Oseltamivir for the treatment of suspected influenza: a clinical and economic assessment

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Authors’ objectives
To perform a systematic review to assess and quantify the efficacy and effectiveness of oseltamivir in individuals who are suspected of having influenza. In addition, to assess the cost-effectiveness of treating suspected influenza with oseltamivir in a primary care setting where standard treatment is no active medical intervention.

Searching
MEDLINE, EMBASE, HealthSTAR, Pascal, SciSearch and TOXLINE were searched from 1997 to 2001. The websites of regulatory agencies, health technology assessment and near technology assessment agencies were also searched. The search terms were provided in the paper. Narrative and systematic reviews, articles and conference abstracts were also handsearched. In addition, the drug manufacturers and leaders in the research field were contacted for additional trial information.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) were eligible for inclusion in the review.

Specific interventions included in the review
Comparisons of oseltamivir with placebo or current therapy (e.g. amantadine, rimantadine, zanamivir, acetaminophen) were eligible for inclusion. Four of the included trials compared 75 mg oseltamivir daily with placebo; the remaining two were 3-arm trials comparing either oseltamivir 75 mg or 150 mg with placebo.

Participants included in the review
Studies that examined adult and adolescent patients with influenza-like illness (natural illness) were eligible for inclusion. Studies involving children aged less than 12 years were excluded. The majority (greater than 70%) of the patients assessed in the included studies were otherwise healthy and aged between 18 and 65 years. Two other studies assessed participants at-risk from developing complications. The first, which involved chronically ill adults, excluded individuals with chronic cardiac disease except chronic idiopathic hypertension, individuals with stage III chronic obstructive pulmonary disease and cystic fibrosis. In the second study, elderly participants were excluded if they presented with unstable or uncontrolled renal, cardiac, pulmonary, vascular, neurological, metabolic or liver disease.

Outcomes assessed in the review
Studies were eligible for inclusion if they assessed the number of patient deaths, serious adverse events, number of hospitalised patients, number of complications, recurrence of illness, time to return to normal activity, time to alleviation of symptoms, reduction in symptom severity, number of adverse events, types of adverse events, number of patients with laboratory-confirmed influenza or the number of patients with oseltamivir-resistant influenza. The primary outcomes reported by the included studies were the duration of illness (defined as time to alleviation of all symptoms), the severity of the symptoms, and time to return to normal activity.

How were decisions on the relevance of primary studies made?
Two reviewers independently assessed any potentially relevant studies. The reviewers do not state whether this was undertaken blind to the source of the paper and the results, or how any disagreements were resolved.

Assessment of study quality
The validity of the included studies was assessed using the 3-item instrument of Jadad et al. (see Other Publications of Related Interest no.1). Information on allocation concealment was also scored using a 3-point system: adequate, inadequate or unclear. The validity of the studies was assessed independently by two reviewers. Any large discrepancies in quality were to be subjected to a sensitivity analysis and included in the discussion.
Data extraction
Two reviewers independently extracted data from the studies, with any disagreements being resolved by discussion and recourse to a third party if required. The following data were extracted and tabulated: the study and year, region, the number and age of the participants, participant characteristics, type of influenza infection, interventions and outcomes reported.

Methods of synthesis
How were the studies combined?
Analyses were performed on an intention-to-treat basis wherever possible. A subgroup of trial participants at risk from developing complications was also analysed wherever possible. Dichotomous outcomes were combined using random-effects (DerSimonian and Laird) and fixed-effect (Mantel-Haenszel) models, while continuous outcomes were combined using random-effects (DerSimonian and Laird) and inverse variance fixed-effect models. Both random-effect and fixed-effect models were applied to all outcome comparisons.

The data from palliative outcomes, where the median was a more appropriate estimate of central tendency, were pooled using a similar approach. The weighted average of medians across the studies were pooled using the same method as that used to pool the means, and standard deviations were derived from the 95% confidence intervals (CIs) around the median values. The estimates derived by this method were validated using a pooled estimate from original data obtained in an FDA review (see Other Publications of Related Interest no.2).

How were differences between studies investigated?
Differences between the studies were investigated using a chi-squared test for statistical heterogeneity. In addition, a subgroup analysis was undertaken on studies that assessed populations at risk of developing complications.

Results of the review
Six RCTs (n=1,735) were included. Two trials (n=469) assessed study populations who were at risk from developing complications.

