

# Steroid harms if given early in COVID-19 viraemia

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## SUMMARY

COVID-19 is a biphasic illness with an initial viraemia phase and later effective adaptive immune phase, except in a minority of people who develop severe disease. Immune regulation is the key target to treat COVID illness. In anticipation, an elderly man self-medicated himself with dexamethasone on the day of symptom onset of a flu-like illness, took other symptomatic measures and was tested positive for SARS-CoV-2. His condition deteriorated with each passing day resulting in hospitalisation. He demanded oxygen and declared as severe COVID. With supportive treatment, he recovered after the 20th day of illness. Immunosuppression and anti-inflammation are likely to benefit when the immune response is dysregulated and turning into a cytokine storm. A medication that has saved many could be the one predisposing to severity if taken as a preventive measure, too early in the disease course, especially the viraemia phase.

## BACKGROUND

Coronavirus outbreak is an alarming situation all over the world and its treatment remains a concern till now and is subject of ongoing trials over the entire globe. The steroid is being a considerable option that has evidenced in reducing mortality of this threatening disease and has recently been included in various guidelines, but the risk–benefit horizon and type, dose and timing of steroid remains dubious and requires delineation.

The RECOVERY trial proved dexamethasone (a steroid) useful for cutting down mortality and the need for mechanical ventilation, also mentioned, mild to moderate cases may not benefit or may deteriorate.<sup>1</sup> In the past, adequate and prolonged steroid supplementation has proved to mitigate the critical illness-related corticosteroid insufficiency, thus enhancing the resolution of lungs and systemic inflammation.<sup>2</sup>

Reckless use of steroid surpasses the benefit and our case exemplifies it. We report a case of wrong timing of dexamethasone use in COVID-19 management resulting in delayed recovery.

## CASE PRESENTATION

A 69-year-old man, a practising physician, was admitted to this hospital because of fatigue, a non-productive cough and continuous moderate fever for 7 days. He had close contact with his brother, who was tested positive for SARS-CoV-2. On the first day of illness, he took dexamethasone four tablets of 0.5 mg once a day, continued it for 7 days with hydroxychloroquine 400 mg once a day for 4 days. His throat swab test report came positive for the SARS CoV-2. Due to worrisome symptoms, he

visited our hospital and got admitted. He did not complain of shortness of breath, haemoptysis, loose stools or any other symptoms. His medical history was notable for diabetes mellitus and intermittent bronchial asthma for 7 years along with medications—metformin, glimepiride and intermittent inhalers.

On the initial evaluation, the temperature was raised, oxygen saturation was 96% while he was breathing ambient air. Possible examinations with PPE was unremarkable. Despite routine care and mild symptoms on presentation, he had persistent fever spikes and became oxygen-dependent on day 2 of admission.

## INVESTIGATION

Coincidentally, dengue IgM came positive but turned out negative on a repeat test after a week. Culture reports were sterile, but fever spikes were persistent. His serum LDH was 435.3 U/L (140–280 U/L), hs-CRP of 26.92 mg/L (<10 mg/L), fibrinogen of 444 mg/dL (200–400 mg/dL), ferritin of 208.55 ug/L (24–336 ug/L) and D-dimer of 2675 (<250 ng/mL), rest within normal limits.

Ultrasonography abdomen suggested grade I fatty liver and left renal calculus without any focus of infections. High-resolution computerised tomography (HRCT) chest revealed widespread patchy areas of peripheral dominant ground glass opacities in bilateral lungs, predominantly in posterobasal segments of lower lobes. Crazy paving (thickened interlobular septae with ground glassing) was seen in posterobasal segments (CO-RAD-6 with CTSS-16/40). Due to persistent oxygen requirement, repeat HRCT was performed after 7 days that suggested CTSS-18/40.

## DIFFERENTIAL DIAGNOSIS

- ▶ Viral pneumonia, mostly COVID-19.
- ▶ Atypical bacterial pneumonia.
- ▶ Acute exacerbation of bronchial asthma.

