-19 pneumonia [10]. At present, however, there is poor evidence of the superiority of one glucocorticoid protocol. Indeed, two small RCTs reported better outcomes with methylprednisolone compared with dexamethasone in COVID-19, but their results are poorly generalisable [11, 12]. Furthermore, molecular target-based bioinformatic studies supported the theoretical advantage of methylprednisolone [13].

The lack of comparative studies on prolonged low-dose glucocorticoids prompted us to perform a RCT comparing methylprednisolone 80 mg bolus followed by 80 mg continuous daily infusion for 8 days followed by slow tapering *versus* dexamethasone 6 mg once daily for up to 10 days in COVID-19 pneumonia requiring oxygen or noninvasive respiratory support.

Methods

Trial design, setting and participants

This is a multicentre, open-label RCT (two parallel arms, allocation ratio 1:1) conducted in 26 Italian centres including internal medicine units, infectious diseases units, emergency medicine departments and respiratory high-dependency units. The study was registered at ClinicalTrials.gov (NCT04636671), and approved by the National Ethics Committee (2020-006054-43) and the Italian Medicines Agency (AIFA). The protocol and trial conduct complied with the Declaration of Helsinki, International Council for Harmonisation E6 Guideline for Good Clinical Practice and European regulations.

The inclusion criteria were: 1) able to understand and sign the written informed consent; 2) real-time PCR-positive for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) on at least one upper respiratory swab or bronchoalveolar lavage; 3) arterial oxygen tension (P_{aO_2}) ⩽60 mmHg or peripheral oxygen saturation (S_{pO_2}) ⩽90%, or on high-flow nasal cannula (HFNC), continuous positive airway pressure (CPAP) or noninvasive ventilation (NIV); and 4) age ⩾18 years. The exclusion criteria were: 1) requiring IMV; 2) heart failure as the main cause of acute respiratory failure; 3) on long-term oxygen or home mechanical ventilation; 4) decompensated liver cirrhosis; 5) immunosuppression (*i.e.* cancer under treatment, post-organ transplantation, HIV-positive or on immunosuppressant therapy); 6) on chronic steroid therapy or other immunomodulant therapy; 7) dialysis dependence; 8) neurodegenerative conditions; 9) dementia or decompensated psychiatric disorder; 10) quadriplegia/hemiplegia or quadriparesis/hemiparesis; 11) do-not-resuscitate order; 12) use of any other investigational drug for COVID-19 treatment; or 13) any other condition that in the opinion of the investigator might significantly impact with the patient's capability to comply with the protocol intervention.

Interventions

All patients meeting the entrance criteria were randomised to one of the following treatment protocols. Arm 1 (methylprednisolone): on day 1, a loading dose of methylprednisolone 80 mg was administered

intravenously in 30 min, followed by a continuous daily infusion of 80 mg in 240 mL normal saline at 10 mL per hour for 8 days. From day 9 and beyond: 1) if the patient was not intubated and P_{aO_2}/F_{IO_2} was >200 mmHg, the treatment was tapered to methylprednisolone 20 mg *i.v.* in 30 min three times a day for 3 days, then 20 mg *i.v.* twice daily for 3 days, then 20 mg *i.v.* once daily for 2 days, then 16 mg *per os* once daily for 2 days, then 8 mg *p.o.* once daily for 2 days, then 4 mg *p.o.* once daily for 2 days; 2) if the patient required IMV or P_{aO_2}/F_{IO_2} was ⩽200 mmHg with at least 5 cmH_2O CPAP, an infusion of methylprednisolone 80 mg in 240 mL of normal saline at 10 mL per hour was continued until P_{aO_2}/F_{IO_2} reached >200 mmHg, then it was tapered as in 1. Arm 2 (dexamethasone): dexamethasone 6 mg *i.v.* in 30 min or *p.o.* from day 1 to day 10 or until hospital discharge (if sooner). Supplementary figure S1 summarises the treatment schedule in both arms. Patients in both study groups had access to the same standard of care, comprising NIV, IMV, extracorporeal membrane oxygenation, antibiotics, antivirals, vasopressors, renal replacement therapy and anticoagulation according to clinical needs.

