

Update on the management of SARS-CoV-2 infection

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Ventilatory support and corticosteroid therapy in SARS-CoV-2

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ABSTRACT

It has been almost two years since COVID-19, a disease caused by a new coronavirus called SARS-CoV-2, was declared a pandemic by the World Health Organization. The entire scientific and medical community was put to the test during the following months to find the best therapeutic strategy to save lives. Although some antivirals and anti-inflammatory drugs are being tested in different clinical trials with some controversial results, this short review will focus on corticosteroids usefulness and ventilatory support principles, as they have become two essential therapeutic pillars for those patients who need hospital admission due to respiratory failure.

Key words: SARS-CoV-2, COVID-19, ARDS, corticosteroids, steroids, ventilatory support, high flow nasal cannulas, non-invasive mechanical ventilation, mechanical ventilation

INTRODUCTION

The respiratory system is the most frequently organ affected by SARS-CoV-2. A mean time from the onset of respiratory symptoms to the onset of pneumonia is estimated to be about 5 days and 7 to 12 days from the development of hypoxemia to admission to the Intensive Care Unit (ICU) because of severe respiratory failure.

Despite COVID-19 is not an autoimmune disease, the lack of effective antivirals and the potential lung damage caused by the inflammatory response to infection has justified investigating the usefulness of steroids in several randomised controlled trials (RCTs) with good results [1], becoming the standard of care for this disease when patients need supplementary oxygen. Nevertheless, not all patients respond to steroids and some concerns regarding a potential viral load clearance delay

produced by steroids have emerged. On the other hand, correcting hypoxemia and protecting the lungs as much as it is possible, is mandatory even when the patient might not refer dyspnoea. However, it is still not clear whether or not an early intubation might modify the disease clinical course, hence we will review these two complementary therapeutic strategies.

CORTICOSTEROID THERAPY

Steroids are agonist compounds that bind to the glucocorticoid receptor (GCR), producing a pharmacological response. Its clinical efficacy depends on dosage, timing of initiation, mode of administration, duration, and dose de-escalation. These extensively used drugs have complex actions not always well understood.

The named "genomic" effects of steroids depend on how much the GCR is saturated, while the "nongenomic" effects, normally achieved with higher doses, are independent of its specific receptor, producing interaction with cellular membranes or other cytosolic proteins. The most desirable anti-inflammatory and immunosuppressive effects of steroids are achieved with genomic doses and are induced by the mechanism named transrepression, by which, synthesis of proinflammatory mediators, such as cytokines and prostaglandins is suppressed through downregulation of nuclear factor Kappa-B (NF-κB).

"Low-dose" (prednisone-equivalent doses lower than 7.5 mg/day) produces GCR saturation less than 40-50% with mild adverse effects. Prednisone-equivalent doses of 7.5-30 mg/day ("medium doses") lead to more than 50% receptor saturation, while "high-dose" refers to prednisone-equivalent doses of 30-100 mg/day (dexamethasone -DXM- 20 mg/day) and result in almost complete saturation of cytosolic GCRs. These doses are not recommended for long-term therapy because of the potential serious adverse effects.

Finally, "very high-dose" of steroids (prednisone-equiva-

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lent of > 100 mg/day) and "pulse" therapy (prednisone-equivalent of ≥ 250 mg/day, usually given for 1–5 days) saturate all GCRs. These doses induce the full range of genomic effects and have additional effects on pharmacodynamics (receptor off-loading and re-occupancy) and receptor synthesis and expression. Even more, receptor saturation is thought to increase the therapeutic benefit via nongenomic effects. Such very high doses are used clinically in the initial treatment of acute or life-threatening exacerbations of rheumatic diseases, but they have not been proved to be useful on the acute respiratory distress syndrome (ARDS). Very high doses of steroids cannot be used as long-term therapy due to their serious adverse effects [2].

The strong involvement of the inflammatory response to infection on the pathophysiology of ARDS [3] has led, for many years, to explore the usefulness of steroids, mainly "high doses", in different RCTs with some controversial results in this setting, but with a globally favourable balance towards steroids in most of the studies performed before the COVID-19 pandemic [4].

The last of these studies, published during the first months of the pandemic, was a Spanish study [5]. Two hundred seventy-seven critically ill patients in 17 ICU with established moderate-to-severe ARDS were randomly assigned to receive treatment with DXM (139 patients) or placebo (139 patients as control group). Treatment group received an intravenous (IV) dose of 20 mg once daily of DXM from day 1 to day 5, which was reduced to 10 mg once daily from day 6 to day 10. Although the study was stopped by the data safety monitoring board due to low enrolment rate after including more than 88% of the planned sample size, the primary outcome, defined as the number of days alive and free from mechanical ventilation (MV) from day of randomisation to day 28, was higher in the DXM group than in the control group (between-group difference 4,8 days [95% CI: 2,57-7,03]; $p < 0,0001$). Secondary outcome, defined as all-cause mortality 60 days after randomisation, was also better in the treatment group while the proportion of adverse events did not differ significantly between both groups.

