RECOVERY
Randomised Evaluation of COVID-19 Therapy

Intervention

Dimethyl fumarate (DMF) 120mg, by mouth or nasogastric tube, every 12 hours for 4 doses, followed by 240mg every 12 hours for 8 days.
Total of 10 days treatment or until hospital discharge, whichever is sooner.

Summary of information on dimethyl fumarate in COVID-19

DMF is thought to prevent NLRP3 inflammasome activation and the process of pyroptosis (inflammatory cell death) through its action on the protein gasdermin D [1]. SARS-CoV-2 induces inflammasome activation and the degree of activation is thought to correlate with disease severity [2]. DMF has demonstrated anti-viral and anti-inflammatory effects against SARS-CoV-2 in vitro [3]. Other inflammasome-modulating drugs, such as colchicine, have demonstrated provisionally promising results in small randomised trials [4, 5]. DMF is licensed to treat relapsing remitting multiple sclerosis and plaque psoriasis as a long-term immunomodulatory agent and is generally well-tolerated with no major safety concerns [6, 7]. The UK COVID-19 Therapeutics Advisory Panel has recommended that RECOVERY investigate the safety and efficacy of DMF in an early phase assessment among patients hospitalised with COVID-19.

Potential harm

DMF may commonly cause side effects of diarrhoea and flushing [8]. However, these are usually mild, and the dose can be adjusted if tolerability an issue.

DMF is contra-indicated in pregnancy and breastfeeding. There are limited data from the use of DMF in pregnant women and animal studies suggest possible reproductive toxicity [8].

Based on the mode of action there are no theoretical grounds to modify the dose in elderly patients, or those with renal or hepatic impairment. Kidney function and markers of liver damage (ALT or AST) will be collected as safety outcomes in the early phase assessment because toxicity to these systems has been reported.

Although the SmPC recommends caution over prolonged lymphopaenia (and associated risk of progressive multifocal leukoencephalopathy [PML])[8], these risks are related to long-term use in people with multiple sclerosis and not relevant to a 10 day course in people with COVID-19. We are not excluding people with known PML for similar reasons, and because it is very rare in the UK population.

Frequently asked questions

1. ***What are the contraindications to DMF?***
   - Pregnancy
   - Breast-feeding
   - Known hypersensitivity to excipients in any oral therapy

   A negative pregnancy test is required before randomising women of child-bearing potential.

2. ***What are the most common side effects? Can anything help with these?***
   Gastrointestinal disturbance and flushing are common side effects.

   If symptoms develop which the participant or their doctor attributes to dimethyl fumarate, its dose may be reduced e.g. from 240 mg twice daily to 120 mg twice daily or 120 mg once daily (or it may be discontinued if considered necessary by the managing clinician or participant).

3. ***Is DMF use contraindicated with renal or liver impairment?***
   No.

   DMF is rapidly metabolised pre-systemically and the primary route of elimination of metabolites is by cellular respiration so there are no theoretical grounds to modify use.
   Renal and liver toxicity has been reported in post-marketing data and creatinine and AST/ALT will be monitored as part of the early phase assessment safety outcomes.

4. ***Is any specific monitoring required while on the study treatment?***
   Blood tests for creatinine, AST/ALT (and CRP) are required on study days 3, 5 and 10.

5. ***Are there any important drug interactions?***
   No.

6. ***Is a pregnancy test required if a woman denies she could be pregnant?***
   A negative pregnancy test during the current admission is required for all women who are post-menarcheal and pre-menopausal and who are capable of becoming pregnant, including those using contraception.

7. **Can parenteral routes be used?**
   No.

References

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4. Lopes, M.I.F., et al., *Beneficial effects of colchicine for moderate to severe COVID-19: an interim analysis of a randomized, double-blinded, placebo controlled clinical trial.* medRxiv, 2020: p. 2020.08.06.20169573.

5. Deftereos, S.G., et al., *Effect of Colchicine vs Standard Care on Cardiac and Inflammatory Biomarkers and Clinical Outcomes in Patients Hospitalized With Coronavirus Disease 2019: The GRECCO-19 Randomized Clinical Trial.* JAMA Network Open, 2020. **3**(6): p. e2013136-e2013136.
6. Bomprezzi, R., *Dimethyl fumarate in the treatment of relapsing-remitting multiple sclerosis: an overview.* Ther Adv Neurol Disord, 2015. **8**(1): p. 20-30.
7. Mrowietz, U., et al., *Efficacy and safety of LAS41008 (dimethyl fumarate) in adults with moderate-to-severe chronic plaque psoriasis: a randomized, double-blind, Fumaderm(®) - and placebo-controlled trial (BRIDGE).* Br J Dermatol, 2017. **176**(3): p. 615-623.
8. *Tecfidera 120mg and 240mg gastro-resistant hard capsules - Summary of Product Characteristics (SmPC)*. [cited 2021 25 February]; Available from: https://www.medicines.org.uk/emc/medicine/28593.