Outcome measures

The primary end-point was mortality proportion at day 28. The secondary end-points were: 1) number of days free from mechanical ventilation (either NIV or IMV) by study day 28; 2) proportion of patients requiring admission to an intensive care unit (ICU); 3) number of days of hospitalisation among survivors; 4) proportion of patients requiring tracheostomy; 5) C-reactive protein level (CRP; $mg \cdot L^{-1}$) at study days 3, 7 and 14; 6) P_{aO_2}/F_{IO_2} ratio (mmHg) at study days 3, 7 and 14; and 7) World Health Organization (WHO) Clinical Progression Scale at study days 3, 7 and 14 [14].

Randomisation and data collection

The randomisation list was generated by the study statisticians with Stata version 14.2 (StataCorp, College Station, TX, USA) using blocks of variable size of 2, 4 or 6 in a random order. The list was implemented in the REDCap randomisation module allowing for centralised allocation of patients through the REDCap platform embedded in a web hosting facility, which granted allocation concealment. Electronic case report forms were developed to collect all relevant information. At each participating centre, one assigned investigator who had secure access to the platform was in charge for the randomisation and data entry. Three independent physicians checked the data.

Statistical methods

This trial was designed as a sequential RCT with two interim analyses, unblinded sample size recalculation and stopping rules for either early efficacy or futility (O'Brien–Fleming design). The experimental hypothesis was that methylprednisolone treatment would have improved 28-day survival from 77% in arm 2 to 87% in arm 1 (10% risk difference). If this hypothesis had been true, the study would have had a one-tail α error <0.025 and an overall power >90% using Fisher's exact test, with a sample size varying between 200 and 680 participants according to the observed effect within the trial sample at each stage (see supplementary material for details). The actual sample size was 680 patients. A list of 690 patients was generated to account for randomisation of not eligible patients.

Data were described using absolute and relative frequencies (percentage) or position indices (mean or median) and relative dispersion indices (standard deviation or interquartile range (IQR)), according to the type and distribution of the variables. Odds ratios and relative 95% confidence intervals were calculated. The difference in numerical variables between groups was calculated using the t-test or Wilcoxon rank-sum test, as appropriate. Differences between study groups concerning categorical and dichotomous variables were evaluated with the Chi-squared test or Fisher's exact test, as appropriate. Time at risk for all-cause death was computed from the date of study enrolment up to the date of death, hospital discharge or 28 days, whichever came first. Event-free probabilities were estimated by the Kaplan–Meier method and differences between groups were assessed by the log-rank test. Prespecified subgroup analyses were performed by the severity of respiratory impairment at randomisation (P_{aO_2}/F_{IO_2} <200 or >200 mmHg) and by the level of respiratory support required at randomisation (low-flow oxygen therapy, HFNC or NIV). Available case analysis was performed for the variation of CRP and P_{aO_2}/F_{IO_2} levels over time. Multivariable logistic regression was used to adjust for imbalance between the two arms and for possible confounders. All tests were two-sided and a p-value of <0.05 was considered statistically significant. All analyses were conducted according to the intention-to-treat principle, but sensitivity per-protocol subanalyses were then carried out.

Results

Patients

Of the 690 patients who underwent randomisation from 14 April 2021 to 4 May 2022, 677 patients were eligible to receive one of the study treatments, while 13 were excluded because they were incorrectly

enrolled in the trial despite meeting exclusion criteria. Of these 677 patients, 337 received methylprednisolone and 340 received dexamethasone (figure 1).

Findings are reported as methylprednisolone *versus* dexamethasone. The two groups had similar baseline characteristics (table 1), except for a lower median (IQR) P_{aO_2}/F_{IO_2} ratio in the methylprednisolone group (178.6 (135.0) *versus* 202 (130.9) mmHg). Accordingly, more patients in the methylprednisolone group were undergoing HFNC compared with low-flow oxygen therapy and NIV at randomisation. All patients included in the analysis received at least one dose of the assigned treatment. The median (IQR) duration of glucocorticoid treatment was 20.0 (6.2) *versus* 9.0 (4.0) days. A similar number of patients (58 (17.2%) *versus* 54 (15.9%); p=0.64) did not comply with the assigned protocol, detailed as: 1) earlier discontinuation due to adverse events (4 (1.2%) *versus* 0 (0.0%)); 2) earlier discontinuation due to physician's decision (35 (10.4%) *versus* 20 (5.8%)); 3) switch to the other arm (10 (3.0%) *versus* 10 (2.9%)); and 4) increase in treatment dosage or duration due to clinical worsening (9 (2.7%) *versus* 24 (7.1%)). Patients who complied with the assigned protocol (279 (82.8%) *versus* 286 (84.1%)) were included in the per-protocol analysis. The number of patients requiring either NIV (205 (60.8%) *versus* 204 (60%); p=0.82) or IMV (32 (9.5%) *versus* 33 (9.7%); p=0.93) by day 28 did not differ. The use of concomitant medications was similar between the two groups (supplementary table S1).

