Dexamethasone for influenza

Intervention

Dexamethasone 6mg by mouth, nasogastric tube or intravenously for 10 days or until discharge, whichever is sooner.

Pregnant women should receive oral prednisolone 40mg once daily or intravenous hydrocortisone 80mg twice daily instead of dexamethasone.

Information on dexamethasone for influenza

RECOVERY and other randomised trials have shown that corticosteroids reduce the risk of death by around one fifth in hypoxic COVID-19 patients.[1,2] There could be a similar benefit in hospitalised influenza patients, but their role in this setting remains uncertain. Corticosteroids have been used in hospitalised influenza patients for many years without good evidence of benefit or safety.[3,4] Although observational studies have reported higher mortality associated with corticosteroids use, these are prone to biases that make them unreliable, particularly if sicker patients are more likely to have received steroid treatment.[3] A large randomised trial is needed to reliably determine any benefits or risks.

Eligibility

- Hospitalised patients with an acute pneumonia syndrome, in general based on:
  a) typical symptoms of new respiratory infection, and
  b) objective evidence of acute lung disease (e.g. compatible imaging [plain X-ray, CT or ultrasound], clinical examination, or new hypoxia), and
  c) alternative causes considered unlikely
- Confirmed influenza A or B infection (laboratory test or point-of-care test if performed by a healthcare worker).
- Hypoxia requiring supplemental oxygen or SpO_2 <92% on air.

Exclusions

- Use of systemic corticosteroids for >24h during the current illness with a glucocorticoid-equivalent of ≥10mg prednisolone per day (equivalent to ≥1.5mg dexamethasone or ≥40mg hydrocortisone).
- Current or expected indication for systemic corticosteroids as determined by the patient's managing clinician (e.g. COPD, septic shock).
- Any contraindication to corticosteroids as determined by the managing clinician.
- Suspected or confirmed SARS-CoV-2 infection (testing is not required unless clinically indicated).

Frequently asked questions

1. ***Can patients receiving regular low-dose systemic corticosteroids be enrolled?***
   Yes, if the dose is lower than specified in the exclusions.
2. ***Can patients who have received a higher dose of systemic corticosteroids be enrolled?***
   Yes, but only if they have received this for <24 hours and there is no indication for continued treatment.
3. ***Can patients receiving inhaled or topical corticosteroids be enrolled?***
   Yes, and this can continue regardless of treatment allocation.

4. ***Can patients who require corticosteroids equivalent to ≥10mg prednisolone for a co-existing medical condition (e.g. COPD) be enrolled?***
   No. They should receive corticosteroids as clinically indicated.
5. ***Can patients with diabetes be enrolled?***
   Yes, but it may not be appropriate for patients with unstable diabetes or acute complications of diabetes.

   Regular glucose monitoring will be required in line with usual clinical practice, with possible adjustment of diabetic therapy to prevent/treat hyperglycaemia. Dexamethasone may be stopped if causing uncontrollable hyperglycaemia.
6. ***Can patients with hepatic impairment be enrolled?***
   Yes, and no dose adjustment is needed.
7. ***Can patients with renal impairment be enrolled?***
   Yes, and no dose adjustment is needed.
8. ***Can pregnant and breast-feeding women be enrolled?***
   Yes, but prednisolone (40mg once daily) or hydrocortisone (80mg twice daily IV) should be used instead of dexamethasone to reduce fetal/infant exposure. Inclusion should be discussed with an obstetric specialist (see protocol appendix 4)
9. ***Can children (age <18) be enrolled?***
   This arm is open to children of any age in the UK (see protocol appendix 3 for dosing). Children are excluded in all other countries.
10. ***Can patients with hospital-acquired influenza be enrolled?***
    Yes, if influenza is thought to be the cause of the patient's pneumonia.
11. ***Is screening for endemic infections (e.g. Strongyloides) required?***
    No, but this can be done if required by local practice.
12. ***Can dexamethasone be used concomitantly with other treatments?***
    The patient's managing clinician and the investigator should decide if corticosteroids are contraindicated due to concomitant medication, based on their usual practice. No specific trial exclusions are related to this.

