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Editorial

Should Steroids be the Standard of Care for all Covid-19 Patients with Respiratory Failure or Just for Some Selected Ones?

Fernando Martinez-Sagasti*

Department of Intensive Care, Hospital Clínico San Carlos, Madrid, Spain

***Corresponding Author:** Fernando Martinez-Sagasti, Department of Intensive Care, Hospital Clínico San Carlos, Madrid, Spain.

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A wide variety of causes provoke a quite similar respiratory failure, firstly described by Ashbaugh [1] more than 50 years ago, named acute respiratory distress syndrome (ARDS). Classifying different patients with respiratory failure as having ARDS facilitates investigating potential beneficial drugs and supportive ventilatory strategies, so several consensus conferences have been published in recent years [2,3]. According to the last one, the Berlin definition of ARDS [3], the respiratory failure is not due to cardiac failure or fluid overload, shows bilateral opacities on chest-X-ray, develops within one week of a known clinical insult and distinguishes 3 grades of hypoxemia, always under a minimum positive end expiratory pressure (PEEP) of 5 cmH_2O: mild (200 mmHg ≥ pO_2/FiO_2 ≤ 300 mmHg), moderate (100 mmHg ≥ pO_2/FiO_2 ≤ 200 mmHg) and severe (pO_2/FiO_2 ≤ 100 mmHg).

The diagnostic workup of ARDS patients must focus on ruling out infectious diseases (bacterial, viral and fungal), ruling out an extra-pulmonary infection, and finally looking for a non-infectious disease [4]. Identifying the particular cause is of paramount importance to optimize the specific treatment. Regrettably, sometimes the initial cause is either not identified or does not have a specific treatment, so physicians can only provide supportive measures [5].

The histopathology of ARDS [6] consists of, first, a exudative phase characterized by "diffuse alveolar damage" (DAD) where alveolar edema, capillary congestion, intra-alveolar hemorrhage, hyaline-membranes and atelectasis are common findings. The second phase or proliferative phase is characterized by the transient expansion of resident fibroblasts and the formation of a provisional matrix, as well as by the proliferation of airway progenitor cells and type 2 pneumocytes, with differentiation into type 1 pneumocytes. Once epithelial integrity has been reestablished and the provisional matrix restores alveolar architecture and function, alveolar edema reabsorbs. Some patients develop the final fibrotic phase of ARDS when the extensive basement membrane damage is inadequately repaired, causing interstitial and intra-alveolar fibrosis. Because of the inflammatory nature of the ARDS, the anti-inflammatory effects of steroids achieved with genomic doses induced by the mechanism named transrepression, by which, synthesis of proinflammatory mediators is suppressed through downregulation of nuclear factor Kappa-B (NF-kB) [7], has justified investigating their usefulness in RCT for many years with controversial results [8] very likely due to the heterogeneity of the patients included into the studies.

In fact, the Berlin definition [3] has shown to have poor specificity for DAD. At postmortem examination, only 40 to 58% of patients with a clinical diagnosis of moderate-to-severe ARDS have DAD. Pulmonary edema and pneumonia without hyaline membranes are the second most common findings, even 14% of patients have no lung injury [6].

Nevertheless, important progress has been made lately to understand how to avoid the ventilator induced lung injury (VILI) in this syndrome. As a syndrome, the outcome of the ARDS will depend on the patient-specific comorbidities, severity of the underlying causes, clinical management and potential specific treatments for the provoking cause. One example of the great variability among patients with

ARDS is that when the initial insult is primary at the pulmonary level, as in cases of gastric aspiration or pneumonia, the alveolar epithelium is most affected with a local alveolar inflammatory response, while in cases of extrapulmonary ARDS the indirect cause affects the vascular endothelium by inflammatory mediators through the bloodstream [9].

These factors explain the huge differences in mortality rates shown among RCT (12 - 64%) performed with steroids in ARDS [8] making it difficult to draw robust conclusions in relation to the effectiveness of these drugs on this syndrome. Many more factors regarding to the administration protocol, such as timing of starting steroids (exudative/proliferative/fibrotic phase), dosage, duration of treatment and tapering dose, might potentially impact the outcome.

Although the current Covid-19 pandemic caused by SARS-Cov-2 [10], has posed a tremendous challenge for doctors and health care systems, it is being an extraordinary opportunity to study a specific ARDS. Even though most of Covid-19 patients have moderate symptoms and usually recover quickly, some patients develop Covid-19 ARDS (CARDS) which might allow us to clarify the role of steroids on a huge homogenous population but I am afraid that the usefulness of steroids in this setting has been taken for granted too soon.

The controlled open-label Recovery trial [11] was decisive in modifying the therapeutic strategy in Covid-19 patients. A total of 2104 patients were allocated to dexamethasone (DXM) group and 4321 to usual care group. Overall, 482 patients (22,9%) in the DXM group and 1110 patients (25,7%) in the usual care group died within 28 days after randomization (age-adjusted RR 0,83; 95% CI: 0,75 - 0,93; P < 0,001). It is worth noting that in the DXM group, the incidence of death was lower than that in the usual care group among patients receiving mechanical ventilation (MV) (29,3% vs. 41,4%; RR 0,64; 95% CI: 0,51 - 0,81) and among those who received oxygen without invasive MV (23,3% vs. 26,2%; RR 0,82; 95% CI: 0,72 - 0,94) but there were no differences between those patients without oxygen supply. These results made that the current standard of care for Covid-19 patients with respiratory failure is DXM 6 mg (oral or IV) once daily for up to 10 days.