Primary outcome

Mortality at 28 days (table 2) did not significantly differ between groups either in the intention-to-treat analysis (35 (10.4%) *versus* 41 (12.1%); p=0.49) or in the per-protocol analysis (24 (7.1%) *versus* 19 (5.6%); p=0.38). Mortality at 60 days was also similar between groups, although it was not a prespecified outcome. Figure 2 shows the Kaplan–Meier curves of the survival probability at 28 and 60 days. We observed no difference in the primary end-point even when stratifying for the severity of respiratory impairment or for the type of respiratory support received at randomisation (table 3). These results did not substantially change when other variables (*e.g.* baseline P_{aO_2}/F_{IO_2}, glucocorticoid use before randomisation, vaccination status and age) were included in the logistic regression models.

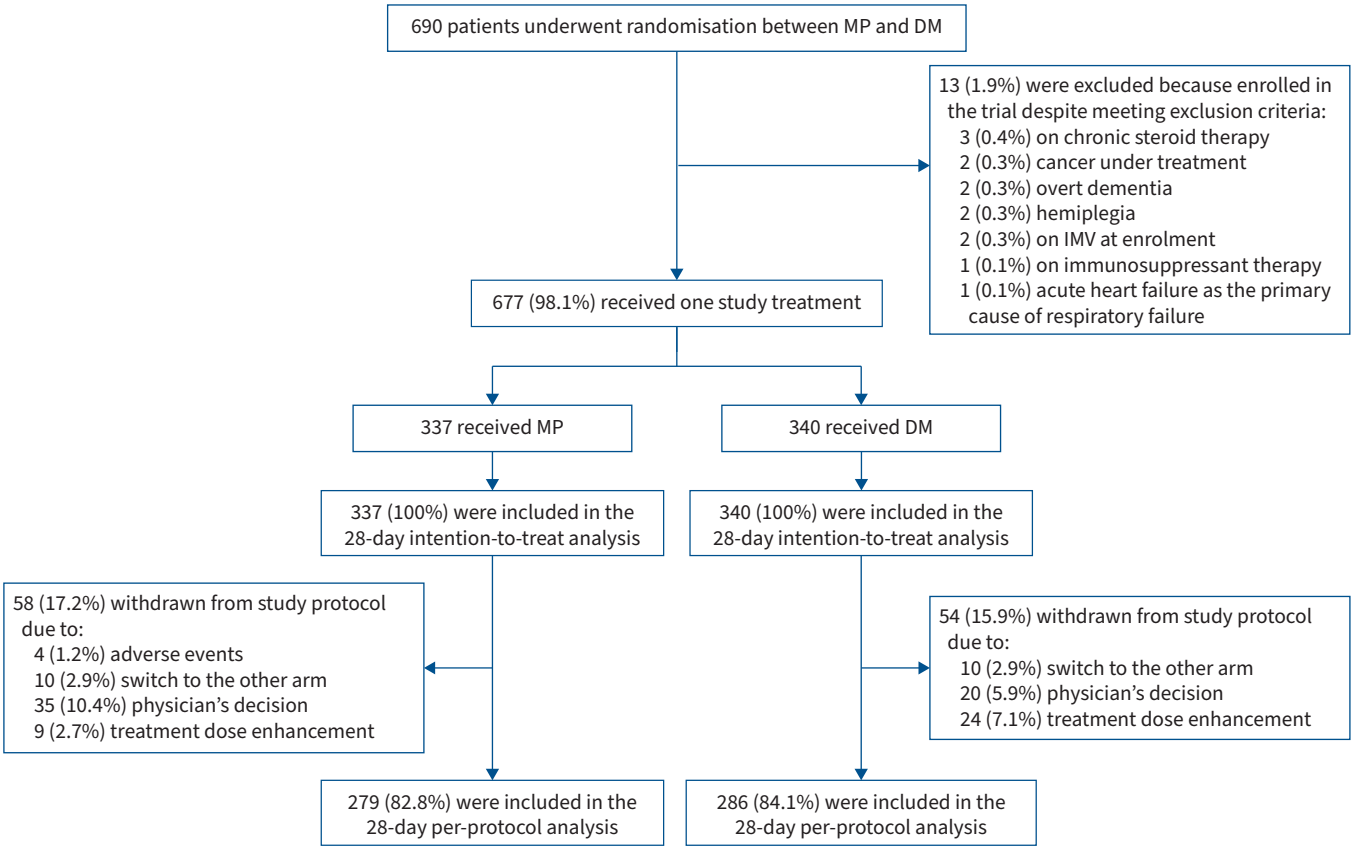

FIGURE 1 Randomisation and inclusion in the primary analysis. MP: methylprednisolone; DM: dexamethasone; IMV: invasive mechanical ventilation.

TABLE 1 Baseline characteristics of the study population

	MP (n=337)	DM (n=340)
Age (years)	64.4±13.6	63±14.1
Sex		
Male	237 (70.3)	233 (68.5)
Female	100 (29.7)	107 (31.5)
BMI (kg·m^{-2})[#]	28.4±5.2	28.1±5.1
Ever-smoker	132 (39.2)	150 (44.1)
Previous coexisting disease		
Any of the listed conditions	247 (73.3)	225 (66.2)
Diabetes[¶]	60 (17.8)	58 (17.1)
Previous cancer[+]	23 (6.8)	28 (8.2)
Arterial hypertension[§]	161 (47.8)	154 (45.3)
Asthma[f]	17 (5.0)	17 (5.0)
COPD[##]	25 (7.4)	26 (7.7)
Bronchiectasis[¶¶]	4 (1.2)	3 (0.9)
Pulmonary embolism[++]	3 (0.9)	10 (2.9)
Chronic kidney disease[§§]	17 (5.0)	16 (4.7)
Atrial fibrillation[ff]	20 (5.9)	23 (6.8)
Ischaemic heart disease[###]	27 (8.0)	26 (7.7)
Heart failure[¶¶¶]	23 (6.8)	22 (6.5)
