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Published in:
European Respiratory Journal

DOI:
10.1183/13993003.00270-2023

Publication date:
2023

A patient-tailored approach for corticosteroid treatment in COVID-19: still not there yet

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Shareable abstract (@ERSpublications)
Other steroids are currently not superior to dexamethasone 6 mg in COVID-19 patients with acute respiratory failure https://bit.ly/3YUkc8G

Cite this article as: Nigro M, Chalmers JD, Aliberti S. A patient-tailored approach for corticosteroid treatment in COVID-19: still not there yet. *Eur Respir J* 2023; 61: 2300270 [DOI: 10.1183/13993003.00270-2023].

Received: 14 Feb 2023
Accepted: 19 Feb 2023

More than 3 years after its first appearance, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is still among the most troublesome respiratory viruses and the coronavirus disease 2019 (COVID-19) pandemic is still not under control globally [1]. A clear association between dysregulated inflammation and adverse clinical outcomes has been demonstrated in COVID-19 since the very beginning of the pandemic with the so-called "cytokine storm" advocated as the key pathogenetic mechanism in severe disease [2, 3]. The scientific community theorised the use of immunomodulating agents to control this process and, among them, systemic corticosteroids have been extensively used during the pandemic since the first evidence that they reduced mortality was published in June 2020 [4]. International guidelines unanimously report moderate-to-strong recommendations in favour of corticosteroids for hospitalised COVID-19 patients with acute respiratory failure (ARF) based on moderate-to-high quality evidence [5–9]. Corticosteroids are not recommended for patients not requiring supplementary oxygen or for outpatients based on the absence of benefit in clinical trials [5–9]. The standard regimen recommended by guidelines is oral or intravenous dexamethasone 6 mg once daily for 7–10 days. However, the last update of the UK National Institute for Health and Care Excellence and US National Institutes of Health guidelines provided some alternatives to dexamethasone, such as prednisolone 40 mg once daily, methylprednisolone 32 mg·day^{-1} and hydrocortisone 150–160 mg·day^{-1} [7, 8]. These doses have been calculated according to the equivalent steroid potency, as dexamethasone has an anti-inflammatory effect 6.25 times greater than prednisolone, 5 times superior to methylprednisolone and 25 times more powerful than hydrocortisone [10]. In addition, the latest guidelines developed by the European Respiratory Society (ERS) and the World Health Organization (WHO) identified the need to better evaluate the optimal corticosteroids to be used in COVID-19, in terms of formulation, dosage, timing and scheme of administration [5, 6].

The choice of dexamethasone 6 mg once daily comes from the RECOVERY study, which was the first published and the largest trial testing the efficacy of corticosteroids in COVID-19 [4]. Since the publication of the preliminary results in June 2020, the 6 mg dexamethasone regimen became standard of care. The reason why this molecule, dose and protocol of administration were initially chosen by the RECOVERY investigators is still unclear, and the clinical community recognises the importance of a patient-tailored approach when systemic corticosteroids are used in other respiratory diseases [11]. In a recently published trial on hospitalised patients with severe COPD exacerbations a lower rate of treatment failure was found in patients with a tailored dose of systemic steroids in comparison to those treated with a fixed-dose approach [11]. This experience highlighted several factors able to predict the best steroid dose, including body weight, previous use of corticosteroids, gas exchange alterations, inflammatory markers and symptomatic burden [11].

The three features of steroid regimens that impact clinical outcomes are the type of molecule, the dosage, and the protocol of administration. The first question concerning COVID-19 is whether different dosages of dexamethasone are superior to the 6 mg standard dose. Several studies conducted during the past few

months have addressed this topic [12–16]. Among them, the largest one was the COVID STEROID 2 trial that showed no difference in days alive without life support if dexamethasone 12 mg *versus* 6 mg was used [12]. Taboada *et al.* [13] detected a reduction in clinical worsening within 11 days using dexamethasone 20 mg *versus* the 6 mg standard dose with no improvement on 28-day mortality. Furthermore, two trials conducted by Maskin *et al.* [14] and Wu *et al.* [15] demonstrated no benefit of higher doses of dexamethasone on hard endpoints, including mortality. Moreover, the COVIDISCUS trial compared dexamethasone 20 mg against the standard of care, but serious methodological issues, such as a protocol amendment after the publication of the RECOVERY data with a replacement of dexamethasone 6 mg in place of placebo in the control group, limit the interpretation of the results [16]. Finally, another important study from the RECOVERY group (not yet published and not peer-reviewed at the time of writing) shows an increase in 28-day mortality using higher dose dexamethasone *versus* 6 mg dexamethasone in hospitalised COVID-19 patients requiring oxygen or with oxygen saturations <92% on room air [17]. The second question is whether other steroid molecules might be better than dexamethasone. From a pharmacological perspective, different steroid molecules have diverse properties, such as potency or relative affinity for the mineralocorticoid or glucocorticoid receptors. Differences in molecules and doses can be responsible for diverse clinical efficacy in various settings, as they critically influence the activity of the glucocorticoid receptor. A greater proportion of genomic effects has been highlighted when low dose steroids are used, while an increasing amount of non-genomic effects is usually associated with higher doses [18]. Notably, the use of the same steroid molecule for every patient is antithetical to the definition of "precision medicine" and the scientific community greets with pleasure every further study exploring the effectiveness of other corticosteroids. So far, results from studies comparing different doses of methylprednisolone against dexamethasone 6 mg in COVID-19 are inconclusive [19–22].

