RECOVERY
Randomised Evaluation of COVID-19 Therapy

Intervention

Colchicine **loading dose** 1mg after randomisation followed by 500 micrograms 12 hours later, then **maintenance dose** 500 micrograms twice daily for a further 9 days or until hospital discharge.

In the RECOVERY Trial we are testing colchicine, an anti-inflammatory drug that may be beneficial in COVID-19.

Summary of information on colchicine in COVID-19

Colchicine is widely used as a treatment for gout and acute pericarditis. It inhibits cellular transport and mitosis by binding to tubulin and preventing its polymerisation. As a consequence, colchicine has a wide range of anti-inflammatory effects, including inhibition of inflammasomes (pattern recognition receptor systems that are activated in response to the detection of pathogens in the cytosol)[1-3]. There is evidence that inflammasomes are activated in COVID-19, and the degree of activation is correlated with disease severity[4, 5]. Colchicine may also protect against microvascular thrombosis and has been shown to reduce cardiovascular events when used for secondary prevention[6].

Emerging data from small randomised trials have suggested a benefit in terms of clinical progression, duration of hospitalisation and need for supplemental oxygen in COVID-19 patients[7, 8].

Colchicine has the benefit of being an anti-inflammatory agent with minimal immunosuppressive effect that is inexpensive and widely available. There is extensive experience of colchicine use and it has a favourable safety profile[9, 10].

Potential harm

Colchicine has the potential to cause gastrointestinal side effects (diarrhoea, nausea or abdominal pain) and should be used with caution in patients with renal impairment or low body weight due to risk of toxicity, principally myelosuppression. There are important drug interactions with CYP3A4 inhibitors that may affect use. Colchicine is contra-indicated in severe hepatic impairment and pregnancy.

Frequently asked questions

1. ***What are the contraindications and cautions for colchicine treatment?***
   These are listed in Appendix 2 of the study protocol:

   Contraindications:
   - Pregnancy or breast-feeding
   - Severe hepatic impairment (defined as requiring ongoing specialist care)
   - Significant cytopenia (e.g. neutrophil count $<1.0x10^9$/L; platelet count $<50x10^9$/L, reticulocyte count $<20x10^9$/L [if available])

- Concomitant use of strong CYP3A4 inhibitors (e.g. clarithromycin, erythromycin, systemic azole antifungals, HIV protease inhibitors) or P-gp inhibitor (e.g. ciclosporin, verapamil, quinidine)
- Hypersensitivity to lactose

Cautions: Loading dose should remain the same but maintenance dose frequency should be halved (to 500 micrograms once daily) in the following circumstances:

- Concomitant use of moderate CYP3A4 inhibitors (e.g. diltiazem, imatinib, letermovir)
- Renal impairment: eGFR<30mL/min/1.73m^2 (either chronic or acute)
- Estimated body weight <70kg

If >1 of these cautions is present, investigator should consider not including colchicine in randomisation

2. **Are there any important drug interactions?**
   Yes, see the list of contraindications and cautions: CYP3A4 inhibitors have the potential to increase colchicine levels. Please check with your pharmacist if unsure.

3. **Is any additional monitoring required while on colchicine treatment in RECOVERY?**
   Participants allocated colchicine should have full blood counts monitored at a frequency determined by their clinician.

4. **How common are the side effects of colchicine?**
   A meta-analysis of over 8000 patients compared the side effect profile of colchicine with placebo or active comparators. Colchicine increased the rate of diarrhoea (17.9% of colchicine users vs 13.1% of comparator groups) but did not significantly increase the rate of liver, infectious or haematological adverse events or death[9].

5. **My patient has mild diarrhoea with colchicine. Should it be stopped?**
   The dosing frequency can be reduced to 500 micrograms once daily if possible before stopping completely.

6. **What is the duration of treatment of colchicine?**
   10 days total or until hospital discharge, whichever is sooner.

7. **Can non-oral routes be used?**
   NG tube administration can be used for patients without an available oral route of administration.

8. **Does colchicine need dose adjustment for elderly patients?**
   Not specifically. Consider cautions listed above and in Appendix 2 of the study protocol.

9. **Does colchicine need dose adjustment with renal impairment?**
   The maintenance dose of colchicine should be reduced to 500 micrograms once daily in patients with eGFR<30/mL/min/1.73m^2.

10. **Does colchicine need dose adjustment with hepatic impairment?**
    Colchicine is contraindicated in patients with severe hepatic impairment (defined as requiring ongoing specialist care)

11. **Can colchicine be given in pregnancy?**
    No. Colchicine is contraindicated in patients who are pregnant or breastfeeding.

References

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