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Short communication

Pros and cons of corticosteroid therapy for COVID-19 patients

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ABSTRACT

In December 2019, an outbreak of severe pneumonia was reported in Wuhan, China. Later described as COVID-19 (coronavirus disease 2019), this infection caused by a virus from the Coronaviridae family (SARS-CoV-2) has spread globally. Effective therapies for this new disease are urgently needed. In this short communication, we will evaluate the use of corticosteroids as an adjunctive pharmacological therapy in the management of COVID-19 and describe its pros and cons in light of the latest available evidence.

1. Introduction

Steroids were commonly used during the 2002–2004 severe acute respiratory syndrome coronavirus 1 (SARS-CoV-1) outbreak, in addition to other drugs, and are currently being administered in many centers for the treatment of coronavirus disease (COVID)-19 caused by SARS-CoV-2 (World Health Organization (WHO, 2020), although the World Health Organization initially recommended against their use outside of clinical trials and only recommended them for strictly specific conditions (World Health Organization (WHO, 2020).

As the pandemic progresses, more evidence on the potential role of corticosteroids in management of COVID-19 is becoming available. In this short communication, we will discuss the recent literature regarding the pros and cons of steroid therapy in COVID-19.

2. Pros

Steroids have been used as an adjuvant therapy for septic shock, especially when adequate fluid resuscitation and treatment with vasopressors are unable to stabilize hemodynamics. Viral infections can lead to a hyperinflammatory state, in which the anti-inflammatory properties of steroids can be an effective therapeutic option. Steroid therapy has demonstrated good efficacy in stabilizing hemodynamics, shortening intensive care unit (ICU) stay and duration of mechanical ventilation, although without a clear beneficial effect on mortality (Venkatesh et al., 2018).

During the first SARS epidemic, an intense activation of proinflammatory cytokines and chemokines was observed, and steroids were found to effectively control the rapid deterioration of clinical condition by attenuating the immune response (Lam et al., 2004). In 2003, patients with SARS-CoV-1 infection showed elevated levels of T-helper lymphocyte type 1 (Th1) cytokine interferon (IFN)-γ, Th1 chemokine IFN-γ-inducible protein-10 (IP-10), proinflammatory cytokines interleukin (IL)-1β, IL-6, IL-8, IL-12, and monocyte chemoattractant protein (MCP)-1 for at least 2 weeks after the onset of symptoms. At that time, methylprednisolone was able to reduce levels of IL-8, MCP-1, and IP-10 5–8 days after treatment initiation. Steroids are also known to inhibit the gene expression of IL-6, IFN-γ (Th1 response), and IL-4 (Th2 response) (Lam et al., 2004) (Fig. 1). Based on the foregoing, the Surviving Sepsis Campaign suggests the use of low-dose steroid therapy in COVID-19 patients with refractory shock, with the aim of mitigating the cytokine storm caused by SARS-CoV-2 and reducing peripheral vasodilation (Alhazzani et al., 2020).

In parallel, a letter reported that use of methylprednisolone (1–2 mg/kg/day for 5–7 days) in 26 patients with severe COVID-19 was associated with better radiographic findings and shorter duration of

