Should dexamethasone be used for COVID-19?

This write-up summarises a rapid evidence review of dexamethasone as a potential treatment for patients with COVID-19. The information may be revised as new evidence emerges.

Background

Recently, online news articles have cited that dexamethasone may be the first drug to reduce mortality in critically ill patients with COVID-19 infection[1,2], however, local experts have also cautioned against widespread use until detailed data are published in a peer-reviewed journal[3].

Dexamethasone is a corticosteroid that has been used since the 1960s to reduce inflammation. It is included in the World Health Organization (WHO) Essential Medicines List[4] and is approved by regulatory agencies (including US FDA, EMA and HSA) for a range of conditions, including adrenocortical insufficiency, inflammatory disorders, cancer and shock.

The full spectrum of COVID-19 infection ranges from asymptomatic disease to mild respiratory tract illness to severe pneumonia, acute respiratory distress syndrome (ARDS), multiorgan failure, and death. Clinical presentation of some critically ill patients with COVID-19 suggest a "Cytokine Storm Syndrome" or hyperinflammatory state in which the immunosuppressive effects of corticosteroids may be beneficial[5].

Corticosteroids were widely used during outbreaks of severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS), however, their efficacy has been controversial, largely based on observational studies with conflicting results[6,7]. Taken together with data showing that corticosteroids delay viral clearance and increase bacterial/fungal superinfections, most guidelines do not recommend the routine use of corticosteroids unless clinically indicated[8-11].

Clinical evidence

Published evidence for dexamethasone to treat COVID-19 is limited, however, preliminary findings from the RECOVERY trial suggest that it reduces mortality in patients with severe disease[12].

RECOVERY is a large, multicentre, open-label, randomised controlled trial (RCT) conducted in the United Kingdom to assess a range of treatments for patients hospitalised with COVID-19. Over 11,500 patients have been enrolled in the trial, of which 2104 patients have been randomised to receive dexamethasone 6 mg orally or intravenously for 10 days. On June 16, 2020, a press release on the preliminary findings from the trial suggested that dexamethasone reduced the risk of 28-day mortality by 35% in patients requiring ventilator support (rate ratio, RR 0.65; 95% CI, 0.48 to 0.88; p=0.0003) and by 20% in patients receiving oxygen (RR 0.80; 95% CI, 0.67 to 0.96; p=0.0021) compared with the usual care control group. Of note, no benefit was seen in patients not requiring respiratory support (RR 1.22; 95% CI, 0.86 to 1.75; p=0.14)[12]. Publication of the study results is currently pending.

The effects of dexamethasone in ARDS have been assessed in a multicentre RCT which included 277 patients with non-COVID-19 related moderate to severe ARDS. Patients were randomised to receive routine care or intravenous dexamethasone 20 mg once daily from day 1 to 5, followed by 10 mg once daily from day 6 to 10. Patients in both groups were also on mechanical ventilator support. Results showed that patients in the dexamethasone group had more ventilator-free days compared to the control group (difference 4.8 days; 95% CI, 2.57 to 7.03; p<0.0001) and lower all-cause 60-day mortality (21% versus 36%; difference -15.3%; 95% CI, -25.9 to -4.9; p=0.0047). The incidence of adverse events did not differ significantly between treatment groups. However, as there was substantial heterogeneity in terms of ARDS aetiology (~ 50% caused by pneumonia), generalisability of these results to COVID-19 patients with ARDS may be limited. In addition, the trial had strict inclusion criteria, excluding 73% of eligible patients because of pre-existing comorbidities[13].

ACE agency for care effectiveness
MINISTRY OF HEALTH SINGAPORE

Several other international trials of dexamethasone for treating COVID-19 have been registered and are in planning or active recruitment stages with data anticipated to mature in the near future (Table 1).

