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COVID-19, Corticosteroids and the Road to Enlightenment

The use of corticosteroids for respiratory diseases has been a matter of discussion. Here, we present recent evidence of corticosteroids benefits for COVID-19, including improvements in mortality and ventilator-free days.

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More than six months riding treacherous waves in the COVID-19 storm had passed until a glimpse of a rudimentary old harbour appeared. Corticosteroids. The first drug to decrease mortality in critically ill COVID-19 patients. And it took only a few seconds after we touched land to hear some sailors whispering that they all knew the way to the corticosteroids harbour and that all maps pointed to its direction. Really? Was the path that clear? We are afraid not. All the maps we had pointed out to the other direction. Of course! They were pre-COVID-19 era maps, ancient history for some. But within each old map there were tips pointing to the true north. And fortunately, we found them.

It may seem unnecessary to discuss the use of corticosteroids in critically ill patients with COVID-19 when high-quality evidence (Horby 2020; Sterne 2020) is available. However, we'd like to move backwards to a moment when there was only uncertainty and possibilities.

Shortly after the COVID-19 outbreak, it was clear that we would face a tsunami of viral pneumonia leading to acute respiratory distress syndrome (ARDS). Fortunately, we know how to support ARDS patients: lung protective ventilation (Brower 2000), prone position (Guérin 2013) and neuromuscular blocking agents (Papazian 2010; Moss 2019) are all well known to intensivists. But was that enough? Probably not.

An overwhelming number of possible repurposing therapeutic drugs begin to pop-up. And with all science misinterpretation, the COVID-19 pandemic was a fertile field for clinical trials and a real time lesson on how low-quality evidence can be detrimental. From hydroxychloroquine to convalescent plasma, lopinavir/ritonavir, ivermectin and tocilizumab had their chance, unfortunately without any real success until now. And of course, corticosteroids.

Looking Back

We have been using corticosteroids in critical care for more than 50 years (McConn 1971). However, looking at published data, we have more doubts than certainties. Corticosteroids for traumatic brain injury? Not effective (Roberts 2004). For refractory septic shock? Why not (Venkatesh 2018; Annane 2018). For chronic pulmonary obstructive lung disease? Always. How about ARDS? Pneumonia? Viral diseases?

Before discussing the role of corticosteroids in COVID-19, we will discuss some evidence of the pre-COVID-19 era.

Corticosteroids for ARDS

A series of trials in late 90s and early 00s investigated the role of corticosteroids for ARDS. Different drugs (mostly hydrocortisone and methylprednisolone) administered in different time-points of the disease (early vs late) were investigated. The essence of these trials might be highlighted by the larger ARDSNet trial (Steinberg 2006), which demonstrated increased ventilator free days and shock free days with corticosteroids but no difference in the primary outcome of mortality at 60 days. And along with this study, most of the well-designed randomised trials of that period showed no mortality benefit. Why was that? Were the trials underpowered for mortality? Or was the timing of the intervention? Most of the studies were indeed underpowered for mortality, and most of them evaluated the intervention late in the disease process. The most recent piece in the puzzle of the evidence for corticosteroids in ARDS was the publication, in early 2020, of the DEXA-ARDS (Villar 2020) randomised controlled trial. Despite some limitations such as small sample size and early interruption for low recruitment, this study showed benefit of early dexamethasone (<24h after ARDS onset) use in moderate-severe ARDS. Patients in the intervention group received dexamethasone 20mg daily for 5 days followed by 10mg daily for 5 days or until extubation, whichever occurred first. Patients in the intervention group

had higher number of ventilator free days at 28 days (12.3 vs 9.0; p<0.001) and lower all-cause mortality at day 60 (19% vs 31%, p=0047). Up to now, the use of corticosteroids in non-COVID-19 ARDS is still an unresolved issue.

Corticosteroids for Community Acquired Pneumonia (CAP)

Several studies and meta-analyses yielded conflicting results regarding the use of corticosteroids for CAP. A meta-analysis published in 2017 (Stern 2017) showed no mortality benefit of corticosteroids for hospitalised patients with severe CAP (Risk ratio = 0.80, 95% CI 0.54-1.19) when analysing only trials with low risk of bias, while another meta-analysis (Siemieniuk 2015) showed a mortality benefit of corticosteroids in this same population (risk ratio 0.39, 95% CI 0.20-0.77). However, the small number of patients included in this analysis undermine the results.

Corticosteroids for Viral Pneumonia

Prior to the COVID-19 pandemic the hypothesis was that corticosteroids increase mortality in viral pneumonia according to the results of two meta-analyses (Lansbury 2019; Ni 2019). Lansbury reported a mortality odds ratio of 2.23 (95% CI 1.54-3.24) for corticosteroid use while Ni reported a mortality risk ratio of 1.75 (95% CI 1.3-2.36). In both meta-analyses the majority of patients had influenza pneumonia and mild disease. Also, early use of corticosteroids increase plasma viral load in patients with SARS-CoV-1 (Lee 2004) and is associated with delayed viral clearance in patients with Middle East Respiratory Syndrome (MERS) (Arabi 2018).