These good results provoked that, throughout the first wave of the pandemic, many critically ill patients were treated following this DXM regimen, although with some concerns about whether or not steroids might cause a possible delay in virus clearance as it had been published regarding MERS, few years earlier [6].

In fact, the role of viral load in plasma 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) [7]. 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. Viral RNAemia did not show significant associations, in

the multivariate analysis, between outpatients and ward patients. On the contrary, both viral RNAemia and plasma viral RNA load were associated with critical illness when in-ward patients were compared to ICU patients. Plasma viral RNA load was also 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.

Besides these findings, as the pandemic was going on, many observational, retrospective and some small RCT showed globally better results in the group of patients treated with steroids.

In this regard, a meta-analysis [8] of 44 studies (37 retrospective observational studies, 5 RCTs, and 2 studies with historical controls) from the first wave of the pandemic, with a varied population of 20,197 hospitalized patients (28/44 studies) to patients admitted to the ICU (15/44 studies), and one study including discharged patients for viral clearance assessment, showed a significant reduced mortality in the steroid group (OR 0,72 [95%CI: 0,57-0,87]) besides they found a signal of delayed viral clearance, but data in the studies were too sparse to draw any definitive conclusions. Fourteen studies reported a positive effect of steroids on need for and duration of MV. It is worth noting that a trend toward more infections and antibiotic use was present amongst patients who received steroids.

More recently, the results of the controlled open-label Recovery trial [9] comparing a range of possible treatments in patients with COVID-19, regarding those who were randomly assigned to receive a dose (oral or IV) of 6 mg once daily of DXM for up to 10 days or to receive usual care alone have been published [9]. The primary outcome was 28-day mortality. A total of 2,104 patients were allocated to DXM arm and 4,321 to usual care group. Overall, 482 patients (22,9%) in the DXM group and 1,110 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; $P < 0,001$). Very importantly, in the DXM group, the incidence of death was lower than that in the usual care group among patients receiving 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 not in the group of patients that was not receiving any respiratory support at randomization (17,8% vs. 14%; RR 1,19; 95% CI: 0,92-1,55) warning about the importance of customizing the treatment to the clinical status. Even more, although these results seem to be highly favorable to steroids, important limitations have been highlighted [10], for instance, there was no stratification between centers, body mass index and ethnicity were not reported, location of patient at randomization (ward/ICU) is unknown, there was age imbalance in the study population, the distribution of the various factors associated with outcome were not specified for the

different subgroups and for patients receiving MV important details as positive end expiratory pressure (PEEP), FiO_2 , $\text{PaO}_2/\text{FiO}_2$ were not collected. Another limitation is that good results at the short day-28 mortality endpoint might not translate into longer-term benefit, particularly in COVID-19 patients where those who need MV often require prolonged ICU and hospital stays.

After publishing the beneficial results of DXM in the Recovery trial, particularly for most severe patients, a prospective meta-analysis of 1,703 critically ill patients who had been randomized to receive systemic DXM, hydrocortisone, or methylprednisolone (678 patients) or to be given usual care/placebo (1,025 patients) was performed [1]. Although this meta-analysis includes 7 RCT, only the Recovery trial(9) had been completed when it was published. The rest of the studies had only randomized between 2.9% to 73.14% of the planned sample. Considering this limitation, 222 subjects died among the 678 (32,74%) patients allocated to steroids and there were 425 deaths among 1,025 (41,46%) patients randomized to usual care/placebo (summary OR, 0,66 [95% CI: 0,53-0,82]; $p < 0,001$ based on a fixed-effect meta-analysis). There was little inconsistency between the trial results, so the authors conclude that the administration of systemic steroids to critically ill patients, compared with control group, was associated with lower 28-day all-cause mortality.

Finally, a recent meta-analysis that compared corticosteroids to placebo or usual care in adult patients with COVID-19 ARDS or not COVID-19 ARDS, deserves mention because it only included those RCT of patients on MV [11]. It contains 6 RCT (833 patients) from previously published meta-analyses and 12 additional RCT for a total of 18 RCT (2826 patients) that met eligibility criteria. The authors concluded that the use of steroids probably reduces mortality in patients with ARDS of any cause (2,740 patients in 16 trials, RR 0,82; 95%CI: 0,72-0,95, ARR 8%; 95%CI: 2,2-12,5%), with moderate certainty. Patients treated with steroids for more than 7 days had higher rates of survival compared to those who received a shorter course. This effect was consistent between corticosteroid types and dosage. It is important to highlight that almost all of the included RCT in this meta-analysis started steroids within the first week of ARDS diagnosis, when the exudative-inflammatory phase of ARDS is still active.