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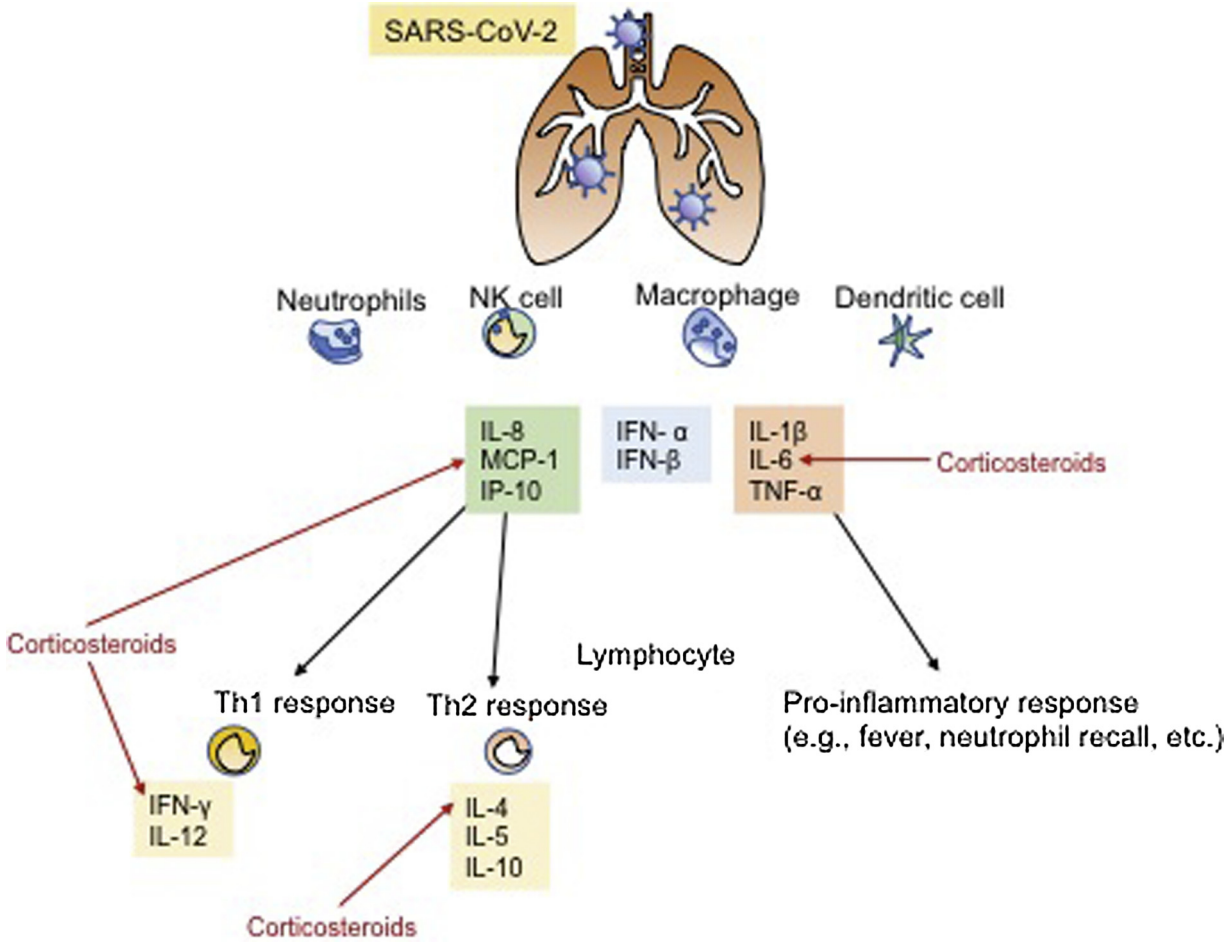

Fig. 1. Modulation of the inflammatory response by corticosteroids. Corticosteroids reduce IL-8, interleukin 8; MCP-1, monocyte chemoattractant protein 1; and IP-10, interferon-γ-inducible protein 10. Moreover, corticosteroids inhibit the ribonucleic acid responses of IL-6, interleukin 6; IFN-γ, interferon gamma (Th1 response), and IL-4, interleukin 4 (Th2 response).

supplemental oxygen therapy (Wang et al., 2020). A recent preprint of a multicenter, randomized, open-label, controlled clinical trial of critically ill patients with COVID-19 demonstrated benefit of dexamethasone (orally or intravenously, 6 mg once daily for 10 days) to those who only received standard treatment. Alternatively, pregnant or breastfeeding women were randomized to receive prednisolone (orally, 40 mg) or hydrocortisone (intravenously, 80 mg twice daily). The RECOVERY trial enrolled 6425 patients in the United Kingdom's National Health System and demonstrated a reduction in mortality by one-third in patients requiring mechanical ventilation and by one-fifth in patients who needed oxygen but no invasive ventilation. No survival benefit was observed among those who did not require supplemental oxygen at admission (Horby et al., 2020). Complete analyses of this study are pending, and peer review is ongoing. Nevertheless, given the compelling evidence of benefit, WHO and several national institutes of health are updating their guidelines to recommend that dexamethasone be administered to COVID-19-patients with hypoxemic respiratory failure (World Health Organization (WHO, 2020). In a recent guideline, the Infectious Diseases Society of America (IDSA) recommended against the use of corticosteroids in COVID-19 based on data from previous coronaviruses in which no benefit was demonstrated (Bhimraj et al., 2020). However, on June 25, 2020, given the findings of the RECOVERY trial, this guideline was updated to advise glucocorticoids rather than no glucocorticoids (preferably dexamethasone, alternatively methylprednisolone or prednisone) in hospitalized patients with severe COVID-19. Steroid therapy remains discouraged in patients without hypoxemia (Bhimraj et al., 2020).