In this issue of the *European Respiratory Journal*, Salton *et al.* [23] report on the latest study related to this latter question. In a well-constructed, multicentre randomised controlled trial (RCT), the authors compared dexamethasone 6 mg *versus* slow infusion of methylprednisolone 80 mg, therefore testing both a different steroid molecule and a higher dose in a single trial. The trial hypothesis was based on previously published data on acute respiratory distress syndrome and a multicentre, observational study on severe COVID-19 patients that showed a reduction in mortality and days of mechanical ventilation when slow infusion of methylprednisolone was used [24, 25]. On the other hand, the same authors did not find a reduction in 60-day mortality in non-COVID-19 patients with severe community-acquired pneumonia when slow infusion of methylprednisolone was used against placebo [26]. In the study published in this issue, the authors included patients who were hypoxaemic and requiring oxygen, high flow nasal oxygen or continuous positive airway pressure, but did not include patients requiring mechanical ventilation. The study enrolled 690 patients with 677 receiving treatment (337 received slow infusion methylprednisolone and 340 received dexamethasone 6 mg) and detected no differences among the two groups on the primary outcome, *i.e.* 28-day mortality, in both the intention-to-treat (ITT) (12.1% *versus* 10.4%; p=0.49) and the per-protocol analysis (5.6% *versus* 7.1%; p=0.38). No statistically significant differences in the ITT analysis were detected on most of the secondary outcomes, namely mechanical ventilation-free days, invasive mechanical ventilation-free days, referral to intensive care unit, need for tracheostomy, improvement of arterial oxygen tension to inspired oxygen fraction ratio at day 3, 7 and 14, and changes in the WHO clinical progression score. Patients treated with methylprednisolone only showed significatively lower serum C-reactive protein at day 7 and 14 and a slightly longer length of hospitalisation, especially in less severe disease. Although the trial failed to reach the primary endpoint, in contrast to the RECOVERY results it did not demonstrate an increase in mortality or adverse events in patients treated with higher doses of corticosteroids, in this case methylprednisolone, in comparison to those who received dexamethasone. The study was conducted rigorously, although 15–20% of patients did not adhere to the protocol. We applaud this huge effort of a large network of investigators towards the identification of alternative steroid regimens for COVID-19 patients. However, the question about which regimen of corticosteroids should be used in COVID-19 patients is still unresolved.

In order to better position the results reported by Salton *et al.* [23] within the already published literature, we conducted a systematic review of RCTs comparing the dexamethasone 6 mg regimen to any other systemic corticosteroid regimen (including dexamethasone at different dosage) in hospitalised patients with ARF due to COVID-19, with 28-day mortality as the primary outcome. We analysed published, peer-reviewed studies available on PubMed until 1 November 2022, using the same search terms for "COVID", "RCTs" and "Corticosteroids" that were used for the ERS living guidelines [5]. Studies were considered eligible for inclusion if they were clinical trials according to the International Committee of Medical Journal Editors definition, used randomisation, were published in English, included hospitalised patients with ARF due to COVID-19, reported mortality at day 28 from hospital admission and tested any systemic corticosteroid regimen against the dexamethasone 6 mg regimen [27]. Data were extracted,

https://doi.org/10.1183/13993003.00270-2023

TABLE 1 Main features of the studies eligible for the meta-analysis, including the total number of patients that underwent randomisation, inclusion/exclusion criteria and detailed intervention and comparison

