South African National Department of Health
Brief Report of Rapid Review
Component: Respiratory - Severe influenza

TITLE: OSELTAMIVIR FOR SEVERE INFLUENZA: EVIDENCE REVIEW OF THE CLINICAL BENEFIT AND HARM

Date: 11 SEPTEMBER 2020

Key findings

- We conducted a rapid review of the effects of oseltamivir, compared with placebo or standard of care, on mortality and duration of hospitalisation, in hospitalised patients with presumed or confirmed influenza
- We found no randomised controlled trials (RCTs) conducted amongst hospitalised patients. RCTs were conducted in the setting of acute uncomplicated influenza, and although they report a reduction of the duration of illness in influenza-infected patients, provided oseltamivir was commenced within 48 hours of onset, they were not powered to demonstrate an effect on mortality in critically ill patients.
- Evidence from reviews of observational studies are inconsistent, with an industry-funded review finding that oseltamivir may reduce the risk for death in severely ill patients with documented influenza infection, especially when started early. Another review showed no mortality benefit amongst hospitalised children and adults after adjusting for time-dependent bias.
- Adverse events that were reported included a risk of nausea, vomiting and neuropsychiatric events amongst adults. Amongst children, oseltamivir-induced vomiting was common, but there were no serious neuropsychiatric adverse events.
- Further evidence from randomised clinical trials is required to determine the safety and efficacy of oseltamivir in severe influenza.

NEMLC RECOMMENDATION:

Type of recommendation	We recommend against the option and for the alternative (strong)	We suggest not to use the option or to use the alternative (conditional)	We suggest using either the option or the alternative (conditional)	We suggest using the option (conditional)	We recommend the option (strong)
				X	

Recommendation: The NEMLC suggests that oseltamivir not be used routinely and encourage clinical trials in this setting. May be considered for use in severely ill patients, at the discretion of the clinician in hospital practice in the context of moderate-to-high local influenza prevalence, administered within 72 hours of symptom onset.
Rationale: Although it is common practice, there is insufficient evidence of efficacy and safety to recommend routine use of oseltamivir in critically ill hospitalised children or adults for management of severe influenza. Further evidence from randomised clinical trials is required to determine the safety and efficacy of oseltamivir in severe influenza.
Level of Evidence: Observational studies

(Refer to appendix 2 for the evidence to decision framework)

BACKGROUND

Influenza is mostly a mild, self-limiting infection of the upper airways and management is symptomatic. Mild infection may occasionally progress to pneumonia, otitis media and dehydration or encephalopathy with or without liver failure. These complications may be caused by the influenza virus; or secondary bacterial infections and/or adverse drug reactions (e.g. antipyretics such as salicylates or other NSAIDs)[1]. Epidemics of seasonal influenza in humans is caused by influenza A and B viruses.[2]

Neuraminidase inhibitors (NAI) are antivirals developed specifically to treat influenza by reducing the ability of the virus to penetrate the mucus in the very early stage of infection,[3] and preventing influenza viruses from exiting host cells.[4] Oseltamivir is the most widely used neuraminidase inhibitor[5].

There is no evidence that oseltamivir benefits patients not infected with influenza virus.[6] As oseltamivir reduces viral replication, this treatment is not effective in otherwise healthy persons when immune responses are already reducing viral titres.[7] However, oseltamivir may be beneficial in severely ill patients with higher viral loads, increased viral shedding, and decreased cytokine response.[8, 9, 10] Observational data suggests that oseltamivir may reduce mortality in patients hospitalised with influenza A(H1N1)[11] or influenza A(H5N1) infections,[12] particularly when treatment is initiated within 48 hours of symptom onset.[13]

A similar review of observational data on the use of NAIs in hospitalised children (0 to 17 years of age) with laboratory-confirmed influenza, found a mortality benefit compared to no treatment (OR 0.36; 95% CI 0.16–0.83) with improved survival if treated within 48 hours of symptoms onset[14]

Post-surveillance safety reports following widespread use of oseltamivir includes increased risk of neuropsychiatric events raised liver enzymes, hepatitis, neuropsychiatric events, cardiac arrhythmia, skin hypersensitivity reactions, metabolic side effects and renal events.[15] Neuropsychiatric events such as depressed mood, behaviour disturbance, panic attack, suicidal ideation, delusion, delirium, convulsion, and encephalitis raised the most concern, more common in children and occurring within 48 hours of NAI administration.[16] [17]A recent Korean population-based retrospective cohort study showed no significant difference in overall neuropsychiatric events risk between the oseltamivir vs control groups amongst influenza-diagnosed in patients over eight years of age[18], although a small increase in the incidence of suicide attempts among children and adolescents was found.