Death.
Only one trial reported a death, but did not report the cause. This trial was conducted in an elderly population, and the death occurred in the placebo arm where the median age was 73 years.

Hospitalisation.
In trials involving healthy adults, a total of 0.8% (5 out of 630) hospitalisations (including deaths) occurred in the placebo group and 0.5% (3 out of 636) occurred in the treatment arms. In the at-risk population, 2.5% (6 out of 241) and 0.9% (2 out of 228) occurred in the placebo and active treatment groups, respectively. Results of the meta-analysis provided an odds ratio (OR) of 0.55 (95% CI: 0.20, 1.57) for a death or hospitalisation occurring in actively treated participants.

Complications.
Complications of illness were defined as otitis, bronchitis or pneumonia. These complications developed in 7.6% (66 out of 871) of the placebo-treated participants and in 6.9% (60 out of 864) of the oseltamivir-treated participants. In trials involving participants at risk for developing complications, complications arose in 13.3% (32 out of 241) and 13.2% (30 out of 228) of the placebo- and oseltamivir-treated participants, respectively. Complications were observed in 5.4% (34 out of 630) and 4.7% (30 out of 636) of the placebo- and oseltamivir-treated, otherwise healthy, participants. The results indicated a combined OR of 0.92 (95% CI: 0.63, 1.33).

Recurrence of illness was reported in only one trial involving healthy participants. The event rates were 2.6% (6 out of 235) and 2.1% (5 out of 241) for placebo- and oseltamivir-treated participants, respectively.
Reduction in all harmful events.

Combining the ORs provided an estimate of 0.84 (95% CI: 0.60, 1.18) for reducing death, hospitalisation, complications and recurrence of illness in all oseltamivir-treated participants.

Time to return to normal activity.

Only one trial reported this outcome for the participants. The difference in medians between oseltamivir and placebo treatment groups for the time to return to normal activity was 57 hours (95% CI: 2.4, 111.6) in favour of treatment for all, otherwise healthy, treated participants.

Time to resolution of symptoms.

Time to resolution of symptoms was reported in two trials. The results showed an overall difference of 19.89 hours (95% CI: 5.72, 34.07) in favour of treatment with oseltamivir. In otherwise-healthy participants with laboratory-confirmed influenza, this effect was greater. Infected participants treated with oseltamivir exhibited a median difference of 30.57 hours (95% CI: 17.92, 43.21) in time to alleviation of symptoms. In infected participants at risk for developing complications, a median difference of 17.04 hours (95% CI: -42.3, 76.3) was observed.

Cost information

Results from the cost-effectiveness analysis indicated that, for healthy populations in terms of the cost per quality-adjusted life-year, treatment with oseltamivir is:

more than $100,000 when using (1) a base-case diagnostic accuracy of 35%, and (2) a 50% diagnostic accuracy if there are substantial numbers of late presenting patients treated inappropriately with oseltamivir;

less than $50,000 only under very favourable assumptions, i.e. 68% diagnosis, few inappropriately-treated late presenting patients, and optimistic assumptions about the clinical effectiveness of oseltamivir.

Authors’ conclusions

There was insufficient evidence that oseltamivir reduces complications, hospitalisations and/or death in individuals suspected of having influenza. There was also insufficient evidence of any benefit in individuals with suspected influenza who are at risk from developing complications. Evidence from one trial suggested that otherwise healthy individuals who are suspected of having influenza, return to normal activity faster when treated with oseltamivir than those receiving placebo. No studies were available to compare the magnitude of this benefit with amantadine, zanamivir or symptom-relieving medications.

CRD commentary

This was a well-conducted and reported review. The study addressed a well-defined question in terms of the participants, interventions and outcomes that were to be assessed. The literature searches undertaken were comprehensive so it is unlikely that any important studies have been missed. The validity of the included studies was assessed systematically by two independent reviewers, and the data extraction was also undertaken in duplicate. Any bias and error that might have occurred in the review process will, therefore, have been minimised. The details of the included studies were adequately presented in tabular format. In addition, the statistical analysis was appropriate and thorough, with an exploration of the sources of heterogeneity between the different studies being undertaken.

Overall, the results of the review and the authors’ conclusions follow from the evidence-base reviewed.

Implications of the review for practice and research

Practice: The authors did not state any implications for practice.

Research: The authors state that further trials are needed to adequately assess whether oseltamivir reduces
complications, hospitalisation and the number of deaths.

**Bibliographic details**

**Original Paper URL**

**Other publications of related interest**

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This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.