RECOVERY
Randomised Evaluation of COVID-19 Therapy

Intervention

Dexamethasone 6mg (equivalent to prednisolone 38 mg) once daily for 10 days or until discharge.

The value of corticosteroids as adjuvant therapy in severe acute respiratory viral infections is widely debated.[1,2] Unfortunately there are no clinical trial data on which to make treatment recommendations.

Existing Practice

Use of corticosteroids in patients hospitalised with an acute respiratory infection is common. A multicentre study of adults hospitalised with acute respiratory infections in Europe between 2016 and 2019 found that amongst 863 admissions, 208 (24%) received oral or intravenous steroids (unpublished data). In a cohort of 404 patients hospitalised with influenza A associated pneumonia in China, 33% of mild-moderate cases and 79% of severe cases received corticosteroid treatment[3].

Existing Guidance

Existing Guidelines regarding the use of corticosteroids in COVID-19 infection vary in their recommendations but are supportive of the evaluation of corticosteroids in a clinical trial.

1. The WHO Guideline (28 Jan 2020) recommends against the routine use of systemic corticosteroids for treatment of viral pneumonia or ARDS outside of clinical trials.
2. The Surviving Sepsis Campaign Guideline (in press) suggests the use of systemic corticosteroids in patients with ARDS but not in patients without ARDS. https://www.sccm.org/getattachment/Disaster/SSC-COVID19-Critical-Care-Guidelines.pdf
3. The NHS Critical Care Guideline (16 March 2020), and Clinical management guideline for adults admitted to hospital with COVID-19 infection (16 March 2020) both distinguish between high-dose corticosteroids (not routinely recommended) versus low-dose corticosteroids (which may be considered as part of a clinical trial). https://www.england.nhs.uk/coronavirus/wp-content/uploads/sites/52/2020/03/specialty-guide-itu-and-coronavirus-v1-16-march-2020.pdf

Clinical outcomes

COVID-19 infection

A retrospective cohort study of 201 patients with COVID-19 pneumonia hospitalised in Wuhan, China, reported that in patients with ARDS (n=84) methylprednisolone therapy was associated with a reduced risk of death (HR 0.38, 95%CI 0.2 to 0.72, p=0.003)[4].

SARS-CoV

During the outbreak of severe acute respiratory syndrome (SARS) in 2003, caused by SARS-CoV-1, oral corticosteroids were commonly used in the hospital setting. They were often given to patients at risk of, or who had developed, pneumonia/ARDS. The majority of patients received moderate-to-high doses of corticosteroids (equivalent to prednisolone > 60 mg daily, including very high pulsed doses of methylprednisolone; 0.5 – 1.0g) with reductions in mortality reported based on cohort analyses.[5,6] A systematic review of 29 studies documenting corticosteroid use for SARS concluded that the available data in relation to clinical outcomes were inconclusive.[7] However, randomised clinical trial data are lacking.

MERS-CoV

In patients with Middle East Respiratory Syndrome coronavirus (MERS-CoV), a retrospective multi-centre evaluation of corticosteroid therapy (median dose hydrocortisone 300 mg per day (equivalent to prednisolone 75 mg per day) x 7 days from 14 Saudi Arabian tertiary care hospitals (n=309) found no significant reduction in mortality (OR 0.75, 95% CI 0.52 to 1.07) after adjustment for time-varying confounders.[8] However, randomised clinical trial data are lacking.[9]

Influenza

The uncertainty as regards the possible benefits of corticosteroids in severe influenza infection is well recognised, as confirmed in the most recent Cochrane systematic review (2019).[10] The vast majority of studies involved moderate (prednisolone >50 mg per day equivalent) to high doses of corticosteroids.[11] In the only study to assess the role of different doses of corticosteroids on mortality, a propensity-score matched case-control analysis (n=2141 patients) found that, in hospitalised patients with H1N1 influenza infection, low-to-moderate doses of corticosteroids were associated with lower mortality (aHR 0.64, 95% 0.43 to 0.96) whereas high-dose corticosteroids (>prednisolone 188 mg daily equivalent) was not (aHR 0.91, 95% CI 0.58 to 1.44).[12]

Pneumonia, ARDS, septic shock

A growing volume of clinical trial data from patients with severe community acquired pneumonia, ARDS and septic shock suggest benefit from low-to-moderate dose corticosteroids in relation to mortality and length of stay.[13-15] The most recent clinical trial in patients with ARDS found dexamethasone (20 mg x 5 days, then 10mg x 5 days) was associated with a reduction in mean ventilator-free days (4.8 days, 95% CI 2.57 to 7.03) and 60-day mortality (-15.3%, 95%CI -25.9% to -4.9%)[14]

Safety

Adverse outcomes

The WHO Guideline mentions potential harm arising from the use of systemic corticosteroids in studies of patients with SARS and MERS. In the systemic review of corticosteroid use in SARS, four studies were reported as being associated with possible harm; finding possible

associations with corticosteroid-induced diabetes and avascular necrosis of the bone.[7] These harms were considered to be related to the high doses of corticosteroids used (average dose >prednisolone 100 - 200 mg per day equivalent). All of these harms are known adverse effects of corticosteroids.