Nevertheless, although these results seem to be highly favourable to steroids, some limitations have been noted [12] such as the lack of stratification between centers, unknown body mass index, ethnicity and location of patient at randomization (ward/ICU), age imbalance in the study population, the distribution of some important factors associated with outcome were not specified for the different subgroups and for patients under MV determined details as PEEP, FiO_2, PaO_2/FiO_2 were not collected. Even more, good results at the short day-28 mortality endpoint might not necessarily lead to longer-term benefit. Despite these limitations, the Recovery trial had a great, albeit hasty impact on the scientific community. Its publication provoked that some of the RCT that were recruiting patients, were stopped (Table 1). After releasing the preliminary beneficial results of DXM in the Recovery trial, a prospective meta-analysis of 1703 critically ill patients who had been randomized to receive systemic DXM, hydrocortisone, or methylprednisolone (678 patients) or to be given usual care/placebo (1025 patients) was published [13]. Surprisingly, although this meta-analysis includes 7 RCT, only the Recovery trial had been completed at that time (Table 1).

	DEXA-COVID19 [14]	CoDEX [15]	Recovery [11]	Cape covid [16]	Covid steroid [17]	REMAP-CAP [18]	Steroids-SARI
Clinical Trials.gov identifier	NCT 04325061	NCT 04327401	NCT 04381936	NCT 02517489	NCT 04348305	NCT 02735707	NCT 04244591
Planned sample size	200	350	NA	290	1000	NA	80
Real sample analyzed	19	256	1007	148	29	197	47

Inclusion criteria	-Intubation -MV -Moderate/severe ARDS -Confirmed Covid-19	-Intubation -MV -Moderate/severe ARDS -Onset ARDS <48 h -Probable or confirmed Covid-19	-Intubation -Suspected or confirmed Covid-19	-Minimal severity Oxygen ≥ 6 L/min -Probable or confirmed Covid-19	-Oxygen > 10 L/min -Confirmed Covid-19	-Admitted to ICU receiving HFNC with FiO_2≥0.4 at ≥ 30 L/min or NIMV or MV or vasopressors -Probable or confirmed Covid-19	-Admitted to ICU with PO_2/FiO_2 < 200 on positive pressure ventilation or HFNC > 45L/min -Confirmed Covid-19
Decision regarding the study plan	Lack of enrollment	Stop recruitment	Finished	Finished	Stop recruitment	Recruiting	Completed (results not available)

Table 1: *Characteristics of included trials in the meta-analysis of the REACT working group [13]. MV: Mechanical Ventilation; NA: Not Available; ICU: Intensive Care Unit; HFNC: High Flow Nasal Cannula; NIMV: No Invasive Mechanical Ventilation; pO_2/FiO_2: Relationship Between Arterial Pressure of Oxygen and the Inspiratory Fraction of Oxygen.*

The rest of the studies had only randomized between 2.9% to 73.14% of the planned sample. Even though this meta-analysis is focused mainly on CARDS patients, a great variability of mortality rate can be seen across the different studies, and what is even more important, there were wide differences in mortality rate among patients allocated to placebo (14.28% - 59.3%) in the different studies and the same occurs among patients allocated to steroids, where mortality rate varies from 14.6% to 54.16% (Table 2).

	Initial dose and administration	**Nº of deaths/total Nº of patients (% of deaths)**	
		Steroids	**No steroids**
Dexamethasone			
Dexa-Covid-19	20 mg/day IV*	2/7 (28,57%)	2/12 (16,66%)
Codex	20 mg/day IV*	69/128 (53,9%)	76/128 (59,37%)
Recovery	6 mg/day orally or IV	95/324 (29,32%)	283/683 (41,43%)
Hydrocortisone			
CAPE-COVID	200 mg/day IV	11/75 (14,66)	20/73 (27,39%)
COVID steroid	200 mg/day IV	6/15 (40%)	2/14 (14,28%)
REMAP-CAP	50 mg/6 hours IV	26/105 (24,76%)	29/92 (31,52%)
Methylprednisolone			
Steroids-SARI	40 mg/12 hours IV*	13/24 (54,16%)	13/23 (56,52%)

Table 2: *All cause-mortality at day 28 in each trial according to steroid type and placebo [13]. *: These doses are considered as "high" doses of steroids.*

Once again, these variable results prove how different the standard of care might be among centers, how it can impact the outcome and how patients included into RCT differ systematically from others in ways that are not easily measurable with the data collected, so stopping those RCT that were recruiting patients when the Recovery trial was published might have not been the best decision.

In fact, some authors have suggested the strong impact that the ventilator management might have on the different outcome of patients with an "identical disease" [19] but these particularities are not displayed in those RCT.