Study and registration ID	Location	Period	Patients, setting	Inclusion criteria	Exclusion criteria	Intervention	Comparison
Munch *et al.* [12] NCT04509973	Europe and India, 26 centres	August 2020 to May 2021	n=1000, hospital	• Age >18 years • Confirmed SARS-CoV-2 infection • Need for supplementary oxygen >10 L·min^{-1}, or noninvasive ventilation, or continuous positive airway pressure, or invasive mechanical ventilation	• Treatment with a steroid dose higher than dexamethasone 6 mg for other reasons • Previous treatment with systemic corticosteroids for COVID-19 (>5 days) • Invasive fungal infection • Active tuberculosis • Hypersensitivity to dexamethasone • Pregnancy	Dexamethasone *i.v.* 12 mg per day for up to 10 days	Dexamethasone 6 mg *i.v.* infusion for up to 10 days
Taboada *et al.* [13] NCT04726098	Spain, single centre	January 2021 to May 2021	n=200, hospital	• Age >18 years • Confirmed SARS-CoV-2 infection • Need for supplementary oxygen	• Pregnancy • Breastfeeding women • Dexamethasone allergy • Contraindication for steroids • Indication for corticosteroids for other reasons • Daily use of corticosteroids in the previous 15 days • Expected death within the next 48 h • Level other than 4 in the WHO-CIS • Need for supplemental oxygen with F_{IO_2} >50%	Dexamethasone 20 mg per day for 5 days, then 10 mg per day for 5 days	Dexamethasone 6 mg for 10 days

Continued

TABLE 1 Continued

Study and registration ID	Location	Period	Patients, setting	Inclusion criteria	Exclusion criteria	Intervention	Comparison
Maskin *et al.* [14] **NCT04395105**	Argentina, 4 centres	June 2020 to March 2021	n=100, ICU	• Age >18 years • Confirmed SARS-CoV-2 infection • ARDS	• Pregnancy • Breastfeeding women • Terminal disease • Therapeutic limitation • Severe immunosuppression • Chronic treatment with glucocorticoids • Participation in another RCT • Previous treatment with dexamethasone for COVID-19 (>5 days)	Dexamethasone *i.v.* 16 mg per day for 5 days, then 8 mg per day for 5 days	Dexamethasone 6 mg for 10 days
Wu *et al.* [15] **NCT04707534**	USA, single centre	January 2021 to December 2021	n=110, hospital	• Age >18 years • Confirmed SARS-CoV-2 infection • Need for supplementary oxygen	• Recent corticosteroid medication • Underlying disease requiring chronic corticosteroids • Severe medical events before admission • Contraindication for steroids • Participation in another RCT	Dexamethasone 20 mg per day for 5 days, then 10 mg per day for 5 days	Dexamethasone 6 mg for 10 days
Ranjbar *et al.* [20] **IRCT20200204046369N1**	Iran, single centre	August 2020 to November 2020	n=93, hospital	• Age >18 years • Confirmed SARS-CoV-2 infection • S_{pO_2} at admission <92% in room air	• Pregnancy • Uncontrolled diabetes mellitus • Uncontrolled hypertension • Previous treatment with steroids • Contraindication for steroids • Immunodeficiencies	Methylprednisolone 2 mg·kg^{-1} per day *i.v.* infusion over 30 min for 5 days, then tapering	Dexamethasone 6 mg *i.v.* infusion for 10 days

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https://doi.org/10.1183/13993003.00270-2023

https://doi.org/10.1183/13993003.00270-2023

TABLE 1 Continued

Study and registration ID	Location	Period	Patients, setting	Inclusion criteria	Exclusion criteria	Intervention	Comparison
Corral-Gudino *et al.* [22] NCT04780581	Spain, 4 centres	February 2021 to August 2021	n=128, hospital	• Age >18 years • Confirmed SARS-CoV-2 infection • Evidence of pulmonary involvement on radiology • Need for supplementary oxygen	• Expected death within the next 24 h • Need for high-flow nasal oxygen, noninvasive ventilation, invasive ventilation, ECMO • Treatment with corticosteroids or inflammation-modifying drugs in the previous 2 weeks	Methylprednisolone 250 mg per day *i.v.* for 3 days	Dexamethasone 6 mg for up to 10 days
Salton *et al.* [23] NCT04636671	Italy, 26 centres	April 2021 to May 2022	n=677, hospital	• Age >18 years • Confirmed SARS-CoV-2 infection • P_{aO_2} ⩽60 mmHg or S_{pO_2} ⩽90% • High-flow nasal cannula or noninvasive ventilation	• Invasive mechanical ventilation • Heart failure as the main cause of respiratory failure • Long-term oxygen or domiciliary ventilation • Decompensated liver cirrhosis • Immunosuppression • Chronic treatment with glucocorticoids or immunomodulants • Dialysis • Neurodegenerative conditions • Dementia or decompensated psychiatric disorders • Quadriplegia/hemiplegia/ quadriparesis/hemiparesis • Do not resuscitate order • Use of any other investigational drug for COVID-19 treatment • Any other condition that in the opinion of the investigator might influence the compliance	Methylprednisolone 80 mg *i.v.* infusion in 30 min, then continuous infusion of methylprednisolone 80 mg in 240 mL of NaCl 0.9% at 10 mL·h^{-1} for 8 days, then tapering if the patient was not intubated	Dexamethasone 6 mg *i.v.* in 30 min or *p.o.* for up to 10 days