## TREATMENT

He had hypoxaemia, diagnosed as severe COVID-19. Supportive treatment like oxygen, paracetamol, vitamin C, vitamin D, calcium and zinc began at the time of admission. He was switched from oral hypoglycaemic agents to insulin, taking into account deranged renal function (serum creatinine of 2.59 mg/dL), higher than baseline. Close monitoring of random blood glucose levels was done. He was continued on hydroxychloroquine 400 mg once a day for 10 days and ribavirin 800 mg two times a day after he was enrolled into an institutional trial after his consent. Dexamethasone was continued but with a higher dose (6 mg intravenous



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once a day, based on RECOVERY trial evidence). Additionally, he was treated empirically with ceftriaxone, azithromycin, and later on, upgraded to piperacillin and tazobactam, and levofloxacin in consideration of rising counts and persistent fever spikes. A possibility of superadded bacterial pneumonia was kept but ruled out with normal procalcitonin and negative blood cultures. Increased D-Dimer values prompted the addition of low molecular weight heparin. He was planned for experimental tocilizumab (IL-6 inhibitor) administration to halt any ongoing inflammatory process as serial HRCT images showed an increase in severity score, but he refused for the same.

### OUTCOME AND FOLLOW-UP

Symptoms improved during 20 days of hospital stay with decrease in fever spikes, and was discharged in a haemodynamically stable condition after being asymptomatic for 3 days and continued with insulin regimen. Dexamethasone was discontinued after 10 days of initiation at hospitalisation. RT-PCR did turn negative after the 20th day of illness.

### DISCUSSION

An old-aged practising doctor who presented with mild COVID-19 symptoms progressed into severe pneumonia with oxygen dependence. The hypothesised reason for delayed recovery is an unusual history of self-medication of dexamethasone tablets from the first day of illness. There was a strong clinical suspicion of superadded bacterial infection but lacked laboratory evidence. On tracing this patient's history, he was a retired doctor who took dexamethasone tablets as soon he experienced flu-like symptoms and had a positive COVID-19 contact in the vicinity. This happened possibly due to media prominence of the role of only drug available, that is, dexamethasone in mortality benefit at that point of time in COVID-19 pandemic. This early consumption of dexamethasone is a likely culprit of delayed recovery.

After the virus has made its way into the body, there is an initial phase of viral replication for a few days, followed by a phase of adaptive immunity. The replicative phase presents an influenza-like illness as a result of the cytopathic effect of the virus. After adaptive immunity comes into action, viral levels decline. The protective response is T cell-dependent, with CD4 helping T cells that directs toward producing specific neutralising antibodies and with cytotoxic CD8 cells for eliminating infected cells. CD8 cells account for 80% of the infiltrating cells in COVID-19.<sup>3</sup> On the contrary, a dysfunctional response, unable to inhibit viral replication and elimination of the infected cells, may result in an exacerbated inflammatory response leading possibly to a cytokine storm, manifested clinically by severe acute respiratory distress syndrome (ARDS) and systemic consequences, such as disseminated intravascular coagulation.<sup>4</sup> Loss of immune regulation between protective and altered responses due to exacerbation of the inflammatory components appears to be the critical point where disease progression ensues.<sup>5</sup> Hence use of antivirals is in the early phase, and immunosuppressive agents in the adaptive immunity phase.<sup>6</sup> Dexamethasone is an anti-inflammatory agent, primarily acts via inhibition of inflammatory cells and suppresses the expression of inflammatory mediators, which indirectly suppresses immunity. Pathogenesis behind a dramatic response of this drug in the late phase is the suppression of cytokine storm. It is to be noted that dexamethasone resulted in delayed clearance of the virus in SARS-CoV-1 and MERS-CoV infection but proof in SARS-CoV-2 is yet to be established.

It was on 16 June, the RECOVERY trial results were released in the press and brought a great deal of attention. It was successful in testing immunosuppression as a therapeutic

option. Until then, the only evidence-based treatment available was remdesivir—an RNA polymerase inhibitor that modestly shortens time to hospital discharge in patients with severe COVID-19 but does not reduce respiratory tract viral load and mortality.<sup>7–9</sup> Treatment of dexamethasone 6 mg daily for up to 10 days reduced 28-day mortality who received either supplemental oxygen or mechanical ventilation.<sup>1</sup> The same trial also reflected non-beneficence or the possibility of harm in those who did not require oxygen. These results were supported by other trials as well<sup>10</sup>; use of intravenous dexamethasone along with standard care compared with standard care alone resulted in a statistically significant increase in the number of ventilator-free days (days alive and free of mechanical ventilation) over 28 days in COVID-19 patients with moderate or severe ARDS.<sup>11</sup>