It is also important to mention that the cytokine profile in CARDS is less exuberant when compared to previous cohorts of patients with non-Covid-19 ARDS and the median interleukin-6 (IL-6) level is 10 to 200 fold lower in CARDS in contrast with the hyperinflammatory phenotype of non-Covid-19 ARDS [20].

Moreover, one prospective study performed to compare the plasma concentration of different biomarkers between 11 ARDS patients and 31 CARDS patients found that at the inclusion time in the study, the plasmatic levels of the receptor for advanced glycation end-products (RAGE) that reflects alveolar epithelial injury, and P-selectin, biomarker of endothelial injury, were higher in ARDS patients than in CARDS patients while the plasmatic levels of Angiopoietin-2 (Ang-2), soluble intercellular adhesion molecule-1 (ICAM-1) and E-selectin, biomarkers of endothelial injury, were lower in ARDS patients than in CARDS patients (all $p < 0.001$) [21].

Either should not be forgotten that in many of the ARDS RCT where steroids show good results, they are given in addition to the best treatment for the underlying disease. For instance, in cases of community-acquired-pneumonia [22] all patients receive antibiotics being randomized to steroids or placebo but in CARDS there is no an effective antiviral, so patients are randomized to steroids or to receive the standard of care which seems to be highly variable across different centers.

Regarding the role of the virus on the outcome of CARDS, plasma viral load or viral RNAemia has proved to be related with the dysregulated immune response to SARS-Cov-2 in a study of 250 Covid-19 patients with different disease severity (50 outpatients, 100 hospitalized ward patients and 100 critically ill) [23]. The rate of viral RNAemia was higher in the critically ill group (78%) compared to ward patients (27%) and outpatients (2%) ($p < 0.001$). Most severe patients had higher viral RNA loads in plasma than non-critically ill patients, with non-survivors showing the highest values. Plasma viral RNA load was correlated with higher levels of chemokines, biomarkers indicative of systemic inflammatory response (IL-6, CRP, ferritin), activation of NK cells (IL-15), endothelial dysfunction, coagulation activation (D-Dimer and INR), tissue damage (LDH, GPT), neutrophil response and immunodepression (PD-L1, IL-10, lymphopenia and monocytopenia), suggesting a major role of uncontrolled viral replication in the pathogenesis of Covid-19.

Another study analysed serum viral load and IL-6 levels in 48 Covid-19 patients admitted to a General Hospital in Wuhan, China [24]. They found that RNAaemia was diagnosed only in the critically ill group and seemed to reflect the severity of the disease. The level of IL-6 in critically ill patients increased significantly, almost 10 times higher than in other patients and the extremely high IL-6 level was closely correlated with the detection of RNAaemia ($R = 0.902$). So, these data suggest that the persistence of high levels of inflammatory mediators is strongly related to the viral load and might not be as inadequate as it is supposed to be. Eliminating the virus should be the key therapeutic target more than trying to tamper the response.

Another single-center, retrospective study with 179 hospitalized patients found, in the multivariable analysis, that older age ($p = 0.016$), albumin level ($p = 0.048$), corticosteroids ($p = 0.021$), and tocilizumab ($p = 0.015$) were significantly associated with late viral clearance [25].

A recent study of Covid-19 autopsies [26] shows a wide range of histological lung features. While DAD is seen in up to 87% of cases, there are also different types of vascular injury like large vessel thrombi in 42% of them and platelet-fibrin microthrombi, at least focally, in 84% of cases. An interesting finding is that acute fibrinous organizing pneumonia (AFOP), commonly responsive to steroids, was seen

in up to 34% of cases, particularly in those autopsies with a longer course of disease (5 - 34 days). Nevertheless, virus has also been identified in airway epithelium and type 2 pneumocytes in areas of ongoing active injury, which might contribute to persistent and temporally heterogeneous lung damage.

It is also important to remember that overall 29 studies of steroid treatment for SARS outbreak of 2002 - 2003, 25 were inconclusive and 4 were classified as causing possible harm [27], so there is too much uncertainty ahead of us to conclude that steroids are undoubtedly the standard of care for CARDS.

Although a recently published systematic review investigating the use of steroids in 2740 patients with ARDS of any aetiology concludes that these drugs probably reduce mortality rate (RR 0.82, 95%CI 0.72 - 0.95) with moderate certainty, in my opinion, the studies that have been stopped should be resumed and the ongoing studies must be finished [28]. An effort should be made to identify subgroups of patients who potentially would benefit from steroids while might be harmful in others. New designs of RCT with steroids vs placebo on Covid-19 patients, based on the actual development of different laboratory tests might allow to randomize patients stratifying them according to the viral load. This strategy might clarify the real influence of the persistence of virus on the immune system response and how steroids modify the outcome. Homogenous MV protocols must be followed regarding ventilatory parameters, when and for how long neuromuscular blockers and prone positioning must be used [5] and how opportunistic infections (bacterial, viral and fungal) are going to be tested and treated. While all these concomitant factors and the viral status of the patients included across the different RCT are not homogeneous, the effectiveness of steroids on CARDS should not be taken for granted.

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