WHO-CIS: seven-point World Health Organization Ordinal Scale for Clinical Improvement; F_{IO_2}: inspiratory oxygen fraction; ICU: intensive care unit; ARDS: acute respiratory distress syndrome; RCT: randomised controlled trial; S_{pO_2}: peripheral oxygen saturation; ECMO: extracorporeal membrane oxygenation; P_{aO_2}: arterial oxygen tension.

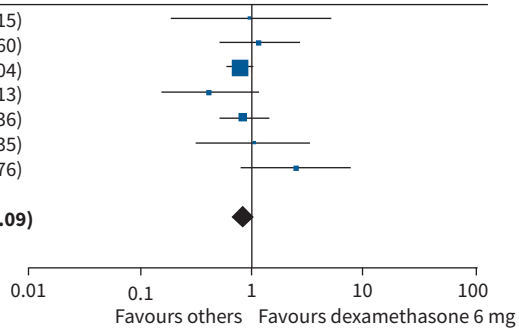
tabulated and entered into Review Manager 5 software version 5.3 for meta-analysis. Data from the ITT population was used for every trial and random effect was used for the analysis, based on both the expected heterogeneity across different treatment regimens and the intention to generalise the results. Finally, a secondary analysis of subgroups defined by the steroid molecule was performed.

Out of the extracted 3468 papers, 1867 were excluded for not being original studies, 1442 were rejected because they were either pre-clinical, observational or quasi-experimental studies and three were not considered because they had neither abstract nor text available online. Out of the remaining 156 RCTs, 44 were not consistent with the defined population, 98 were not testing the dexamethasone 6 mg regimen against another corticosteroid protocol and three reported no mortality data at 28 days. After removal of three duplicates and the exclusion of the COVIDISCUS trial for the above-mentioned reasons, seven studies were considered eligible for the final analysis and are summarised in table 1 [12–15, 20, 22, 23]. All the studies had a superiority-based design. Although no statistically significant difference in mortality was demonstrated, the forest plots shown in figure 1 revealed an interesting trend towards the superiority of regimens different from the standard. The subgroup analysis shows the consistency of the results comparing methylprednisolone against dexamethasone, while no significant differences can be appreciated

a)

Study or subgroup	Others Events	Others Total	Dexamethasone 6 mg Events	Dexamethasone 6 mg Total	Weight %	Odds ratio M-H, random (95% CI)
Corral-Gudino *et al*. [22]	3	64	3	64	2.1	1.00 (0.19–5.15)
Maskin *et al*. [14]	20	49	19	51	8.4	1.16 (0.52–2.60)
Munch *et al*. [12]	133	503	155	497	53.5	0.79 (0.60–1.04)
Ranjbar *et al*. [20]	8	47	15	46	5.7	0.42 (0.16–1.13)
Salton *et al*. [23]	35	337	41	340	21.9	0.85 (0.52–1.36)
Taboada *et al*. [13]	6	98	6	102	4.1	1.04 (0.32–3.35)
Wu *et al*. [15]	11	55	5	55	4.3	2.50 (0.81–7.76)
Total (95% CI)		**1153**		**1155**	**100.0**	**0.86 (0.67–1.09)**
Total events	216		244			

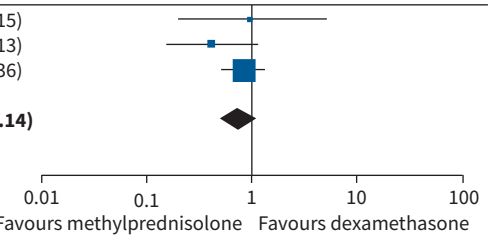
Heterogeneity: Tau²=0.01; Chi²=6.41, df=6 (p=0.38); I²=6%
Test for overall effect: Z=1.28 (p=0.20)



b)