Although we have seen that several meta-analyses show a globally beneficial signal for steroids in this setting, clinicians should make an effort to customize the treatment. Remembering that ARDS is not a disease but a "syndrome" helps us understand that steroids will improve the outcome only when the predominantly underlying pathological changes are cortico-sensitive, as might happen in the early exudative phase of the ARDS or when the histologic pattern is characterized by an extensive intra-alveolar fibrin deposit called fibrin "balls" which is recognised as acute fibrinous and organizing pneumonia (AFOP).

At the beginning of the pandemic, some authors questioned whether or not the lung injury caused by coronavirus

was a conventional ARDS. They described, based on pulmonary mechanics and function, two patterns: a phenotype L characterized by low elastance, low ventilation to perfusion ratio, low lung weight and low lung recruitability and a phenotype H defined by high elastance, high right-to-left shunt, high lung weight and high lung recruitability [12].

A recent review of the literature [13] does not support the existence of such a clear clinical dichotomy and there seems to be a continuum between both phenotypes, so worsening patients are supposed to progress from type L to type H. A post-mortem study of pulmonary biopsies [14] found, in a patient who died five days after the beginning of fever, a lymphocytic viral pneumonia pattern that could be considered as phenotype L. Nevertheless, for five other patients, who died around 20 days after complaining of symptoms with a phenotype H, the histologic pattern was AFOP, rather than hyaline membranes.

In fact, several studies of autopsies of patients who died due to COVID-19 reveal a wide range of histological lung features. While some of these findings are the landmark of the ARDS such as diffuse alveolar damage (DAD) 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. It is worth noting that AFOP, commonly responsive to steroids, was seen up to 34% of cases, particularly in those autopsies with a longer disease duration (5-34 days) [15].

For all these reasons, it is difficult to determine the best dose and time to start steroids and for how long they should be given. In the early exudative phase, most benefited patients would be those with low viral load to prevent disease progression without facilitating viral replication, which has been proved to maintain lung injury, but those patients who develop late AFOP would also benefit from steroids. We have seen [16] significantly higher plasma levels of LDH, D-Dimers, CRP and PCT within 5 days of ending a standard regimen of steroid therapy in mechanically ventilated non-survivors of COVID-19-associated ARDS compared to survivors, suggesting a reactivation of inflammation after stopping steroid treatment in those patients with a worse prognosis, so tailoring the duration of therapy to the degree of inflammation and viral status of each patient might be of paramount importance and warrants further investigation.

Although it is very likely that the best effect of steroids will be achieved with a dose sufficient to reach close to maximal GCR saturation (methylprednisolone 80-100 mg or DXM 20 mg/day), to clarify this issue, there will be to wait to the results of the currently open-label, randomized controlled MEDEAS trial (Methylprednisolone vs. DXM in COVID-19 Pneumonia trial, ClinicalTrials.gov Identifier: NCT04636671). This study has planned to enrol 680 patients. The study drug is methylprednisolone given as an initial IV bolus of 80 mg to achieve close-to-maximal GCR saturation, followed by a continuous 8-day infusion to maintain high response levels throughout treatment, with the option of adjusting treatment duration

based on parameters of clinical severity (intubated vs not intubated) and followed by dosage gradual de-escalation to avoid inflammation rebound. The comparator is DXM as given in Recovery trial.

In summary, there seems to be a globally beneficial effect of steroids in COVID-19 respiratory failure when the patient needs at least supplementary oxygen. Although questions regarding the timing for steroids treatment, the optimal dose, duration and type of steroids remain to be clarified, a "high genomic dose" (prednisone-equivalent doses of 30–100 mg/day or DXM 20 mg/day) customized to the inflammatory status of the patient and very likely given when the viral load is decreasing, might be the best approach.

VENTILATORY SUPPORT PRINCIPLES

Although hypoxemia produced by COVID-19 can be well tolerated giving a false sense of safety, severe respiratory failure treatment due to SARS-CoV-2 must follow the general principles of the ARDS and correcting hypoxemia is mandatory.