The Centers for Disease Control and Prevention (USA)[19] and National Institute for Communicable Disease (South Africa) Guidelines[20] recommend oseltamivir and other neuraminidase inhibitors for severe disease in hospitalised patients with laboratory-confirmed influenza, administered within 48 hours of symptoms using standard dosing. In 2017 the World Health Organisation changed oseltamivir from a core[1] to a complementary essential medicine for the treatment and prophylaxis of influenza amongst persons with suspected or confirmed influenza who have severe or progressive disease, are hospitalised, or are at high risk of complications from influenza.[21]

We reviewed current published evidence to determine the efficacy and harms of oseltamivir in treating severe influenza in hospitalised patients.

RESEARCH QUESTION: Should oseltamivir be used for the management of severe influenza in hospitalised patients?

METHODS

We conducted a rapid review of the evidence including systematic searching of two electronic databases (PubMed and the Cochrane library). We excluded single case or case series reports. Screening of records and data extraction was conducted by one reviewer (TL), with results reviewed and checked by another reviewer (NS). We extracted relevant records in a narrative table of results. No appraisal or meta-analysis was performed. The search strategy is shown in Appendix 1.

[1] Core WHO essential medicine may be used in all settings; Complementary WHO essential medicine may be used where specific facilities are available – e.g. influenza PCR

Eligibility criteria for review

Population: Patients with presumed or confirmed influenza, no restriction to age but severe disease requiring hospitalisation.

Intervention: Oseltamivir, oral (neuraminidase inhibitor, NAI).

Comparators: Any (standard of care/placebo) or zanamivir (the alternative NAI available in South Africa)

Outcomes: Length of ICU stay; mortality; duration of oxygen support/ventilatory support; days of progression to mechanical ventilation; duration of mechanical ventilation; adverse events, adverse reactions.

Study designs: Systematic reviews with (of RCTs and observational studies), individual patient data (IPD) meta-analysis, RCTs and observational studies; no restriction on language or date of publication.

RESULTS

We searched PubMed and the Cochrane library on 2 September 2020. Details of each search are provided in Appendix 1. One reviewer screened 62 records. No RCTs related to the PICO question could be identified, but 2 systematic reviews and meta-analyses of observational data were identified for review and are described in **Table 1.**

The available published evidence for NAIs has largely been industry funded and selective reporting has been identified with a high risk of bias.[2] Methodologies such as individual patient data (IPD) analysis may be used to address these limitations[22], which was incorporated in the methodologies of the two reviews studies, however confidence in the conclusions of the reviews is still highly dependent on both the quality and freedom from bias of the underlying observational studies.

Mortality benefit:
Muthuri et al's (2014)[11] industry-funded IPD meta-analysis (29 234 patient records from observational studies) showed that early NAI (administered within 48 hours of symptom onset) significantly reduced mortality amongst influenza A(H1N1) infected adult hospitalised patients, compared to no treatment, aHR 0.50 (95% CI 0.37 to 0.67). This association between oseltamivir and mortality benefit was not apparent in children. Only 20% (78 of 401) centres contacted for IPD were able to contribute data to the analysis.

The statistical model was reported to have been adjusted for time, propensity to treat, and patient coexisting conditions. Crude analysis of the data reported in the publication showed an increased mortality rate associated with NAIs. Crude mortality rate was 9.19% (959/10,431) with no NAI treatment vs. 9.70% (1825/18,803) after exposure to NAIs any time after symptom onset. Taking into account time-dependent bias the aHR was reported as 0.51 (95% CI 0.45 to 0.58), p<0·0001), suggesting a protective effect of NAIs. Time-dependent bias occurs when the analysis misallocates the time from initiation of the study to start of NAI therapy. Other methodological concerns of the study by Muthiuri et al (2014) included that the observational studies from which the individual patient data was sourced were not quality-assessed and there appears to be a large proportion of missing data (potentially over 80%.)

*Heneghan et al. (*2016)[23] authored a systematic review of 30 studies and an individual patient data analysis (3071 patient records from 4 of the 30 observational studies.) This review found no mortality advantage amongst critically ill-hospitalised adult and paediatric patients infected with 2009A/H1N1 influenza who were administered oseltamivir. The IPD information was analysed using 5 different models, none of which demonstrated a mortality advantage from exposure to the medication (for instance in a Cox regression with time dependent treatment exposure, mortality HR was 1.11, 95% CI 0.75 to 1.65). Cautious interpretation of the IPD findings is appropriate in view of the modest sample size.

