Intensive Care Med (2020) 46:2108–2110
https://doi.org/10.1007/s00134-020-06230-z

LETTER

Steroids in ARDS: more light is being shed

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Dear Editor,

The RECOVERY study recently reported significant mortality improvement from dexamethasone in hospitalized patients affected by Coronavirus Disease 2019 (COVID-19) [1]. The impressive 35% reduction in the relative risk of mortality achieved in the ventilated subset of patients was surprising given that such a clear signal has not been seen in previous extensive research either into viral pneumonia or acute respiratory distress syndrome (ARDS). This prompted us to examine past randomised controlled trials (RCTs) in ARDS more closely in terms of impact of the type of glucocorticoid, dosing and commencement of treatment on mortality.

Previous studies of glucocorticoid use in viral influenza have lacked rigorous RCT interrogation. An association was however suggested between steroid use and an increased risk of mortality [2]. This may relate to impaired production of type I interferons, the first line of defence against severe viral respiratory infections [3]. The use of steroids in previous coronavirus outbreaks (SARS and MERS) was overall associated with more complications and delayed viral clearance [4, 5]. Expert opinion and clinical trials support the use of corticosteroids in severe community-acquired pneumonia [6, 7]. However, no clear outcome benefit has been shown for steroid use in ARDS despite decades of research (Table 1) (Search methodology available in Online Resource). Accordingly, the World Health Organisation initially advised against routine use of corticosteroids in COVID-19 disease outside a clinical trial [8] and the Surviving Sepsis Campaign gave a weak recommendation with some of the experts deferring judgment until higher quality direct evidence was available [9].

At first glance, it is difficult to reconcile how steroids, with no clear evidence in ARDS and potential harm in viral pneumonitis, can be associated with such a mortality benefit in COVID-19 associated severe respiratory failure in RECOVERY. Methodological queries will doubtless be raised as this was an open-label study with withdrawals and crossovers and an unspecified treatment duration. While an impressive outcome was achieved in the sicker cohorts, it is difficult to explain why benefit was only seen in male patients under 70 years old; a signal-to-harm was seen in a sizeable proportion of patients who were not receiving oxygen at the time of enrolment; and a marked outcome difference was seen using a 7-day cut-off from symptom onset, especially as few would have been hospitalised within the first 5 days.

The RECOVERY study may have shed some light on the different results achieved in the various ARDS RCTs where low-dose dexamethasone appears to provide the greatest benefit. Of all glucocorticoids, only dexamethasone lacks any mineralocorticoid activity. The role of mineralocorticoid activity in the progression of pulmonary hypertension is suggested by pre-clinical data [10]. The lower dose regimen may strike the right balance between anti-inflammatory and immunosuppressive effects. Indeed, higher doses of steroids (methylprednisolone) were associated with harm, and this was most evident in early sepsis studies [11]. The benefit from later commencement in COVID-19 disease may relate to a beneficial effect on the resolution of lung injury with less clinical impact from any delay in viral clearance after 7 days. The timing of viral clearance with COVID-19 is shorter than SARS or MERS [12].

While the results of the RECOVERY cannot be extrapolated beyond COVID-19, and does warrant further scrutiny, the use of early low-dose dexamethasone in ARDS merits further attention.

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Table 1 Randomised controlled trials of steroids in ARDS

Author (Year)	Setting	Enrolment criteria	Aetiology of ARDS	Initiation timing	Protocol	Hydrocortisone equivalent dose for 70 kg adult	Mortality in control arm	Mortality in treatment arm	Risk ratio for death
Bernard (1987) [13]	7 ICUs, USA	PaO_2/FiO_2 ≤ 300 mmHg	Multifactorial	Within 24 h	30 mg/kg of methyl-prednisolone 6 h/day for 24 h	42,000 mg × 1 day	31/49 (63%)	30/50 (60%)	0.95 (0.69–1.29)
Meduri (1998) [14]	4 ICUs, USA	AEC definition and 'lung injury score'	Multifactorial	After 7 days of ventilation	2 mg/kg of methyl-prednisolone followed by 2 mg/kg for 14 days then tapering	700 mg stat 700 mg × 14 days Then tapering	5/8 (63%)	0/16 (0%)	0.05 (0–0.78)
Steinberg (2006) [15]	25 ICUs, USA	PaO_2/FiO_2 < 200 mmHg	Multifactorial	Between days 7 and 28	2 mg/kg of methyl-prednisolone followed by 0.5 mg/kg 6 hourly for 14 days then tapering	700 mg stat 700 mg × 14 days Then tapering	26/91 (29%)	26/89 (29%)	1.02 (0.65–1.62)
Meduri (2007) [16]	5 ICUs. USA	AEC definition	Multifactorial	Within 72 h	1 mg/kg of methyl-prednisolone followed by infusion of 1 mg/kg/day for 14 days then tapering	350 mg stat 350 mg × 14 days Then tapering	17/28 (61%)	48/63 (76%)	1.25 (0.9–1.74)
Liu (2012) [17]	1 ICU, China	PaO_2/FiO_2 ≤ 200 mmHg	Multifactorial	Within 72 h	100 mg TDS of hydrocortisone for 7 days	300 mg × 7 days	7/14 (50%)	2/12 (17%)	0.33 (0.08–1.31)
Rezk (2013) [18]	1 ICU, Kuwait	PaO_2/FiO_2 ≤ 200 mmHg	Pneumonia Trauma	Within 48 h	1 mg/kg of methyl-prednisolone followed by infusion of 1 mg/kg/day for 14 days then tapering	350 mg stat 350 mg × 14 days Then tapering	3/9 (33%)	0/18 (0%)	0.08 (0–1.32)
Tongyoo (2016) [19]	1 ICU, Bangkok	AEC definition	Pneumonia Sepsis	Within 12 h	50 mg of hydrocortisone 6 hourly for 7 days	200 mg × 7 days	40/99 (40%)	34/98 (35%)	0.86 (0.6–1.23)
Villar (2020) [20]	17 ICUs, Spain	PaO_2/FiO_2 ≤ 200 mmHg	Multifactorial	Within 24 h	20 mg dexamethasone once daily for 5 days then 10 mg for other 5 days	500 mg × 5 days 250 mg × 5 days	50/138 (36%)	29/139 (21%)	0.58 (0.39–0.85)
Recovery (2020)	176 ICUs, UK	Patients admitted with COVID-19	COVID-19	Not stated	Dexamethasone 6 mg daily for up to 10 days (median 6 days)	150 mg x ≤ 10 days	1065/4321 (25%)	452/2104 (22%)	0.83 (0.74–0.92)
		No oxygen requirement					137/1034 (13%)	85/501 (17%)	1.22 (0.86—1.75)
		Supplemental oxygen ± NIV					650/2604 (25%)	275/1279 (22%)	0.8 (0.67—0.96)
		Mechanical ventilation					278/683 (41%)	94/324 (29%)	0.65 (0.44–0.88)

AEC American European Consensus; *NHLBI* National Heart, Lung, Blood Institute; *NIV* non-invasive ventilation

Electronic supplementary material
The online version of this article (https://doi.org/10.1007/s00134-020-06230-z) contains supplementary material, which is available to authorized users.

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Funding
Not applicable.

Availability of data and material

Not applicable.

Compliance with ethical standards

Conflicts of interest
The authors declare that they have no conflict of interest.

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Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Accepted: 21 August 2020
Published online: 4 September 2020

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