3. Cons

Some data have shown discouraging outcomes when steroids are used in viral lung infections. Evidence from observational studies suggests a higher mortality rate when steroids are used in influenza-induced acute lung injury. A recent meta-analysis of 10 studies enrolling a total of 6548 patients reported that the use of steroids was associated with increased mortality and length of ICU stay in patients with influenza pneumonia (Ni et al., 2019); this effect could be due to the immunosuppressant effect of steroids leading to prolonged viremia, as well as to increased risk of bacterial superinfection. Moreover, steroids may increase the risk of developing other systemic complications, such as autoimmune and cardiovascular events, and can promote resistance to neuromuscular blocking agents, which are widely used during mechanical ventilation in patients with SARS (Ni et al., 2019).

In 2006, a meta-analysis on the use of steroids in patients with SARS. Among the 29 evaluated studies, 25 were inconclusive and four concluded that steroids should not be used in SARS-CoV-1 infection, since they were associated with increased mortality (Stockman et al., 2006). Additionally, high-dose of steroid therapy was associated with diabetes and with SARS-related psychosis. A study of 30 patients with SARS-CoV-1 infection treated with methylprednisolone showed that the initial stage of the disease is characterized by a reduction of $CD4^+$, $CD8^+$, and $CD3^+$ cells and, therefore, immunosuppression can be worsened by the administration of high-dose steroids, increasing the risk of serious secondary infections. Finally, in a study of SARS-CoV-1 patients in which ribavirin and hydrocortisone therapy were compared

versus placebo, suggested that corticosteroid administration could be associated with increased viral load in plasma of patients who had received the combination treatment compared to placebo group (Stockman et al., 2006).

Similarly, Middle East respiratory syndrome (MERS)-CoV patients treated with steroids appeared to experience worse outcomes than those not given steroids, including sustained viral replication, increased need for mechanical ventilation, vasoconstrictors, and renal replacement therapy, and a higher mortality rate. However, after statistical correction for some biases and confounders, steroid therapy was not found to be associated with 90-day mortality (Arabi et al., 2018).

Despite of dearth of previous conclusive studies on steroid therapy in COVID-19 and the steadily increasing number of infected patients, the Chinese Thoracic Society (CTS) released an expert consensus on the use of steroids, declaring that: (i) the benefits and risks must be carefully weighed before using steroids; (ii) steroids should be used with caution in critically ill patients; (iii) greater caution should be paid for patients with hypoxemia due to underlying diseases or who regularly use steroids for chronic diseases; and (iv) the dose administered should be low to moderate ($\leq 0.5-1$ mg/kg/day methylprednisolone or equivalent), and the duration short (≤ 7 days). Additionally, CTS experts recommend against the indiscriminate use of steroids in COVID-19 (Zhang et al., 2020).

Finally, steroids are generally safe drugs in short-term use, despite the potential for adverse effects such as temporary hyperglycemia. Prolonged use, however, may be associated with adverse events such as glaucoma, cataracts, fluid retention, hypertension, psychological effects, weight gain, or increased risk of infections and osteoporosis. Also, clinicians should be aware of possible drug–drug interactions, since dexamethasone is a moderate inducer of cytochrome P450 (CYP)3A4, and may thus impact the concentration and effects of other medications that might be CYP3A4 substrates (World Health Organization (WHO, 2020).

4. Conclusion

In summary, the lack of substantial beneficial evidence for the use of steroids in general COVID-19 patients and data against their use during the past coronavirus epidemics has led the World Health Organization to state that routine steroid use should be avoided, except in specific cases such as management of asthma and chronic obstructive pulmonary disease exacerbation; septic shock; ARDS; and acute respiratory failure (World Health Organization (WHO, 2020). Further well-designed clinical trials are urgently needed to evaluate the safety and efficacy of steroid therapy in COVID-19.

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CRediT authorship contribution statement

Paula Mattos-Silva: Investigation, Writing - original draft, Writing - review & editing. **Nathane Santanna Felix:** Investigation, Writing - original draft, Writing - review & editing. **Pedro Leme Silva:** Writing - review & editing. **Chiara Robba:** Writing - review & editing. **Denise Battaglini:** Writing - review & editing. **Paolo Pelosi:** Conceptualization, Writing - review & editing. **Patricia Rieken Macedo Rocco:** Conceptualization, Visualization, Supervision, Writing - review & editing. **Fernanda Ferreira Cruz:** Conceptualization, Visualization, Supervision, Writing - review & editing.

Declaration of Competing Interest

None.

