RECOVERY
Randomised Evaluation of COVID-19 Therapy

Intervention

Oseltamivir 75mg twice a day for 5 days, given by mouth or nasogastric tube.
The course should be completed at home if discharged. Treat for 10 days if the patient is immunosuppressed in the opinion of the treating clinician. Dose adjustment is needed for renal impairment or if weight is <40kg, detailed below.

Summary of information on oseltamivir in influenza

The neuraminidase inhibitors (NAIs) oseltamivir and zanamivir are influenza specific antivirals that prevent budding of the virus from infected cells, and so interfere with the viral replication cycle. They have been shown to shorten the duration of symptoms of uncomplicated influenza by around one day if given within the first two days of symptoms, but they have not been shown to be effective in patients hospitalised with influenza[1]. Although some observational studies have suggested a benefit in hospitalised patients, others have not, and evidence from randomised trials is lacking.[1,2]

An expert group convened by the Academy of Medical Sciences and the Wellcome Trust concluded that a randomised trial of NAIs in patients hospitalised with influenza was a high priority.[3] A subsequent survey of senior UK clinicians involved in treating such patients found that use of NAIs in hospitalised patients was very variable.[4] Most did not believe NAIs were effective at reducing mortality in these patients, and the large majority were in favour of a randomised trial.

Eligibility

- Hospitalised with viral pneumonia syndrome (e.g. fever, cough and/or shortness of breath with compatible chest X-ray changes)
- Confirmed influenza infection (laboratory test or point-of-care test performed by a healthcare worker)

Contraindications

- Recent or planned use of a neuraminidase inhibitor for the current illness (either oseltamivir or zanamivir)
- Hypersensitivity to oseltamivir or the drug product excipients

Significant drug interactions

None known

Potential harm

The commonest adverse effects are headache, nausea and vomiting. Occasional hypersensitivity reactions have been reported.

Frequently asked questions

1. ***The usual care for patients admitted to our hospital with flu includes an NAI. If a patient is allocated 'usual care alone' in this arm can they still receive an NAI?***

Usual care in this arm means management without an NAI. Patients should ***not*** be included in this arm if it is anticipated that they will receive an NAI regardless of their treatment allocation.

2. ***Public Health England (PHE) and local guidance recommends that NAIs should be given to all patients hospitalised with influenza, is it acceptable for these patients not to receive an NAI in RECOVERY?***
   In the absence of randomised trials in hospitalised patients with influenza, PHE guidance relies on observational data, so many clinicians remain uncertain of the benefits of NAIs in this setting.[4,5] In COVID-19, several treatments that showed similar promise in observational studies were subsequently found to be ineffective in randomised trials.

   If patients and their clinicians are happy for them to be enrolled in this arm then it's acceptable to include them, even though this could mean they don't receive a treatment they would have been given outside of the trial.

3. ***Can oseltamivir be given to pregnant or breastfeeding women?***
   Yes. Oseltamivir is used in pregnant women, and observational data in >1000 women exposed to oseltamivir during the first trimester found no evidence of adverse fetal effects. It is excreted in breast milk, but at low concentrations that would be subtherapeutic to the infant.

4. ***Can oseltamivir be given to children?***
   This arm is open to children of any age. Paediatric dosing is in the protocol.

5. ***Can oseltamivir be given to patients with liver or renal failure?***
   Yes, but dose adjustment is needed with renal failure
   - eGFR 10-29 mL/min/1.73m^2: 75mg once daily
   - eGFR <10 mL/min/1.73m^2: 75mg as a single dose only

6. ***Does oseltamivir need weight-based dose adjustment?***
   For adults weighing <40kg the dose is 60mg. Weight-based dosing for children is detailed in protocol appendix 3. In the case of renal impairment use the weight-based dose but reduce frequency as above.

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

References

1. Heneghan CJ, Onakpoya I, Jones MA. Et al. Neuraminidase inhibitors for influenza: a systematic review and meta-analysis of regulatory and mortality data. Health Technol Assess. 2016 May;20(42):1-242. PMC4904189.
2. Muthuri SG, Venkatesan S, Myles PR, et al. Effectiveness of neuraminidase inhibitors in reducing mortality in patients admitted to hospital with influenza A H1N1pdm09 virus infection: a meta-analysis of individual participant data. Lancet Respir Med. 2014 May;2(5):395-404. PMC6637757.

3. Use of neuraminidase inhibitors in influenza. Academy of Medical Sciences, October 2015 (https://acmedsci.ac.uk/policy/policy-projects/treating-influenza)
4. Bradbury N, Van-Tam J, Lim WS. Clinicians' attitude towards a placebo-controlled randomised clinical trial investigating the effect of neuraminidase inhibitors in adults hospitalised with influenza. BMC Health Serv Res. 2018 May 2;18(1):311.PMC5930775
5. Influenza: treatment and prophylaxis using anti-viral agents. Public Health England, October 2019 (https://www.gov.uk/government/publications/influenza-treatment-and-prophylaxis-using-anti-viral-agents)