RECOVERY
Randomised Evaluation of COVID-19 Therapy

High-dose corticosteroids for COVID-19

Intervention

Dexamethasone 20mg for 5 days followed by dexamethasone 10mg for 5 days, stopped on discharge if this occurs before the 10 day course is complete. Pregnant women should receive an alternative corticosteroid as below.

It is anticipated that patients who are allocated usual care in this arm will receive corticosteroids at standard doses instead (6mg dexamethasone/day or equivalent).

Summary of information on high-dose corticosteroids

RECOVERY showed that 6mg dexamethasone provided a significant reduction in mortality in patients hospitalised with COVID-19.[1] Combining the IL-6 inhibitor tocilizumab with low dose dexamethasone resulted in a further reduction in mortality, but even with this combination mortality remained high at 29%.[2] Higher doses of dexamethasone (>15mg/day) would completely saturate cytosolic glucocorticoid receptors and may also have enhanced non-genomic effects.[3]

Although other randomised trials in COVID-19 patients have used doses of dexamethasone up to 20mg and reported clinical benefit, these doses have not been compared with the lower dose used in RECOVERY.[4] Uncertainty remains about whether higher dose corticosteroids provide additional benefit in adults with hypoxia hospitalised with COVID-19, and whether they are associated with greater hazards.

Eligibility

- Adults (aged ≥18) hospitalised with a viral pneumonia syndrome and confirmed SARS-COV-2 infection
- Respiratory failure requiring non-invasive ventilation (including CPAP and BiPAP), high-flow nasal oxygen (e.g. Airvo), invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO)*

Contraindications

- Current or anticipated use of intermediate/high-dose corticosteroids (≥7mg dexamethasone/day or equivalent)
- Any medical history that would put the patient at significant risk if they were to participate in the trial, in the opinion of the attending clinician.
- Patients with known or suspected influenza infection (influenza testing is not required if not indicated for routine care)
- Current use of Paxlovid or other potent CYP3A inhibitors (including clarithromycin, HIV protease inhibitors, and itraconazole). Recent use is not a contraindication.

* Recruitment of patients not requiring oxygen, or requiring simple oxygen only, was stopped on 13th May 2022 because of safety concerns. The Data Monitoring Committee encouraged randomisation to continue for patients requiring higher levels of respiratory support.

Cautions

- Other immunomodulatory therapies are not contraindicated, but investigators should consider the total burden of therapy (e.g. combining IL-6 receptor antagonist therapy with high-dose dexamethasone).

Frequently asked questions

1. ***Can patients already taking systemic corticosteroids be enrolled?***
   Yes, as long as they are not receiving the equivalent of ≥7mg dexamethasone/day. Patients who are taking low-dose dexamethasone for COVID-19 and those on steroids for another indication are eligible.

2. ***My patient had a dose of corticosteroids today and has been randomised to high-dose dexamethasone now, should this be topped up?***
   Yes, give additional dexamethasone so they receive the equivalent of 20mg in total today, and start dexamethasone 20mg/day tomorrow morning (e.g. if 6mg was taken earlier, give another 14mg dexamethasone now).

3. ***How long after starting low-dose corticosteroids for COVID-19 can patients be enrolled?***
   There is no time limit, but we would encourage randomisation as soon as possible after treatment for COVID-19 has started. This trial arm is not aiming to assess high-dose steroids as rescue therapy for those with worsening infection despite standard treatment.

4. ***Can patients on inhaled corticosteroids be enrolled in this arm?***
   Yes, and this can continue regardless of treatment allocation.

5. ***Can patients with diabetes be enrolled in this arm?***
   Yes, patients with diabetes can be enrolled but it may not be appropriate to enrol patients with unstable diabetes, or with acute complications of diabetes.

6. ***Is any additional monitoring required for patients with diabetes?***
   Patients with diabetes will require regular glucose monitoring according to usual clinical practice with appropriate adjustment of diabetic therapy to prevent/treat any emergent hyperglycaemia.

7. ***If hyperglycaemia cannot be controlled, what should be done?***
   Dexamethasone may be stopped (or the dose reduced) if causing uncontrollable hyperglycaemia.

8. ***What routes of administration can be used?***
   Dexamethasone can be given orally, via a feeding tube, or intravenously. For the purposes of the trial, doses are equivalent whether tablet, liquid, or intravenous formulations are used.

9. ***How precise does dosing need to be?***
   Vials of IV dexamethasone may come in concentrations that make it difficult to draw up exactly 20mg. Up to 10% over or under dosing is reasonable if this makes administration more practical e.g. it is acceptable to use 5ml of 3.8mg/ml solution (slight under dose of 19mg).

10. ***Can dexamethasone be given during pregnancy?***
    To reduce foetal exposure, an alternative corticosteroid should be used that does not cross the placenta so readily. Pregnant women should receive either prednisolone orally (130mg for 5 days then 65mg for 5 days), hydrocortisone intravenously (540mg for 5 days then 270mg for 5 days), or methylprednisolone intravenously (100mg for 5 days then 50mg for 5 days).

11. ***Do patients with renal or liver impairment need dose adjustment?***
    No.

12. ***Can treatment be stopped abruptly, or does it need to be withdrawn gradually?***
    Gradual withdrawal is not required by the trial protocol, as for most patients it will be reasonable to stop abruptly. However, the need for gradual withdrawal should be considered for each patient, and is at the discretion of the clinical team (as is the rate of withdrawal).

    The SPC has the following advice[5]:
    "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 repeatedly taking doses in the evening.
    - Patients receiving doses of systemic corticosteroid greater than 6mg daily of dexamethasone."

    The final point applies to all participants receiving high-dose dexamethasone in RECOVERY, so particular consideration should be given to gradual withdrawal in patients with additional risk factors.

13. ***Can high-dose dexamethasone be continued beyond day 10 from randomisation?***
    Use of dexamethasone beyond day 10 is outside the trial protocol and is a matter of individual clinical judgement.

14. ***Do biological samples need to be taken from patients in this arm?***
    No, these are only required for participants in the antiviral arms

References

1. RECOVERY Collaborative Group *et al.* Dexamethasone in Hospitalized Patients with Covid-19. *N Engl J Med* **384**, 693–704 (2021).
2. RECOVERY Collaborative Group. Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. *Lancet* **397**, 1637–1645 (2021).
3. Stahn, C. & Buttgereit, F. Genomic and nongenomic effects of glucocorticoids. *Nat Clin Pract Rheumatol* **4**, 525–533 (2008).
4. The WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group. Association Between Administration of Systemic Corticosteroids and Mortality Among Critically Ill Patients With COVID-19: A Meta-analysis. *JAMA* **324**, 1330–1341 (2020).
5. Dexamethasone 2mg Tablets - Summary of Product Characteristics (SmPC) - (emc). http://www.medicines.org.uk/emc/product/5411