Chronic liver disease	6 (1.8)	6 (1.8)
Vasculopathy	11 (3.3)	8 (2.4)
Use of glucocorticoids before enrolment[+++]	158 (46.9)	160 (47.3)
Days of glucocorticoid use, median (IQR)	2 (3.0)	3 (4.0)
Prednisone-equivalent cumulative dose (mg), median (IQR)[§§§]	75 (112.5)	100 (118.7)
Anticoagulation before enrolment[fff]	33 (9.8)	40 (11.8)
Days of hospitalisation before randomisation, median (IQR)	1 (1.0)	1 (1.0)
Respiratory support at randomisation[####]		
Low-flow oxygen	142 (42.3)	174 (51.6)
High-flow nasal cannula	74 (22.0)	45 (13.3)
Noninvasive mechanical ventilation	120 (35.7)	118 (35.0)
Anti-SARS-CoV-2 vaccination (at least one dose)[¶¶¶¶]	80 (23.7)	76 (22.4)
P_{aO_2}/F_{IO_2} (mmHg), median (IQR)	178.6 (135.0)	202 (130.9)
CRP (mg·L^{-1}), median (IQR)	69.7 (81.8)	74 (87.1)

Data are presented as mean±SD or n (%), unless otherwise stated. MP: methylprednisolone; DM: dexamethasone; BMI: body mass index; IQR: interquartile range; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; P_{aO_2}/F_{IO_2}: ratio of arterial oxygen tension (mmHg) to inspiratory oxygen fraction; CRP: C-reactive protein. [#]: missing data: 35 MP, 23 DM; [¶]: missing data: 3 MP, 7 DM; [+]: missing data: 4 MP, 2 DM; [§]: missing data: 2 MP, 1 DM; [f]: missing data: 4 MP, 3 DM; [##]: missing data: 7 MP, 6 DM; [¶¶]: missing data: 6 MP, 4 DM; [++]: missing data: 21 MP, 20 DM; [§§]: missing data: 2 MP, 2 DM; [ff]: missing data: 2 MP, 1 DM; [###]: missing data: 5 MP, 2 DM; [¶¶¶]: missing data: 5 MP, 5 DM; [+++]: missing data: 8 MP, 13 DM; [§§§]: calculated as ((daily mg MP×1.25×days)+(daily mg DM×6.25×days)+(daily mg prednisolone×days)); [fff]: missing data: 13 MP, 8 DM; [####]: missing data: 1 MP, 3 DM; [¶¶¶¶]: missing data: 129 MP, 126 DM.