Nevertheless, besides the high number of patients attended to the ICU, it is still not clear the best time to intubate the patients because some of them can be maintained with non-invasive oxygenation devices, particularly with high flow nasal cannulas (HFNC), avoiding the potential damage caused by invasive MV, known as ventilator-induced lung injury (VILI). The mechanisms of VILI are due to barotrauma (high pressure inside the airway), volutrauma (high tidal volume -TV- that produces high transpulmonary pressure and alveolar overdistention), atelectrauma (injury caused by cyclical opening and closing of unstable alveoli) and biotrauma (lung injury due to inflammatory mediators). The pulmonary distention pressure or "driving pressure = ΔP " is the most common and important modifiable determinant of this VILI, so it is recommended to keep it below 15 cmH₂O. Driving pressure is determined by the difference between the inspiratory (plateau) pressure in the airway (Pp) and the positive end expiratory pressure (PEEP): $\Delta P = P_p - PEEP$. Considering this concept, the main objective of MV, whatever mode chosen, will be protecting the lung while ensuring oxygenation. It is important to remember that transpulmonary pressure (P_L) is the result of subtracting the value of the pleural (esophageal) pressure (Ppl) from the airway inspiratory pressure (Pp): $P_L = P_p - P_{pl}$, so not only the driving pressure should be kept low but also the P_L should be as low as possible because the greater the stretching forces acting on the lung, the greater the lung injury.

Starting with oxygen through HFNC when oxygenation cannot be assured with the conventional devices (ventimask or ventimask-reservoir) is preferred over non-invasive mechanical ventilation (NIMV) because HFNC will not significantly increase the P_L. On the contrary, when the patient is put on NIMV the most commonly mode is Pressure Support (PS). The clinician programs an inspiratory pressure level that supports spontaneous breathing, while the patient regulates the respiratory

rate. The resulting TV will depend on the mechanical characteristics of the respiratory system, the programmed PS level and the effort of the patient. When the respiratory effort is very intense the negative inspiratory pressure will increase P_L causing or aggravating VILI. Sometimes this concept is not well understood, so it is mistakenly assumed that P_L is equivalent to subtracting PEEP from the level of PS applied, but this difference is the driving pressure not the P_L. It is worth noting that as the Ppl is always negative with the spontaneous inspiratory effort, P_L might be much greater when applying positive inspiratory pressure with NIMV in case that inspiratory effort does not decrease.

This is the reason why the increase in P_L generated by the patient, might be higher with low PS levels (trying to decrease driving pressure) that produces an increase in inspiratory effort to maintain an appropriate TV to the mechanical conditions of the respiratory system. Consequently, in PS, transpulmonary pressure will depend on lung compliance rather than on the level of inspiratory pressure set, so this might be detrimental to the lung if the patient receives NIMV or invasive MV.

Taking these considerations into account, a rational approach to manage the respiratory failure might be to begin with HFNC when the ventimask is not able to achieve a minimum safety oxygenation. Monitoring patient's oxygen saturation measured by pulseoximetry (SatpO₂) and his work of breathing is mandatory once he is receiving HFNC because intubation should not be delayed when the SatpO₂ does not improve. Although a clear parameter to indicate the intubation has not been established, the ROX index (IROX) might be a useful tool to facilitate the decision. It is defined as the ratio of SatpO₂/FiO₂ to respiratory rate. The lower the IROX in the following hours after beginning with HFNC, the higher the likelihood of needing MV. An IROX lower than 2.85, lower than 3.47, and lower than 3.85 at 2, 6, and 12 hours of HFNC initiation, respectively, have shown to be good predictors of HFNC failure [17] in respiratory insufficiency due to pneumonia. Another single-centre retrospective study in COVID-19 patients showed that an IROX > 5.37 was significantly associated with a lower risk for intubation after 4 hours of receiving HFNC [18]. Accordingly, once the patient is put on HFNC it seems reasonable observing how SatpO₂, work of breathing and respiratory rate change throughout the following hours. When the work of breathing increases or the IROX decreases the intubation should not be delayed because transpulmonary pressure will increase provoking VILI. In case of deciding a trial of NIMV it is important to mention that some patients will move large TV although the clinician programs a low PS. An expired TV greater than 9.5 mL/kg predicted body weight (PBW) has been strongly associated with NIMV failure [19] and delaying intubation might worsen the outcome.

Finally, regarding invasive MV, general guidelines of protective ventilation must be followed [20]. Although discussing in detail these guidelines is out of the scope of this short review, the main principles are the following: a) set TV of 6 mL/kg PBW, b) keep driving pressure below 15 cmH₂O, c) maintain high PEEP levels (>10-15 cmH₂O), d) when PaO₂/FiO₂ ratio <

150 mmHg, neuromuscular blockade for the first 48 hours is recommended and e) in most severe cases, particularly if PaO₂/FiO₂ ratio < 120 mmHg prone positioning for at least 12 hours results beneficial.

CONFLICTS OF INTEREST

The authors declare no conflict of interests.

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