Corticosteroids for COVID-19

If we, somehow, were able to sail back to early 2020, abstracting the knowledge we now have, the most scientifically honest discussion on the prospects of corticosteroids use in COVID-19 would follow this rationale:

All the available evidence we have show that corticosteroids use in respiratory viral diseases might be harmful. Also, we cannot rule out a possible benefit of corticosteroids in community-acquired pneumonia and there is recent evidence of a potential mortality benefit when used early in moderate and severe ARDS. However, there might be an intersection zone, which is exactly the one missing in the corticosteroids' trials for influenza: critically ill patients with viral pneumonia. Also, what if COVID-19 does not behave like the other viral diseases? Inflammation, coagulopathy and ARDS histopathology, which now are clear for us, were not at that time.

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A comparison of histologic lung examination between deceased patients with COVID-19 and severe influenza pneumonia shows diffuse alveolar damage, oedema, and fibrin deposition, hallmarks of ARDS in both diseases (Ackermann 2020). However, differently from influenza, patients with COVID-19 have the distinctive features of endothelial injury, microangiopathy and angiogenesis. Data suggest that corticosteroids administration can downregulate the inflammatory pathways responsible for these findings (Arabi 2020). Thus, COVID-19 shares some of the physiopathology features of other viral diseases, such as influenza, but also has its own features.

Therefore, this unique set of events: a new relatively homogeneous disease, knowledge on the effects of corticosteroids in ARDS, and the scientific perception that maybe in the severely ill patients with COVID-19 corticosteroids might play a role, set the ground for future research. At that time, surely nobody could affirm that corticosteroids would work. Equipoise it's all there was.

Shortly, randomised controlled trials started to recruit patients and sooner or later we would be able to make decisions according to evidence-based medicine. As Neil deGrasse Tyson once said: "The good thing about science is that it's true whether or not you believe in it." Of course, in the meantime we saw all forms of flamed passions defending one therapy or another, without any evidence-based discussion.

In mid-June the results of the corticosteroids-arm of the RECOVERY Trial (Horby 2020) were published. In an unprecedent effort they were able to randomise more than 6000 patients to either dexamethasone 6mg daily or standard of care. Overall, dexamethasone use resulted in lower 28-day mortality than control (rate ratio 0.83, 95% CI 075.0.93). However, a subgroup analysis showed that this mortality benefit was mainly driven by patients requiring oxygen support, with a possible sign of harm with dexamethasone use in patients without oxygen support. Although from a subgroup analysis, this information merged with the previous data on the possible harms of corticosteroids in other viral diseases allowed us to suggest the subgroup of patients that would mostly benefit from this intervention. Even though the evidence is compelling, the RECOVERY trial had its limitations. The lack of important data, such as organ dysfunctions, severity of hypoxaemia, infection rates, among others (De Backer 2020) elicit questions regarding the balance between treatment arms and subgroups.

Another trial (CoDEX) including only patients with moderate or severe ARDS due to COVID-19 (Tomazini 2020) showed that dexamethasone increased ventilator-free days. A meta-analysis (Sterne 2020) of randomised trials also showed a mortality benefit of corticosteroid use in critically ill patients. All the trials included in the meta-analysis had their limitations. Some were open label, different corticosteroids and doses were used, and all trials but RECOVERY stopped before the target sample size was reached (after the RECOVERY publication). Also, data on safety and long-term outcomes are still scarce.

Now steroids are used for all hospitalised patients with COVID-19 under oxygen support. However, since science is always tricky, there are still gaps to be filled. Which corticosteroid is better? Which dosage? Does time from disease onset matter? We cannot rule out a corticosteroid class effect, but the evidence available today shows that dexamethasone might be the drug of choice. However, as recommended by the WHO guidelines (Lamontagne 2020), if dexamethasone is not available, it is reasonable to assume a class effect and use any corticosteroid available. The matter of dosage is more difficult and it is hard to make any recommendations. As for the time from disease onset, although the RECOVERY trial found no benefit in early use (<7 days) we should keep in mind that time from disease onset and disease severity are extremely collinear. Therefore, the trigger for initiating corticosteroids should be the severity, despite the time the disease started.

In the end, we cannot precise right now the exact pathway in which corticosteroids exert their beneficial effects in COVID-19. What we did was to use all the available evidence at the time together with scientific reasoning to propose an intervention that should face the test of randomised controlled trials. Fortunately, the effect was positive on mortality, but it would have paid off even if it was not. Because although we all want to find drugs and interventions to benefit our patients, ultimately, we're searching for evidence-based answers. Scientia vinces.

Conflict of interest

Bruno Tomazini and Luciano Azevedo report receiving research grants from Ache Laboratorios Farmaceuticos to carry out a trial on corticosteroids for COVID-19. ■

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