Study or subgroup	Methylprednisolone Events	Methylprednisolone Total	Dexamethasone Events	Dexamethasone Total	Weight %	Odds ratio M-H, random (95% CI)
Corral-Gudino *et al*. [22]	3	64	3	64	6.4	1.00 (0.19–5.15)
Ranjbar *et al*. [20]	8	47	15	46	18.0	0.42 (0.16–1.13)
Salton *et al*. [23]	35	337	41	340	75.5	0.85 (0.52–1.36)
Total (95% CI)		**448**		**450**	**100.0**	**0.75 (0.50–1.14)**
Total events	46		59			

Heterogeneity: Tau²=0.00; Chi²=1.66, df=2 (p=0.44); I²=0%
Test for overall effect: Z=1.33 (p=0.18)



c)

Study or subgroup	Dexa high Events	Dexa high Total	Dexa low Events	Dexa low Total	Weight %	Odds ratio M-H, random (95% CI)
Maskin *et al*. [14]	20	49	19	51	20.5	1.16 (0.52–2.60)
Munch *et al*. [12]	133	503	155	497	56.0	0.79 (0.60–1.04)
Taboada *et al*. [13]	6	98	6	102	11.4	1.04 (0.32–3.35)
Wu *et al*. [15]	11	55	5	55	12.0	2.50 (0.81–7.76)
Total (95% CI)		**705**		**705**	**100.0**	**1.02 (0.66–1.56)**
Total events	170		185			

Heterogeneity: Tau²=0.07; Chi²=4.36, df=3 (p=0.23); I²=31%
Test for overall effect: Z=0.07 (p=0.94)

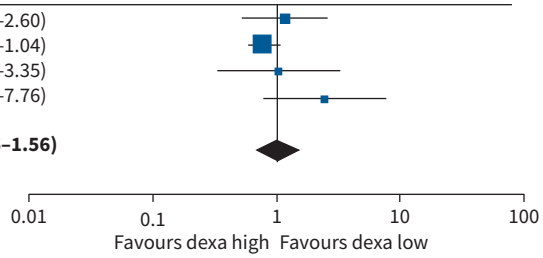


FIGURE 1 Forest plots showing: a) effects of other steroidal regimens (including higher doses of dexamethasone) over dexamethasone 6 mg on 28-day mortality in hospitalised patients with acute respiratory failure (ARF) due to COVID-19; b) effects of methylprednisolone regimens over dexamethasone 6 mg on 28-day mortality in hospitalised patients with ARF due to COVID-19; and c) effects of higher doses of dexamethasone over dexamethasone 6 mg on 28-day mortality in hospitalised patients with ARF due to COVID-19.

in the high *versus* standard dose dexamethasone comparison. The heterogeneity expressed through the I^2 statistics was absent or low in all the analyses performed.

The available evidence does not support the use of one steroid regimen over dexamethasone 6 mg and further research on this topic is needed, with the following caveats. First, the anti-SARS-CoV-2 vaccines have modified the population affected by COVID-19, with fewer patients being admitted to the hospital with ARF and proportionately more immunocompromised subjects suffering from this disease. Further studies on corticosteroids in COVID-19 should specifically address this population. Second, other effective immunomodulatory and antiviral drugs, such as tocilizumab, baricitinib and remdesivir, are suggested by international guidelines and their interactions with different steroids scheme should be evaluated. Third, a deeper characterisation of the host–pathogen interaction, based on the detection of clinical phenotypes, endotypes and precise biomarkers, is mandatory to implement tailored therapies and to treat patients according to their immune status. Finally, molecular, biometrical, anamnestic, functional and clinical features should be considered in designing future research on this topic.

Conflict of interest: M. Nigro has nothing to disclose. J.D. Chalmers has received research grants from AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Gilead Sciences, Grifols, Novartis, Insmed and Trudell, and received consultancy or speaker fees from Antabio, AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Insmed, Janssen, Novartis, Pfizer, Trudell and Zambon. S. Aliberti reports grants from Insmed Incorporated, Chiesi and Fisher & Paykel, royalties from McGraw Hill, consulting fees from Insmed Incorporated, Insmed Italy, Insmed Ireland Ltd, Zambon, AstraZeneca UK Limited, AstraZeneca Pharmaceutical LP, CSL Behring GmbH, Grifols, Fondazione Charta, Boehringer Ingelheim, Chiesi Farmaceutici Spa, ZCUBE Srl, Menarini, MSD Italia Srl, Physioassist SAS and GlaxoSmithKline Spa, lecture honoraria from GlaxoSmithKline Spa, Thermofisher Scientific, Insmed Italy, Insmed Ireland Ltd, Zambon and Fondazione Internazionale Menarini, and advisory board membership for Insmed Incorporated, Insmed Italy, AstraZeneca UK Limited and MSD Italia Srl, outside the submitted work.

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