Adverse events:
Muthuri et al. (2014) did not report on harms associated with NAIs.

Amongst adult patients, the review by Heneghan et al. (2016) reported an increased risk of nausea and vomiting, and a decreased risk of diarrhoea associated with oseltamivir vs placebo (pooled analyses were highly heterogeneous).

The cardiac effects of oseltamivir were unclear with a reduction of cardiac general events with oseltamivir vs. placebo. Reports of psychiatric adverse events were rare, and increased in a dose-dependent fashion.

Oseltamivir-induced vomiting was more common in children, but serious neuropsychiatric adverse events were not reported.

Other considerations:
It is noteworthy that NICD surveillance reported one laboratory-confirmed influenza case in South Africa, during the 2020 influenza season, probably due to the precautionary measures taken to prevent transmission of SARS-CoV-2.

CONCLUSION

No RCT evidence for oseltamivir in critically ill, hospitalised patients with influenza could be identified. Available evidence from observational studies shows disparate mortality benefits. Further evidence from high quality adequately powered randomised controlled trials will be required to determine the safety and efficacy of oseltamivir in critically ill patients.

Reviewers: Trudy Leong (TL): Essential Drugs Programme, Affordable Medicines Directorate, National Department of Health; Andy Parrish (AP): Walter Sisulu University; Prakash Jeena (PJ): University of KwaZulu Natal, Albert Luthuli Hospital; Natalie Shellack (NS): Sefako Makgatho Health Sciences University.

Declaration of interests: TL, AP, NS and PJ have no interests to declare in respect of oseltamivir. PJ declared honoraria for previous talks for Astra-Zeneca, Abbott, Pfizer, GSK, Aspen, MSD.

Table 1: Characteristics of included reviews of observational studies

Author, date	*Type of study*	n	Population	Comparators	Primary outcome	Effect sizes	Comments
Muthuri et al, 2014 [11]	Individual patient data (IPD)analysis	29 234 patients	Hospitalised patients (all ages) with laboratory confirmed or clinically diagnosed pandemic influenza A H1N1pdm09 – global data	NAIs vs no treatment	Mortality	• *NAIs (irrespective of timing):* Mortality risk reduced (aOR 0.81; 95% CI 0.70 to 0.93; p=0·0024). • *Early (<48 hrs of symptom onset) vs later treatment:* Mortality risk reduced (aOR 0.48; 95% CI 0.41 to 0.56; p<0·0001). • *Early vs no treatment*: Mortality risk reduced (aOR 0.50; 95% CI 0.37 to 0.67; p<0·0001). • There was an increase in the mortality hazard rate with each day's delay in initiation of treatment up to day 5 vs early treatment (aHR 1.23; 95% CI 1.18 to 1.28; p<0·0001).	• Observational studies have a high risk of bias and presence of confounders. • Reduced mortality risk were less pronounced and not significant in children. • Limitations include heterogeneity between studies, inadequate adjustment for confounders. • Quality assessment of observational studies was not reported. • Study funded by pharmaceutical industry funded, and funding of observational studies which provided the individual patient data was not reported.
Heneghan et al, 2016 [23]	• Systematic review and metaanalysis (30 observational studies) • IPD analysis (data from 4 of the 30 observational studies)	• n= 11,013 • n= 3071	All ages and pregnant women, hospitalised or critically ill	• OTV vs none	• Mortality	Systematic review/metaanalysis: • 1301 deaths (12%); percentage of deaths of OTV vs no OTV: 83% vs. 82%. IPD analysis: Adjusting for time-dependent bias, potential confounding variables, and the competing risk of hospital discharge, IPD analysis showed insufficient evidence that OTV reduced the risk of mortality: HR 1.03, 95% CI 0.64 to 1.65. Adverse events: (oseltamivir vs none) *Adults:* • Increased risk of nausea: RD 3.66%, 95% CI 0.90% to 7.39%; NNTH 28, 95% CI 14 to 112.	• Observational studies have a high risk of bias and presence of confounders. • Confounding by indication possible with sicker patients more likely to get treatment. • Prevalence of some comorbidities appeared higher for treated patients compared to untreated patients, possibly overestimating the risk of mortality. • IPD analysis only included 4 studies, reducing the statistical power of the analysis. • Some data missing from IPD analysis - missing data for time

Author, date	*Type of study*	n	Population	Comparators	Primary outcome	Effect sizes	Comments
						• Increased risk of vomiting: RD 4.56%, 95% CI 2.39% to 7.58%; NNTH 22, 95% CI 14 to 42. • Decreased risk of diarrhoea: RD 2.33%, 95% CI 0.14% to 3.81%; NNTB 43, 95% CI 27 to 709. • Decreased risk of cardiac events: RD 0.68%, 95% CI 0.04% to 1.00%; NNTB 148, 95% CI 101 to 2509. • No significant increase in risk of overall psychiatric events: RR 0.93, 95% CI 0.43 to 2.03; I^2 = 0%; dose-response effect seen in 2 pivotal trials. *Children:* • Increased risk of vomiting: RD 5.34%, 95% CI 1.75% to 10.29%; NNTH 19, 95% CI 10 to 57.	to death/discharge and time to treatment.