Secondary outcomes

The secondary outcome results are summarised in table 4. The median (IQR) mechanical ventilation-free days by day 28 were similar (23.0 (14.0) *versus* 24.0 (16.0) days; p=0.49), as well as were IMV-free days

TABLE 2 Primary end-points

	Intention-to-treat analysis			Per-protocol analysis		
	MP (n=337)	DM (n=340)	p-value[#]	MP (n=279)	DM (n=286)	p-value[#]
Death at 28 days	35 (10.4)	41 (12.1)	0.49	24 (7.1)	19 (5.6)	0.38
Death at 60 days	44 (13.1)	44 (12.9)	0.96	28 (8.3)	21 (6.2)	0.26

Data are presented as n (%). MP: methylprednisolone; DM: dexamethasone. [#]: p-value of the Chi-squared or Fisher's exact test for dichotomous variables.

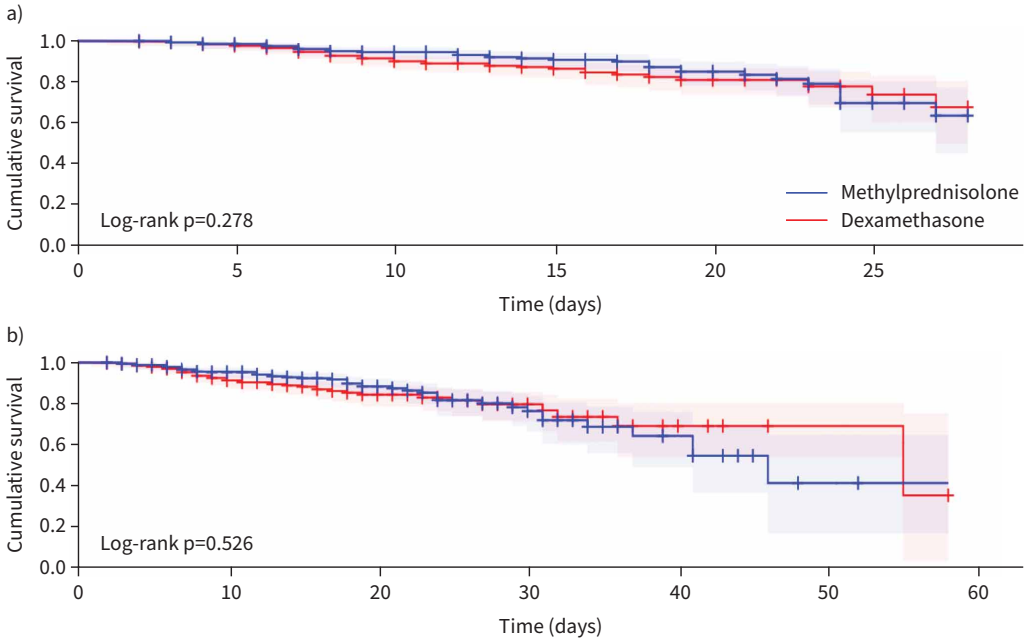

FIGURE 2 Kaplan–Meier estimates of a) 28-day and b) 60-day survival probability.

by day 28 (28.0 (0.0) *versus* 28.0 (0.0) days; p=0.92). These results did not significantly change in the per-protocol analysis nor after stratification for baseline severity (supplementary table S2). The number of patients who required referral to an ICU was comparable (41 (12.2%) *versus* 45 (13.2%); p=0.68), although it was significantly lower in the methylprednisolone group according to the per-protocol analysis (7 (2.1%) *versus* 19 (5.6%); p=0.02). In the stratified analysis (supplementary table S3), statistical significance was only reached in the subgroup of patients who had P_{aO_2}/F_{IO_2} <200 mmHg at randomisation. Survivors in the methylprednisolone group required a longer median (IQR) duration of hospitalisation (15.0 (11.0) *versus* 14.0 (11.0) days; p=0.005), which was confirmed in the per-protocol analysis (15.0 (10.0) *versus* 13.0 (10.0) days; p=0.001). However, this result was only consistent in patients with a less severe respiratory involvement (*i.e.* those with P_{aO_2}/F_{IO_2} ⩾200 mmHg and those requiring oxygen alone, but not HFNC and NIV) at randomisation (supplementary table S4). No differences were observed in the need for tracheostomy between groups (8 (2.4%) *versus* 9 (2.6%) patients; p=0.82). The median (IQR) level of CRP was significantly lower in the methylprednisolone group at day 7 (8.6 (21.9) *versus* 12.4 (28.9) $mg \cdot L^{-1}$; p=0.006) and day 14 (5.0 (21.8) *versus* 11.5 (36.2) $mg \cdot L^{-1}$; p=0.0001), but not at day 3 (supplementary figure S2). There were no significant differences in the median P_{aO_2}/F_{IO_2} ratio at days 3, 7 and 14 (supplementary figure S2). Patients in both groups did not show significant changes in WHO Clinical Progression Scale at days 3, 7 and 14 (supplementary tables S5 and S6).