In trials of low-to-moderate doses of corticosteroids, the main adverse effect has been hyperglycaemia.[14,16] A systematic review of (mainly low-dose) corticosteroid trials in severe sepsis and septic shock did not identify any increased risk of gastroduodenal bleeding, superinfection or neuromuscular weakness; an association with an increased risk of hyperglycaemia (RR 1.16, 95% CI 1.07 to 1.25) and hypernatraemia (RR 1.61, 95% CI 1.26 to 2.06) was noted.[17]

Viral shedding

Slower clearance of viral RNA has been observed in patients with SARS, MERS and influenza treated with systemic corticosteroids.[8,18,19] The clinical significance of this delayed viral RNA clearance is unknown.

Summary

Overall, there remains widespread uncertainty regarding the benefit on clinical outcomes (specifically mortality) of systemic corticosteroids in the treatment of viral pneumonia and ARDS. Some studies indicate possible benefit, but none are conclusive. Opinions and guidelines have been developed based on weak to very weak data providing inconclusive results.

The harms associated with systemic corticosteroid use are related to known adverse effects from corticosteroids and which are mostly dose-dependent. The increase in duration of viral shedding observed in studies involving SARS and MERS is of uncertain clinical significance (as recognised by the Surviving Sepsis Guideline development group).

The uncertainty generated by the weak evidence base is reflected in the current differences in clinical guidance and clinical practice globally. This clinical equipoise is an important reason to conduct an adequately powered clinical trial. The results from such a trial will have immediate global impact by clarifying the role of low-dose systemic corticosteroids in viral pneumonia/ARDS.

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FAQs for dexamethasone arm

1. Can someone on regular (>2 months duration) oral corticosteroids at the time of hospital admission be enrolled in the dexamethasone arm? No. They should continue on a clinically-appropriate dose of corticosteroids as clinically indicated (either usual dose, or an increased "stress" dose if needed).

2. Can someone on regular (>2 months duration) inhaled corticosteroids at the time of hospital admission be enrolled in the dexamethasone arm? Yes.

3. Can someone who requires initiation of oral corticosteroids for treatment of a co-existing medical condition (eg. exacerbation of COPD) be enrolled in the dexamethasone arm? No. They should receive corticosteroids as clinically indicated.

4. Can someone who is diabetic be enrolled in the dexamethasone arm? Yes. Patients with diabetes (diet, drug or insulin controlled) can be enrolled. Diabetes is not an exclusion criterion. However, it may not be clinically appropriate to enrol patients with unstable diabetes, or acute complications of diabetes, to the dexamethasone arm.

5. For patients with diabetes who are enrolled in the dexamethasone arm, is any additional monitoring required? 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.

6. If dexamethasone-induced hyperglycaemia cannot be controlled, what should be done? Dexamethasone may be stopped if causing uncontrollable hyperglycaemia. Dexamethasone-induced hyperglycaemia is not a SUSAR (it is a known adverse effect of dexamethasone).

7. Is dexamethasone safe when given during pregnancy? Yes. "Following a review of the data on the safety of systemic corticosteroids used in pregnancy and breast-feeding the CSM (May 1998) concluded that corticosteroids vary in their ability to cross the placenta but there is no convincing evidence that systemic corticosteroids increase the incidence of congenital abnormalities such as cleft palate or lip. Pregnant women with fluid retention should be monitored closely when given systemic corticosteroids." (source: BNF)

8. Are the tablet and liquid preparations of dexamethasone inter-changeable? Yes. For the purposes of this trial, the available tablet and liquid preparations of dexamethasone are dose-equivalent.

9. Can liquid dexamethasone be administered down an NG tube? Yes.

10. Are IV preparations of dexamethasone dose equivalent to PO preparations? Yes. Vials of IV dexamethasone may come in concentrations (eg. 3.33 or 3.8 mg per ml) that make

it difficult to draw up 6 mg of dexamethasone exactly. An approximate 10% over or under dosing is reasonable as a practical measure eg. accept 1.5 ml of 3.8 mg per ml solution (slight under dose of 5.7 mg) and 2 ml of 3.33 mg per ml (slight over dose of 6.6 mg) as being acceptable for a dexamethasone 6 mg dose.

11. In renal impairment, is any dose adjustment required? No.

12. In hepatic impairment, is any dose adjustment required? No.

13. Can dexamethasone be stopped abruptly after 10 days of treatment? Yes. At the dose and duration prescribed for the RECOVERY Trial, acute adrenal insufficiency upon withdrawal is unlikely.

    BNF advice is that "systemic corticosteroids may be stopped abruptly in those whose disease is unlikely to relapse *and* who have received treatment for 3 weeks or less *and* who are not included in the patient groups described below:

    - received more than 40 mg prednisolone (or equivalent) daily for more than 1 week;
    - been given repeat doses in the evening;
    - received more than 3 weeks' treatment;
    - recently received repeated courses (particularly if taken for longer than 3 weeks);
    - taken a short course within 1 year of stopping long-term therapy;
    - other possible causes of adrenal suppression."

14. If the patient is being discharged before Day 10 from randomisation, should dexamethasone be prescribed as take-home medication? No. The trial intervention (dexamethasone) is stopped on the day of hospital discharge, or at Day 10 whichever is sooner.

15. Can dexamethasone be continued beyond Day 10 from randomisation? Use of dexamethasone beyond Day 10 is outside the trial protocol and is a matter of individualised clinical judgement.

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