    Concomitant use of potent CYP3A inhibitors, including clarithromycin and erythromycin, is not contraindicated but the possible risk of increased corticosteroid side-effects should be considered (note azithromycin, an alternative macrolide used for CAP, is not a potent CYP3A inhibitor).

    Concomitant use of other immunomodulatory therapies is not contraindicated, but the total burden of therapy should be considered.
13. ***Are tablet and liquid preparations of dexamethasone interchangeable?***
    Yes, they are dose-equivalent for the purposes of the trial.
14. ***Can liquid dexamethasone be administered down an NG tube?***
    Yes.
15. ***Are oral and IV preparations of dexamethasone interchangeable?***
    Yes, they are dose-equivalent for the purposes of the trial. An approximate 10% over or under dosing is acceptable if the IV formulation makes exact dosing is difficult.

16. Can dexamethasone be stopped abruptly after 10 days of treatment?

Yes, acute adrenal insufficiency on withdrawal is unlikely with the dose and duration used in RECOVERY. However, if the managing clinician believes the patient is at high risk for adrenal insufficiency they may choose to reduce the dose gradually according to their usual practice. If so, they should determine the appropriate withdrawal regimen.

The SmPC advises "Abrupt withdrawal of doses of up to 6mg daily of dexamethasone for 3 weeks is unlikely to lead to clinically relevant HPA-axis suppression in the majority of patients. In the following patient groups, gradual withdrawal of systemic corticosteroid therapy should be *considered* even after courses lasting 3 weeks or less:

- Patients who have had repeated courses of systemic corticosteroids, particularly if taken for greater than 3 weeks.
- When a short course has been prescribed within one year of cessation of long-term therapy (months or years).
- Patients who may have reasons for adrenocortical insufficiency other than exogenous corticosteroid therapy.
- Patients receiving doses of systemic corticosteroid greater than 6mg daily of dexamethasone.
- Patients repeatedly taking doses in the evening"

17. Should dexamethasone be prescribed as take-home medication if the patient is discharged before day 10?

No, trial dexamethasone should be stopped on the day of hospital discharge, or at day 10, whichever is sooner.

18. Can dexamethasone be continued beyond day 10?

Use of dexamethasone beyond day 10 is outside the trial protocol, and is at the discretion of the managing clinician.

19. Can dexamethasone be stopped before day 10?

The trial regimen is dexamethasone for 10 days or until discharge. However, the managing doctor may stop treatment earlier if they think the risks of treatment outweigh any potential further benefit (for example in a patient who is medically ready to be discharged but remains in hospital for other reasons). This would not be considered a protocol deviation. If this happens then make sure that the number of days of treatment actually received is recorded on the follow up form.

20. Is dexamethasone dosing to be adjusted for weight in adults?

No, a fixed dose of 6 mg dexamethasone is to be given.

References

1 RECOVERY Collaborative Group, Horby P, Lim WS, *et al.* Dexamethasone in Hospitalized Patients with Covid-19. *N Engl J Med* 2021; **384**: 693–704. PMID 32678530

2 WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group, Sterne JAC, Murthy S, *et al.* Association Between Administration of Systemic Corticosteroids and Mortality Among Critically Ill Patients With COVID-19: A Meta-analysis. *JAMA* 2020; **324**: 1330–41. PMID 32876694

3 Lansbury L, Rodrigo C, Leonardi-Bee J, Nguyen-Van-Tam J, Lim WS. Corticosteroids as adjunctive therapy in the treatment of influenza. *Cochrane Database Syst Rev* 2019; **2**: CD010406. PMID 30798570

4 Lim WS, Brittain C, Duley L, *et al.* Blinded randomised controlled trial of low-dose Adjuvant Steroids in Adults admitted to hospital with Pandemic influenza (ASAP): a trial 'in hibernation', ready for rapid activation. *Health Technol Assess* 2015; **19**: 1–78, vii–viii. PMID 25716702