Table 1: Studies registered internationally for dexamethasone in patients with COVID-19

Study identifier	Study Design	Intervention	Comparator(s)	Date of primary completion
NCT04381936[14] EudraCT 2020-001113-21[15] (RECOVERY)	MC*, OL, phII/III, randomised, factorial assignment	6 intervention groups: • Dexamethasone (low dose) • Lopinavir-ritonavir • Azithromycin • Convalescent plasma • Tocilizumab • Hydroxychloroquine	Standard of care	December 2020
NCT04325061[16] EudraCT 2020-001278-31[17] (DEXA-COVID19)	MC^, OL, phIV, randomised, parallel assignment	Dexamethasone	Standard of care	October 2020
NCT04347980[18] EudraCT 2020-001333-13[19] (DHYSCO)	MC‡, SB, phIII, randomised, parallel assignment	Dexamethasone plus hydroxychloroquine	Hydroxychloroquine	June 2020
NCT04395105[20]	MC†, OL, phIII, randomised, parallel assignment	Dexamethasone	Standard of care	December 2020
NCT04344730[21] EudraCT 2020-001457-43[22] (COVIDICUS)	MC‡, QB, randomised, factorial assignment	Dexamethasone	Placebo	December 2020
NCT04360876[23]	SC#, DB, phIIa, randomised, parallel assignment	Dexamethasone	Placebo	September 2020
NCT04327401[24] (CoDEX)	MCα, OL, phIII, randomised, parallel assignment	Dexamethasone	Standard of care	August 2020
IRCT20151227025726N17[25]**	SC, OL, phII/III, randomised, parallel assignment	Dexamethasone plus standard of careΔ	Standard of careΔ	NA
IRCT20120215009014N354[26]	SC, QB, phII, randomised, parallel assignment	3 intervention groups: • Dexamethasone • Methylprednisolone • Hydrocortisone	Standard of care	NA

Abbreviations: DB, double blind; MC, multicenter; NA, not available; OL, open label, phII, phase II; phIII, phase III; phIV: phase IV; QB, quadruple blind; SB, single blind; SC, single center.
*UK; ^Spain; ‡France; †Argentina; #USA; αBrazil; ** Iran; Δ includes lopinavir/ritonavir

Recommendations from professional bodies

Guidelines issued by the WHO, National Institutes of Health (NIH, USA), European Society of Intensive Care Medicine and the Society of Critical Care Medicine (ESICM/SCCM) and the National Centre for Infectious Diseases (NCID, Singapore) do not recommend the routine use of systemic corticosteroids for COVID-19 unless patients are in refractory shock or were previously on chronic corticosteroid therapy prior to COVID-19 diagnosis[8-11].

For mechanically ventilated patients with COVID-19 and ARDS, NIH guidelines remain neutral while ESICM/SCCM guidelines suggest that corticosteroids may be used[9,11].

The WHO is currently coordinating a meta-analysis on the evidence for dexamethasone and will be updating their clinical guidance on the appropriate use of dexamethasone for treating COVID-19 once outcomes are available.

Conclusion

Current evidence on the efficacy and safety of dexamethasone for treating COVID-19 infection is limited. No firm scientific conclusion can be made, although the drug appears to be effective in severely ill patients with COVID-19 based on preliminary data. Several ongoing studies of dexamethasone for COVID-19 are likely to report results in the months ahead, and their findings will determine whether dexamethasone should be used more widely in this setting.