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References

Alhazzani, W., Møller, M.H., Arabi, Y.M., Loeb, M., Gong, M.N., Fan, E., Oczkowski, S., Levy, M.M., Derde, L., Dzierba, A., Du, B., Aboodi, M., Wunsch, H., Cecconi, M., Koh, Y., Chertow, D.S., Maitland, K., Alshamsi, F., Belley-Cote, E., Greco, M., Laundy, M., Morgan, J.S., Kesecioglu, J., McGeer, A., Mermel, L., Mammen, M.J., Alexander, P.E., Arrington, A., Centofanti, J.E., Citerio, G., Baw, B., Memish, Z.A., Hammond, N., Hayden, F.G., Evans, L., Rhodes, A., 2020. Surviving Sepsis Campaign: guidelines on the management of critically ill adults with Coronavirus Disease 2019 (COVID-19). Intensive Care Med. 46, 854–887.

Arabi, Y.M., Mandourah, Y., Al-Hameed, F., Sindi, A.A., Almekhlafi, G.A., Hussein, M.A., Jose, J., Pinto, R., Al-Omari, A., Kharaba, A., Almotairi, A., Al Khatib, K., Alraddadi, B., Shalhoub, S., Abdulmomen, A., Qushmaq, I., Mady, A., Solaiman, O., Al-Aithan, A.M., Al-Raddadi, R., Ragab, A., Balkhy, H.H., Al Harthy, A., Deeb, A.M., Al Mutairi, H., Al-Dawood, A., Merson, L., Hayden, F.G., Fowler, R.A., Saudi Critical Care Trial Group, 2018. Corticosteroid therapy for critically ill patients with middle east respiratory syndrome. Am. J. Respir. Crit. Care Med. 197, 757–767.

Bhimraj, A., Morgan, L., R.L, Shumaker, A.H., Lavergne, V., Baden, L., Cheng, V.C., Edwards, K.M., Gandhi, R., Muller, W.J., O'Horo, J.O., Shoham, S., Murad, M.H., Mustafa, R.A., Sultan, S., Falck-Ytter, Y., 2020. Infectious Diseases Society of America Guidelines on the Treatment and Management of Patients With COVID-19. (Accessed June 28, 2020). https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/#toc-5.

Horby, P., Lim, W.S., Emberson, J., Mafham, M., Bell, J., Linsell, L., Staplin, N., Brightling, C., Ustianowski, A., Elmahi, E., Prudon, B., Green, C., Felton, T., Chadwick, D., Rege, K., Fegan, C., Chappell, L.C., Faust, S.N., Jaki, T., Jeffery, K., Montgomery, A., Rowan, K., Juszczak, E., Baillie, K., Haynes, R., Landray, J.M., RECOVERY Collaborative Group, 2020. Effect of Dexamethasone in Hospitalized Patients With COVID-19: Preliminary Report. https://doi.org/10.1101/2020.06.22.20137273. published online June 22.

Lam, C.W., Chan, M.H., Wong, C.K., 2004. Severe acute respiratory syndrome: clinical and laboratory manifestations. Clin. Biochem. Rev. 25, 121–132.

Ni, Y.N., Chen, G., Sun, J., Liang, B.M., Liang, Z.A., 2019. The effect of corticosteroids on mortality of patients with influenza pneumonia: a systematic review and meta-analysis. Crit. Care 23, 99.

Stockman, L.J., Bellamy, R., Garner, P., 2006. SARS: systematic review of treatment effects. PLoS Med. 3, e343.

Venkatesh, B., Finfer, S., Cohen, J., Rajbhandari, D., Arabi, Y., Bellomo, R., Billot, L., Correa, M., Glass, P., Harward, M., Joyce, C., Li, Q., McArthur, C., Perner, A., Rhodes, A., Thompson, K., Webb, S., Myburgh, J., ADRENAL Trial Investigators and the Australian–New Zealand Intensive Care Society Clinical Trials Group, 2018. Adjunctive glucocorticoid therapy in patients with septic shock. N. Engl. J. Med. 378, 797–808.

Wang, Y., Jiang, W., He, Q., Wang, C., Wang, B., Zhou, P., Dong, N., Tong, Q., 2020. A retrospective cohort study of methylprednisolone therapy in severe patients with COVID-19 pneumonia. Sig. Transduct. Target Ther. 57. https://doi.org/10.1038/s41392-020-0158-2.

World Health Organization (WHO), 2020. Coronavirus Disease (COVID-19) Situation Dashboard. (Accessed June 28, 2020). https://www.who.int/emergencies/diseases/novel-coronavirus-2019.