To resolve the conflicts of usage of dexamethasone in COVID-19 patients, a New York-based study was conducted with the primary aim to determine the association of early glucocorticoid treatment with mortality or the need for mechanical ventilation. Early use of glucocorticoids was not associated with any reduction in hospital mortality or free of mechanical ventilation. Rather early glucocorticoid use and initial hs-CRP of less than 10 mg/dL posed patients at risk of mortality or mechanical ventilation usage. In contrast, hs-CRP of 20 mg/dL or higher was associated with a significant reduction.<sup>12</sup> We failed to report the level of inflammation or inflammatory markers of the patient when he took dexamethasone. Since it was early in the course of the disease, it is assumed to be low. Early timing and low inflammatory status were considered to be synonymous. As we know single case study may not answer this vital question: whether steroid to be started on the day of symptom onset in the viraemia phase, however, as we can see based on the above pieces of evidence we should start steroids during the immunological phase that usually comes after 7 days of illness. With more studies, soon it will be cleared what is the best time to start steroid in COVID-19 management.

Importantly, tempering a maturing immune response to the SARS-CoV-2 virus is different from having underlying immunosuppression at the time of infection or induced immunosuppression from early use of dexamethasone. It is empirical to determine the right candidature for glucocorticoid treatment to maximise the likelihood of benefit and not to void the ethical principle of non-maleficence, which says 'no harm.' Since dexamethasone is cheap, easily available over the counter, its self-administration becomes a matter of public health and a message to be delivered with caution to buyers and sellers.

### Learning points

- ▶ Dexamethasone should be taken only in severe COVID-19 disease, as it is beneficial in suppressing the overt immune response.
- ▶ If taken early at the time of viraemia (mostly in the first few days of illness), it may suppress protective innate response as well resulting in delayed recovery.

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#### REFERENCES

- 1 RECOVERY Collaborative Group, Horby P, Lim WS, *et al*. Dexamethasone in Hospitalized Patients with Covid-19 - Preliminary Report. *N Engl J Med* 2020. doi:10.1056/NEJMoa2021436. [Epub ahead of print: 17 Jul 2020].
- 2 Veronese N, Demurtas J, Yang L, *et al*. Use of corticosteroids in coronavirus disease 2019 pneumonia: a systematic review of the literature. *Front Med* 2020;7:170.
- 3 García LF, Luis F. Immune response, inflammation, and the clinical spectrum of COVID-19. *Front Immunol* 2020;11:1441.
- 4 Sharma R, Agarwal M, Gupta M. Clinical characteristics and differential clinical diagnosis of novel coronavirus disease 2019 (COVID-19). *Coronavirus Disease 2019 (COVID-19)* 2020:55–70.
- 5 García LF, Response I. Immune response, inflammation, and the clinical spectrum of COVID-19. *Front Immunol* 2020;11:1441.
- 6 Arabi YM, Mandourah Y, Al-Hameed F, *et al*. Corticosteroid therapy for critically ill patients with middle East respiratory syndrome. *Am J Respir Crit Care Med* 2018;197:757–67.
- 7 Beigel JH, Tomashek KM, Dodd LE, *et al*. Remdesivir for the Treatment of Covid-19 - Final Report. *N Engl J Med* 2020;383:1813–26.
- 8 Wang Y, Zhang D, Du G, *et al*. Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial. *Lancet* 2020;395:1569–78.
- 9 Goldman JD, Lye DCB, Hui DS, *et al*. Remdesivir for 5 or 10 days in patients with severe Covid-19. *N Engl J Med* 2020;383:1827–37.
- 10 Mahase E. Covid-19: low dose steroid cuts death in ventilated patients by one third, trial finds. *BMJ* 2020;369:m2422.
- 11 Tomazini BM, Maia IS, Cavalcanti AB, *et al*. Effect of dexamethasone on days alive and Ventilator-Free in patients with moderate or severe acute respiratory distress syndrome and COVID-19: the Codex randomized clinical trial. *JAMA* 2020;324:1307.
- 12 Keller MJ, Kitsis EA, Arora S, *et al*. Effect of systemic glucocorticoids on mortality or mechanical ventilation in patients with COVID-19. *J Hosp Med* 2020;15:489–93.

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