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Steroids in COVID-19: Tailor-made or "one size fits all"?

Abstract

Since the RECOVERY trial, steroids have been endorsed by all guidelines for treating moderate-severe COVID-19. The prescribed dose is 6mg dexamethasone or its equivalent for ten days. However, in clinical practice, there are numerous occasions where the role of steroids cannot be extrapolated from current evidence: patients on immunosuppression, patients with persistent oxygen requirement after ten days of therapy, etc. We highlight the existing caveats and the need for further research and discussion.

Key words: coronavirus disease 2019, COVID-19, steroids

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Introduction

The first phase of coronavirus disease 2019 (COVID-19) associated illness is characterized by fever and cough due to the active replication of the virus within the respiratory tract. This is followed by the hyper inflammation phase (cytokine storm), usually occurring after 9–12 days, during which patients might develop acute respiratory distress syndrome, shock, and other complications [1, 2]. A few randomized controlled trials have shown the efficacy of steroids and anticoagulation in severe COVID-19, while the jury is still out over antiviral agents like remdesivir and convalescent plasma [3, 4]. Since the landmark RECOVERY trial, the use of steroids have been endorsed by leading health organizations [3]. According to existing guidelines, steroids (6 mg dexamethasone or equivalent dose of other steroids) are given to patients requiring oxygen or ventilatory support for a total of ten days or discharge (whichever is earlier) [5]. However, in clinical practice, there are numerous occasions where the role of steroids cannot be extrapolated from current evidence. We highlight below three of the common scenarios which are encountered in clinical practice.

Case presentation

Case 1

Middle-aged female, a diagnosed case of dermatomyositis (biopsy-proven) on treatment with prednisolone 50 mg once daily and methotrexate 25 mg once weekly for the last 3 months, came with complaints of fever, cough, and shortness of breath for 7 days. She tested positive for Covid-19 by real time reverse transcriptase polymerase chain reaction (RT-PCR) positive for COVID-19, and high resolution computed tomography (HRCT) showed the presence of bilateral, basal subpleural ground-glass opacities. As her room air saturation was 76%, she was categorized as severe COVID-19 infection and admitted to COVID-19 facility. As the patient developed symptoms of COVID-19 while on immunosuppression, augmented and unchecked viral replication was considered theoretically a as the principal reason for her deterioration. She was started on antiviral therapy with remdesivir (convalescent plasma not available), prophylactic anticoagulation, and immunosuppressive medication was modified (methotrexate stopped and steroid dose tapered). She gradually recovered, was weaned off oxygen over the next ten days, and discharged.

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The ideal treatment protocol for immunosuppressed patients (background disease/treatment-induced) is unknown. None of the trials, including RECOVERY, have included enough number of these patients to draw any meaningful conclusions. Subgroup analysis of the RECOVERY trial failed to show any benefit of steroids when administered within seven days of disease onset. A tendency towards harm was also noted when steroids were administered to patients without oxygen requirement, indicating the efficacy of steroids only in the presence of hyperinflammation [3]. Immunosuppressed patients can have augmented viral replication with poor outcomes when compared to other patients [6]. Guidelines have been largely silent about the optimal management strategy in these cases, and some have advocated treating them along similar lines [7]. Continuing or adding immunosuppression (steroids) in these patients can further worsen disease and also increase the risk of opportunistic infections. The use of an antiviral agents seems rational, with one study showing the efficacy of convalescent plasma in reducing hospital stay and mortality in patients with hematological malignancies [8].

Case 2

Middle-aged male with no prior co-morbidities came with complaints of fever, cough, and shortness of breath. He was found to be COVID-19 positive by RT-PCR and had a room air saturation of 78%. He was categorized under severe COVID-19 infection and started on high flow oxygen support (FiO_2 requirement of 70% with 50 L/min flow), dexamethasone 6 mg, and enoxaparin 40 mg. Ten days after treatment, he improved but continued to have an oxygen requirement of 3 L/min by nasal cannula with markedly elevated C-reactive protein, ferritin and interleukin-6. Though the patient had increased inflammatory markers, a decision was taken to stop steroids as per existing guidelines. He improved gradually, was weaned off oxygen over the next 5 days, and was subsequently discharged after 12 days of hospitalization.

There is uncertainly with regard to the ideal duration of steroid therapy in COVID-19 patients There is uncertainly with regard to the. Guidelines endorse giving them for a fixed duration of ten days or till discharge (as per the RECOVERY and CoDEX trials) [3, 9]. However, the role of continuing steroids in the background of raised inflammatory markers and persistent oxygen support remains questionable. Certain pertinent questions warrant further deliberation: Should patients having persistent oxygen requirements after 10 days of steroid therapy continue treatment? Would the continuation of treatment hastens recovery or merely leads to untoward side effects? Would discontinuation of therapy lead to worsening of the disease due to worsening inflammation?

Case 3

Middle-aged male with no prior co-morbidities came with complaints of fever, cough, and shortness of breath. He was found to be COVID-19 positive by RT-PCR and had a room air saturation of 80%. He was treated with dexamethasone 6 mg, enoxaparin 40 mg OD, and oxygen therapy. The patient became afebrile after 2 days and was gradually weaned off oxygen. Dexamethasone was discontinued after 10 days (day of illness: 16) as per the existing guidelines. The next day he had fever spikes (102-103deg F). The evaluation revealed normal total leukocyte counts, negative procalcitonin, rising C-reactive protein and ferritin levels, sterile blood and urine cultures, and no interval changes on HRCT chest. He was restarted on dexamethasone 6 mg once a day which was continued and gradually tapered over 7 days. He became afebrile after starting steroids and remained afebrile even after discontinuing steroids and was subsequently discharged.

Discussion

Recurrence of fever in COVID-19 patients after stopping steroids could have various reasons: hospital-acquired infection, "saddleback fever" and persistent inflammation or rebound inflammation being amongst the common differentials. Saddle back fever has been previously seen in around 9.9% patients of COVID-19 with good outcomes [10]. The study however excluded patients on oxygen supplementation. Whether the recurrence of fever heralds clinical deterioration, thereby necessitating reinitiation of steroids, needs to be probed in future studies.

Conclusions

In the last one and half years of the pandemic, a lot has been learned about this new virus and disease, and the knowledge has been utilised for saving millions of human lives. However, moving ahead we must focus our research on the finer and hitherto unexplored facets of the disease. Guidelines, taking cue from evolving scientific data, also need to be broadened to include such scenarios to ensure evidence-based treatment for all.

Conflict of interest

None declared.

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