RECOVERY
Randomised Evaluation of COVID-19 Therapy

Intervention

Two doses of baloxavir marboxil 40mg (or 80mg if weight ≥80kg) by mouth or nasogastric tube to be given on day 1 and day 4, with the course completed at home if discharged.

Summary of information on baloxavir in influenza

Baloxavir is an influenza specific antiviral that inhibits the viral cap dependent endonuclease enzyme, which is essential for genome replication.[1] It is licensed to treat uncomplicated influenza in people aged ≥12 year, and in this group it has a similar effect to neuraminidase inhibitors (NAIs), shortening the duration of symptoms by around one day. Baloxavir appears to reduce viral load more quickly than NAIs, but resistance mutations are more likely to develop during therapy.[2,3]

Like NAIs, baloxavir has not been shown to be effective in patients hospitalised with influenza. A randomised trial of baloxavir in 363 hospitalised patients did not find a significant reduction in time to clinical improvement, but it also did not rule out a substantial benefit.[4] A larger study is need to determine whether baloxavir has modest but clinically relevant benefits in hospitalised patients.

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).
- Age ≥12 and weight ≥40kg

Contraindications

- Recent or planned use of baloxavir for the current illness
- Hypersensitivity to baloxavir or the drug product excipients

Significant drug interactions

None known

Potential harm

Occasional hypersensitivity reactions have been reported but there are no other established side effects.

Frequently asked questions

1. ***Can baloxavir be given along with a neuraminidase inhibitor, such as oseltamivir?***
   Yes, there is no contraindication to giving these drugs together, and given their different mechanisms of action they may have additive effects.

2. ***Can baloxavir be given to pregnant or breastfeeding women?***
   Treatment in these groups can be considered, but there are limited data from the use of baloxavir in pregnant or breastfeeding women. Animal studies do not indicate reproductive toxicity, and baloxavir may be of particular benefit to pregnant women with influenza as they are at increased risk of developing severe disease. Animal models of exposure in pregnancy have not shown evidence of adverse fetal effects at doses up to five times the human therapeutic dose. The risk of harm from baloxavir in pregnancy is likely to be low given the animal model data, and because the therapeutic target for baloxavir is a viral enzyme. It is unknown whether baloxavir is excreted in human milk.

3. ***Can baloxavir be given to patients with liver or renal failure?***
   Yes

4. ***Does baloxavir need dose adjustment with renal impairment?***
   No

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

6. ***What happens if a dose is missed?***
   Ideally the first dose should be given within 6 hours of randomisation. If delays arise, give the first dose as soon as possible and maintain the standard spacing between doses (e.g. if the first dose is given on day 2 post-randomisation, give the second dose on day 5).
   If the second dose is missed, consider whether or not the patient is still unwell with the current infection. If so, the second dose can be given late. If they have already recovered from the current infection, they are unlikely to benefit from the second dose. Whether or not the second dose was given will be recorded in the follow-up information.

References

1. Xofluza Summary of Product Characteristics (https://www.medicines.org.uk/emc/product/12879)
2. Hayden FG, Sugaya N, Hirotsu N, et al. Baloxavir Marboxil Investigators Group. Baloxavir Marboxil for Uncomplicated Influenza in Adults and Adolescents. N Engl J Med. 2018 Sep 6;379(10):913-923. PMID: 30184455.
3. Ison MG, Portsmouth S, Yoshida Y, et al. Early treatment with baloxavir marboxil in high-risk adolescent and adult outpatients with uncomplicated influenza (CAPSTONE-2): a randomised, placebo-controlled, phase 3 trial. Lancet Infect Dis. 2020 Oct;20(10):1204-1214. PMID: 32526195.
4. Study to Assess Efficacy and Safety of Baloxavir Marboxil In Combination With Standard-of-Care Neuraminidase Inhibitor In Hospitalized Participants With Severe Influenza. https://clinicaltrials.gov/ct2/show/NCT03684044