TABLE 3 Odds of death at 28 days according to the severity of respiratory impairment at randomisation

Stratification variable	Intention-to-treat analysis				Per-protocol analysis			
	MP	DM	OR (95% CI)	p-value[#]	MP	DM	OR (95% CI)	p-value[#]
None	35/337 (10.4)	41/340 (12.1)	0.84 (0.52–1.36)	0.49	24/279 (7.1)	19/286 (5.6)	1.32 (0.71–2.47)	0.38
P_{aO_2}/F_{IO_2} ⩾200 mmHg	10/150 (6.7)	10/174 (5.7)	1.17 (0.47–2.89)	0.73	5/123 (4.1)	3/156 (1.9)	2.16 (0.51–9.22)	0.30
P_{aO_2}/F_{IO_2} <200 mmHg	23/184 (12.5)	31/163 (19.0)	0.61 (0.34–1.09)	0.10	18/154 (11.7)	16/128 (12.5)	0.93 (0.45–1.90)	0.84
Low-flow oxygen	7/142 (4.9)	13/174 (7.5)	0.64 (0.25–1.65)	0.36	5/122 (4.1)	6/157 (3.8)	1.07 (0.32–3.61)	0.91
HFNC	6/74 (8.1)	6/45 (13.3)	0.57 (0.17–1.90)	0.36	4/66 (3.1)	5/38 (13.2)	0.42 (0.10–1.69)	0.23
NIV	22/120 (18.3)	21/118 (17.8)	1.04 (0.54–2.00)	0.91	15/90 (16.7)	7/89 (7.9)	2.34 (0.91–6.06)	0.08

Data are presented as events n/total events n (%), unless otherwise stated. MP: methylprednisolone; DM: dexamethasone; P_{aO_2}/F_{IO_2}: ratio of arterial oxygen tension (mmHg) to inspiratory oxygen fraction; HFNC: high-flow nasal cannula; NIV: noninvasive ventilation. [#]: odds ratio of event among MP group *versus* DM group, estimated using logistic regression model.

TABLE 4 Secondary end-points

	Intention-to-treat analysis			Per-protocol analysis		
	MP (n=337)	DM (n=340)	p-value[#]	MP (n=279)	DM (n=286)	p-value[#]
Mechanical ventilation-free days at 28 days	23.0 (14.0)	24.0 (16.0)	0.49	24.0 (10.0)	26.0 (8.0)	0.09
Invasive mechanical ventilation-free days at 28 days	28.0 (0.0)	28.0 (0.0)	0.92	28.0 (0.0)	28.0 (0.0)	0.93
Days of hospitalisation among survivors	15.0 (11.0)	14.0 (11.0)	0.005	15 (10.0)	13 (10.0)	0.001
Tracheostomy, n (%)	8.0 (2.4)	9.0 (2.6)	0.82	3.0 (1.1)	6.0 (2.1)	0.33
CRP ($mg \cdot L^{-1}$)						
Day 3	32.0 (57.5)	37.7 (56.6)	0.16			
Day 7	8.6 (21.9)	12.4 (28.9)	0.006			
Day 14	5.0 (21.8)	11.5 (36.2)	0.0001			
P_{aO_2}/F_{IO_2} (mmHg)						
Day 3	187.0 (132.0)	192.0 (138.0)	0.40			
Day 7	213.0 (146.0)	227.4 (151.0)	0.20			
Day 14	253.2 (159.0)	264.4 (165.5)	0.67			
ICU referral, n (%)	41.0 (12.2)	45.0 (13.2)	0.68	7.0 (2.1)	19.0 (5.6)	0.02

Data are presented as median (interquartile range), unless otherwise stated. MP: methylprednisolone; DM: dexamethasone; CRP: C-reactive protein; P_{aO_2}/F_{IO_2}: ratio of arterial oxygen tension (mmHg) to inspiratory oxygen fraction; ICU: intensive care unit. [#]: p-value of the Mann–Whitney test for numerical variables, or the Chi-squared test or Fisher's exact test for dichotomous variable, as appropriate.