Appendix 1: Search strategy

Cochrane library

ID	*Search*	*Hits*
#1	neuraminidase inhibitors in Cochrane Reviews, Trials (Word variations have been searched)	197
#2	influenza	8146
#3	systematic reviews	15602
#4	#1 AND #2 AND #3	13

Output: 13 records; no appropriate records

PubMed

Search strategy: (("neuraminidase"[MeSH Terms] OR "neuraminidase"[All Fields]) AND ("antagonists and inhibitors"[Subheading] OR ("antagonists"[All Fields] AND "inhibitors"[All Fields]) OR "antagonists and inhibitors"[All Fields] OR "inhibitors"[All Fields]) AND ("influenza, human"[MeSH Terms] OR ("influenza"[All Fields] AND "human"[All Fields]) OR "human influenza"[All Fields] OR "influenza"[All Fields])) AND (Meta-Analysis[ptyp] OR systematic[sb])

Output: 52 records, 49 after removing duplicates (1 duplicate record from Cochrane search)

2 records were identified, relevant to the PICO

Appendix 4: Evidence to decision framework

	JUDGEMENT	EVIDENCE & ADDITIONAL CONSIDERATIONS
QUALITY OF EVIDENCE OF BENEFIT	**What is the certainty/quality of evidence?** High [ ] Moderate [ ] Low [ ] Uncertain [x] *High quality:* confident in the evidence *Moderate quality:* mostly confident, but further research may change the effect *Low quality:* some confidence, further research likely to change the effect *Very low quality:* findings indicate uncertain effect	See discussion regarding observational evidence, above.
EVIDENCE OF BENEFIT	**What is the size of the effect for beneficial outcomes?** Large [ ] Moderate [ ] Small [ ] Uncertain [x]	See discussion regarding observational evidence, above.
QUALITY OF EVIDENCE OF HARM	**What is the certainty/quality of evidence?** High [ ] Moderate [ ] Low [ ] Very low [x] *High quality:* confident in the evidence *Moderate quality:* mostly confident, but further research may change the effect *Low quality:* some confidence, further research likely to change the effect *Very low quality:* findings indicate uncertain effect	Ongoing studies may provide more evidence in future.
EVIDENCE OF HARMS	**What is the size of the effect for harmful outcomes?** Large [ ] Moderate [ ] Small [ ] Uncertain [x]	See discussion regarding observational evidence, above.
BENEFITS & HARMS	**Do the desirable effects outweigh the undesirable harms?** Favours intervention [ ] Favours control [ ] Intervention = Control *or* Uncertain [x]	The balance of benefits and harms is uncertain.
FEASABILITY	**Is implementation of this recommendation feasible?** Yes [x] No [ ] Uncertain [ ]	Oseltamivir is SAHPRA registered and used as standard of care nationally and internationally since the SARS influenza pandemic.
RESOURCE USE	**How large are the resource requirements?** More intensive [x] Less intensive [ ] Uncertain [ ]	Price of medicines: **Medicine** / **Tender price (ZAR)** / **SEP (ZAR)*** Oseltamivir, oral 75mg capsules (10) / n/a / 284.87 Oseltamivir, oral 6mg/ml, 100 ml syrup / n/a / 195.12 Oseltamivir, oral 12mg/ml, 100 ml syrup / n/a / 376.02 *SEP database, March 2020 https://mpr.code4sa.org/ - ex manufacturer price of cheapest generic option **Additional resources:**

VALUES, PREFERENCES, ACCEPTABILITY	**Is there important uncertainty or variability about how much people value the options?** Minor [ ] Major [ ] Uncertain [x] **Is the option acceptable to key stakeholders?** Yes [ ] No [ ] Uncertain [x]	No data.

Version	Date	Reviewer(s)	Recommendation and Rationale
First	2 September 2020	TL, AG, NS, PJ	Oseltamivir not recommended routinely, but in the context of local clinical trials. May be considered for use in severely ill patients, at the discretion of the clinician in hospital practice in the context of moderate-to-high local influenza prevalence, administered within 72 hours of symptom onset.

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