EUROPEAN RESPIRATORY *journal*

FLAGSHIP SCIENTIFIC JOURNAL OF ERS

Early View

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Corticosteroids in Covid-19: One size does not fit all

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Please cite this article as: Gogali A, Kyriakopoulos C, Kostikas K. Corticosteroids in Covid-19: One size does not fit all. *Eur Respir J* 2021; in press (https://doi.org/10.1183/13993003.00224-2021).

This manuscript has recently been accepted for publication in the *European Respiratory Journal*. It is published here in its accepted form prior to copyediting and typesetting by our production team. After these production processes are complete and the authors have approved the resulting proofs, the article will move to the latest issue of the ERJ online.

Letter to the Editor

Title: "Corticosteroids in Covid-19: One size does not fit all"

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Conflicts of interest: The authors declare they have no conflict of interest

Dear Editor,

Edalatifard and colleagues, in a single-blind randomised controlled clinical trial showed that methylprednisolone pulse administration (250 mg·day^{-1} intravenously for 3 days) to hospitalized, not intubated patients with severe coronavirus disease 2019 (COVID-19), significantly improved survival and duration of recovery compared to standard care; the effect was more prominent in patients receiving non-invasive ventilation and reservoir mask support [1].

The dose of systemic corticosteroids used is remarkably higher compared with the one used in the RECOVERY trial [2], which was the first to demonstrate the beneficial survival effect of systemic corticosteroids in severely and critically ill COVID-19 patients requiring respiratory support (proportional reduction of mortality of one fifth and one third respectively); the dose used in RECOVERY was 6 mg of dexamethasone administered for 10 days. In line with RECOVERY, the living WHO guideline on drugs for COVID-19 provided a strong recommendation for systemic corticosteroids in patients with severe and critical COVID-19, and a weak or conditional recommendation against systemic corticosteroids in patients with non-severe disease, i.e. in those not requiring respiratory support. Although dosing and optimal timing of drug initiation remains uncertain, a relatively low dose, equivalent to 6 mg of dexamethasone, is proposed. The guideline release was supported by a prospective meta-analysis of seven randomized clinical trials by the WHO Rapid Evidence Appraisal for COVID-19 Therapies Working Group, which also confirmed that administration of corticosteroids(in various types and doses) in critically ill patients with COVID-19 was associated with lower 28-day all-cause mortality, compared with usual care or placebo [3]. This analysis was not powered to assess the optimal dose and duration of treatment, leaving this question unanswered.

Even though the living WHO guideline proposes the use of low corticosteroid doses, the current study suggests that the use of pulses of high corticosteroid doses is efficacious and has an acceptable short-term safety profile. There is additional evidence that even higher doses would be worthy of consideration in selected cases of severe COVID-19. Firstly, a beneficial mortality effect of high dose dexamethasone has been recently shown in moderate and severe Acute

Respiratory Distress Syndrome, with no excess of adverse events compared to placebo [4]. Although diffuse alveolar damage has been described in severe COVID-19, there are also reports suggesting that Organizing Pneumonia and Acute Fibrinous and Organizing Pneumonia (OP/AFOP) represents the predominant pattern in pathological samples of COVID-19 patients. A systematic review of COVID-19 pathological findings revealed AFOP features in 26% of patients [5]. Moreover, CT scans of COVID-19 patients often present OP features, including peripheral bilateral ground-glass opacifications with or without consolidation or intralobular lines and atoll signs [6].

OP/AFOP may be the consequence of viral alveolar epithelial injury, which generates immune responses at a later stage of the disease. Notably, dexamethasone is more beneficial in patients treated after the first week of COVID-19 illness, when inflammatory, rather than infectious, mechanisms are predominant. Since rapidly progressive and extensive OP require treatment with high doses of corticosteroids, we suggest that critically ill COVID-19 patients may benefit more from even higher systemic corticosteroid doses, especially in the presence of OP/AFOP radiological features.

The use of high corticosteroid dose in clinical practice is not without adverse events and its consequences in virus clearance is unknown, thus we suggest that the decision for higher systemic corticosteroid doses in patients with severe COVID-19 should rely upon the recognition of OP/AFOP features in CT scans by experienced respiratory physicians and radiologists.

References

1. Edalatifard M, Akhtari M, Salehi M, Naderi Z, Jamshidi A, Mostafaei S, Najafizadeh SR, Farhadi E, Jalili N, Esfahani M, Rahimi B, Kazemzadeh H, Mahmoodi Aliabadi M, Ghazanfari T, Sattarian M, Ebrahimi Louyeh H, Raeeskarami SR, Jamalimoghadamsiahkali S, Khajavirad N, Mahmoudi M, Rostamian A. Intravenous methylprednisolone pulse as a treatment for hospitalised severe COVID-19 patients: results from a randomised controlled clinical trial. *Eur. Respir. J.* [Internet] 2020; 56Available from: http://dx.doi.org/10.1183/13993003.02808-2020.

2. Group TRC, The RECOVERY Collaborative Group. Dexamethasone in Hospitalized Patients with Covid-19 — Preliminary Report [Internet]. New England Journal of Medicine 2020.Available from: http://dx.doi.org/10.1056/nejmoa2021436.

3. WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group, Sterne JAC, Murthy S, Diaz JV, Slutsky AS, Villar J, Angus DC, Annane D, Azevedo LCP, Berwanger O, Cavalcanti AB, Dequin P-F, Du B, Emberson J, Fisher D, Giraudeau B, Gordon AC, Granholm A, Green C, Haynes R, Heming N, Higgins JPT, Horby P, Jüni P, Landray MJ, Le Gouge A, Leclerc M, Lim WS, Machado FR, McArthur C, et al. Association Between Administration of Systemic Corticosteroids and Mortality Among Critically Ill Patients With COVID-19: A Meta-analysis. *JAMA* 2020; 324: 1330–1341.

4. Villar J, Ferrando C, Martínez D, Ambrós A, Muñoz T, Soler JA, Aguilar G, Alba F, González-Higueras E, Conesa LA, Martín-Rodríguez C, Díaz-Domínguez FJ, Serna-Grande P, Rivas R, Ferreres J, Belda J, Capilla L, Tallet A, Añón JM, Fernández RL, González-Martín JM, dexamethasone in ARDS network. Dexamethasone treatment for the acute respiratory distress syndrome: a multicentre, randomised controlled trial. *Lancet Respir Med* 2020; 8: 267–276.

5. Polak SB, Van Gool IC, Cohen D, von der Thüsen JH, van Paassen J. A systematic review of pathological findings in COVID-19: a pathophysiological timeline and possible mechanisms of disease progression. *Mod. Pathol.* 2020; 33: 2128–2138.

6. Güneyli S, Atçeken Z, Doğan H, Altınmakas E, Atasoy KÇ. Radiological approach to COVID-19 pneumonia with an emphasis on chest CT. *Diagn. Interv. Radiol.* 2020; 26: 323–332.