Adverse events

As detailed in supplementary tables S7 and S8, there were no differences between groups in the occurrence of adverse events related to the study treatment (147 (43.6%) *versus* 126 (37.0%); p=0.08) nor in in-hospital complications of any type (169 (50.1%) *versus* 158 (46.5%); p=0.36). The most frequent adverse event was hyperglycaemia (113 (33.5%) *versus* 93 (27.4%); p=0.15). In four cases the treatment was interrupted due to adverse events, reported as agitation (two cases), hyperglycaemia and gastrointestinal bleeding. There were no reports of serious adverse reactions related to the study treatment.

Discussion

In our study there were no statistically significant differences in 28-day mortality between patients affected by SARS-CoV-2-related pneumonia treated with methylprednisolone and those treated with dexamethasone. While the duration of mechanical ventilation and IMV was similar between groups, patients in the methylprednisolone group with P_{aO_2}/F_{IO_2} <200 mmHg at randomisation who completed the assigned treatment protocol experienced a lower rate of ICU admission. Conversely, patients in the dexamethasone group with a less severe respiratory involvement at randomisation had a shorter median length of hospital stay. Methylprednisolone was associated with a significant reduction of CRP at days 7 and 14. Previous data associated a faster reduction of CRP with a lower 1-year mortality after severe pneumonia and sepsis [15, 16], and there is evidence that persistently elevated CRP and need for ICU admission are independent risk factors for the development of post-COVID conditions, which were not followed-up in this trial [17, 18]. Both treatment protocols were equally safe as we observed a similar incidence of adverse events and no serious adverse reactions, consistent with previous data [19, 20].

To date, two smaller RCTs have compared methylprednisolone with dexamethasone in COVID-19. Both studies investigated a single bolus of methylprednisolone 2 $mg \cdot kg^{-1}$ daily for 5 days followed by 1 $mg \cdot kg^{-1}$ daily for the other 5 days *versus* dexamethasone 6 mg daily for 10 days [11, 12]. A statistically significant reduction in mortality was only observed in the study by Saeed *et al.* [12] (n=414), in which mechanically ventilated patients were selectively included. This inclusion criterion could explain the discordant result with our study. Indeed, there is strong evidence of a proportional benefit of glucocorticoids among patients who require mechanical ventilation rather than other lower intensity respiratory support modalities [3]. The duration of mechanical ventilation was lower in the methylprednisolone group in both studies, while Ranjbar *et al.* [11] (n=86) also found a significant reduction in the length of hospitalisation.

One recent RCT found no benefit of 1 g methylprednisolone boluses for 3 consecutive days *versus* placebo in addition to dexamethasone 6 mg daily for 10 days on the duration of hospitalisation nor on survival [21]. Despite this study design not being comparable with ours, pulsed high-dose methylprednisolone had already proven detrimental [8].

Our results are also concordant with those of both the COVID STEROID 2 trial [22] and the recent RCT by TABOADA *et al.* [23] on the effect of higher *versus* lower doses of dexamethasone on clinical worsening.

We believe there are two leading causes underlying the longer duration of hospitalisation among patients treated with methylprednisolone in our study. First, the methylprednisolone protocol had a more extended administration schedule due to both titration based on clinical response and an *i.v.* de-escalation phase. Indeed, the differential length of hospital stay was even larger among patients who completed the assigned treatments (table 4). Second, patients in the methylprednisolone group suffered from a more severe respiratory involvement at randomisation. Furthermore, we observed an inversely proportional trend between the severity of respiratory status at baseline and the difference in the duration of hospitalisation between groups, which is consistent with a possible higher benefit of methylprednisolone treatment in the most severe subgroups.