References

1. Channel News Asia. Steroid dexamethasone first drug shown to save lives of severest COVID-19 cases. Published on 16 June 2020. Accessed on 23 June 2020. at: https://www.channelnewsasia.com/news/world/covid-19-steroid-dexamethasone-first-drug-shown-to-save-lives-12841956.
2. WHO welcomes preliminary results about dexamethasone use in treating critically ill COVID-19 patients. Accessed on 23 June 2020 at: https://www.who.int/news-room/detail/16-06-2020-who-welcomes-preliminary-results-about-dexamethasone-use-in-treating-critically-ill-covid-19-patients.
3. Channel New Asia. Why Steroids not recommended in Singapore treatment of COVID-19 patients despite 'major breakthrough' in UK. Published on 22 June 2020. Accessed on 23 June 2020.
4. WHO Model Lists of Essential Medicines 21st List 2019. Accessed on 23 June 2020 at: http://www.who.int/medicines/publications/essentialmedicines/en/.
5. Mehta, P, McAuley DF, Brown M, et al. COVID-19: consider cytokine storm syndromes and immunosuppression. The Lancet. 2020;395(10229):1033-4.
6. Yang, Z, Liu J, Zhou Y, et al. The effect of corticosteroid treatment on patients with coronavirus infection: a systematic review and meta-analysis. Journal of Infection. 2020.
7. Ye, Z, Wang Y, Colunga-Lozano LE, et al. Efficacy and safety of corticosteroids in COVID-19 based on evidence for COVID-19, other coronavirus infections, influenza, community-acquired pneumonia and acute respiratory distress syndrome: a systematic review and meta-analysis. CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne. 2020.
8. World Health Organization (WHO) Interim Guidance. Clinical management of COVID-19. Published 27 May 2020. Accessed on 23 June 2020. at: https://www.who.int/publications/i/item/clinical-management-of-covid-19.
9. NIH Coronavirus Disease 2019 (COVID-19) treatment guidelines. [Available from: https://www.covid19treatmentguidelines.nih.gov/.
10. National Centre for Infectious Diseases (NCID) Singapore. Interim Treatment Guidelines for COVID-19. (Version 2.0, dated 15 June 2020) [Available from: https://www.ncid.sg/Documents/Interim%20Treatment%20Guidelines%20for%20COVID-19%20v2%2015-6-2020.pdf.
11. Alhazzani, W, Møller MH, Arabi YM, et al. Surviving Sepsis Campaign: guidelines on the management of critically ill adults with Coronavirus Disease 2019 (COVID-19). 2020;46(5):854-87.
12. University of Oxford Press Release. Low-cost dexamethasone reduces death by up to one third in hospitalised patients with severe respiratory complications of COVID-19. at: http://www.ox.ac.uk/news/2020-06-16-low-cost-dexamethasone-reduces-death-one-third-hospitalised-patients-severe.
13. Villar, J, Ferrando C, Martínez D, et al. Dexamethasone treatment for the acute respiratory distress syndrome: a multicentre, randomised controlled trial. The Lancet Respiratory Medicine. 2020;8(3):267-76.
14. Clinicaltrials.gov. Accessed 23 June 2020 at: https://www.clinicaltrials.gov/ct2/show/NCT04381936.
15. Clinicaltrialsregister.eu. Accessed 23 June 2020 at: https://www.clinicaltrialsregister.eu/ctr-search/trial/2020-001113-21/GB.
16. Clinicaltrials.gov. Accessed 23 June 2020 at: https://www.clinicaltrials.gov/ct2/show/NCT04325061.
17. Clinicaltrialsregister.eu. Accessed 23 June 2020 at: https://www.clinicaltrialsregister.eu/ctr-search/trial/2020-001278-31/ES.
18. Clinicaltrials.gov. Accessed 23 June 2020 at: https://www.clinicaltrials.gov/ct2/show/NCT04347980.
19. Clinicaltrialsregister.eu. Accessed 23 June 2020 at: https://www.clinicaltrialsregister.eu/ctr-search/trial/2020-001333-13/FR.
20. Clinicaltrials.gov. Accessed 23 June 2020 at: https://www.clinicaltrials.gov/ct2/show/NCT04395105.
21. Clinicaltrials.gov. Accessed 23 June 2020 at: https://www.clinicaltrials.gov/ct2/show/NCT04344730.
22. Clinicaltrialsregister.eu. Accessed 23 June 2020 at: https://www.clinicaltrialsregister.eu/ctr-search/trial/2020-001457-43/FR.
23. Clinicaltrials.gov. Accessed 23 June 2020 at: https://www.clinicaltrials.gov/ct2/show/NCT04360876.
24. Clinicaltrials.gov. Accessed 23 June 2020 at: https://www.clinicaltrials.gov/ct2/show/NCT04327401.
25. Iranian Registry of Clinical Trials. Accessed 23 June 2020 at: https://www.en.irct.ir/trial/48153.
26. Iranian Registry of Clinical Trials. Accessed 23 June 2020 at: https://www.en.irct.ir/trial/48043.

ACE agency for care effectiveness
MINISTRY OF HEALTH SINGAPORE