One major finding was the lower ICU admission incidence in the methylprednisolone group, which reached statistical significance in patients who had P_{aO_2}/F_{IO_2} <200 mmHg at randomisation and completed the assigned treatment protocol. This could be apparently discordant with the similar number of days free from IMV at 28 days between groups; however, it is important to observe that this was a multicentre study involving different types of hospital units and that not all of them were able to provide mechanical ventilation. Therefore, in several centres, patients who deteriorated were moved to the ICU regardless of the need for IMV. The MEDEAS trial was implemented to provide a rapid assessment of a potentially higher benefit of the infusive methylprednisolone protocol over the widely used dexamethasone administration schedule. An open-label design was best suited for the purposes of this study, as it also is accepted from previous reports in similar settings [3]. However, one major limitation pertains to the study design itself. Indeed, we calculated the sample size hypothesising 23% mortality in patients treated with dexamethasone. While this datum was extrapolated from previous literature and primarily from the RECOVERY trial, the actual 28-day mortality in the dexamethasone group was halved (12.1%) as a result of the different pandemic periods, different viral strains, and the increasingly better knowledge of COVID-19 and its management. For this reason, interim analyses were not performed, as we deemed it necessary to reach the highest pre-planned sample size. Nevertheless, it is likely that the overestimation of overall mortality was of minor relevance, given the closeness of agreement between the primary outcome results in the two groups. Although the same standard of care was used among the 26 participating centres, it is possible that some centres experienced variations in internal protocols, limitations in the availability of ICU beds or delays in the initiation of mechanical ventilation due to the variable pressure on the hospitals in different pandemic periods. Supplementary figure S3 shows the number of enrolled patients per month and the corresponding incidence of new COVID-19 cases in Italy.

A further limitation pertains to the use of glucocorticoids in the home care setting, which was contraindicated at the time this trial was designed, but became increasingly frequent during the following months [24]. As this was not a prespecified exclusion criterion, the dose, type and duration of glucocorticoid treatment were recorded, and the median cumulative prednisone-equivalent dose before randomisation was calculated, finding no differences between groups (table 1). The proportion of vaccinated patients in our study was lower than that of the general population in the same time frame. However, it is concordant with the literature reporting on hospitalised patients affected by moderate to severe COVID-19, and we did not find differences between groups in death rates within those vaccinated and nonvaccinated [25]. One last potential limitation relates to the predictability of the randomisation list that may result from block randomisation. To avoid this, blocks of different sizes were used in a random order.

In conclusion, a protocol of infusive, prolonged, higher dose methylprednisolone did not show major advantages over conventional dexamethasone in COVID-19 pneumonia, confirming the favourable drug class effect of prolonged low-dose glucocorticoids postulated by current guidelines.

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Author contributions: F. Salton conceived and designed the study, analysed and interpreted the data, drafted, revised and approved the work. P. Confalonieri designed the study, collected and interpreted the data, revised and approved the work. S. Centanni collected and interpreted the data, revised and approved the work. M. Mondoni collected and interpreted the data, revised and approved the work. N. Petrosillo conceived and designed the study, collected the data, revised and approved the work. P. Bonfanti collected and interpreted the data, revised and approved the work. G. Lapadula collected and interpreted the data, revised and approved the work. D. Lacedonia collected and interpreted the data, revised and approved the work. A. Voza collected and interpreted the data, revised and approved the work. N. Carpenè collected and interpreted the data, revised and approved the work. M. Montico designed the study, analysed and interpreted the data, drafted, revised and approved the work. N. Reccardini analysed and interpreted the data, drafted, revised and approved the work. G.U. Meduri conceived and designed the study, interpreted the data, revised and approved the work. B. Ruaro collected and interpreted the data, revised and approved the work. M. Confalonieri conceived and designed the study, interpreted the data, drafted, revised and approved the work. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

This study is registered at ClinicalTrials.gov with identifier number NCT04636671. Data availability: de-identified participant data will be made available upon motivated request to the corresponding author. The proposed use of the data and analyses must be approved by the Scientific Committee.

Conflict of interest: F. Salton, P. Confalonieri, S. Centanni, M. Mondoni, N. Petrosillo, D. Lacedonia, A. Voza, N. Carpenè, M. Montico, N. Reccardini, G.U. Meduri, B. Ruaro and M. Confalonieri have no conflicts of interest to disclose. P. Bonfanti received personal fees from ViiV Healthcare, Gilead, Janssen, Merck and Pfizer, not related to this work. G. Lapadula received personal fees from ViiV Healthcare and Pfizer, not related to this work.

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