Antivirals for influenza: a summary of a systematic review and meta-analysis of observational studies

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†Prepared this summary of the original work which was published in the Annals of Internal Medicine (Hsu J, et al. Antivirals for treatment of influenza: a systematic review and meta-analysis of observational studies. Ann Intern Med 2012; 156:512–524.) Reproduced with permission from the Annals of Internal Medicine.

Despite the use of antivirals to treat patients with severe influenza, questions remain with respect to effects and safety. Although a recent systematic review has provided some indication of benefit, the analysis is limited by the quality of the available evidence from randomized controlled trials. To supplement the existing information, the authors conducted a systematic review of observational studies of antiviral treatment for influenza. This report summarises the findings of that review. Similar to the randomised trials, the confidence in the estimates of the effects for decision-making is low to very low primarily due to the risk of selection and publication bias in the observational studies. From these observational studies, the summary estimates suggest that oseltamivir may reduce mortality, hospitalisation and duration of symptoms compared with no treatment. Inhaled zanamivir may also reduce symptom duration and hospitalisations, but patients may experience more complications compared with no treatment. Earlier treatment with antivirals is generally associated with better outcomes than later treatment. Further high-quality evidence is needed to inform treatment guidelines because of the overall low to very low quality of evidence.

Keywords antiviral, influenza, M2 ion channel blocker, neuraminidase inhibitor, observational study.

Introduction

Influenza remains a major global health concern. Most cases of influenza are self-limiting, and prevention through annual influenza vaccination may be an effective strategy. However, antivirals, such as neuraminidase inhibitors (oseltamivir and zanamivir) and M2 ion channel blockers (amantadine and rimantadine), are used to reduce symptoms and prevent hospitalisation or death in patients with severe illness.

Evidence about the effects and safety of antivirals continues to accumulate, and although a recently updated systematic review of randomised control trials (RCTs) offered some indication of treatment benefit, concerns remain over the quality of evidence from published and unpublished randomized trials. The evidence from randomized trials is further limited by the lack of high-quality evidence for patient-important outcomes and lingering questions about the treatment of specific groups such as hospitalised or immunocompromised patients. Observational studies may provide additional information or higher quality evidence than the currently available RCTs for certain elements of antiviral treatment. This report summarises the results of a recently published systematic review of observational studies of antiviral treatment. This review was intended to inform WHO guidelines, and the WHO essential medicine list about the antiretroviral treatment of influenza.
Methods

Electronic databases and grey literature were searched up to 16 November, 2010, using pre-defined eligibility criteria, without restriction on publication language or study type. Observational studies examining the effects of non-intravenous antiviral treatment with oseltamivir, zanamivir, amantadine or rimantadine compared with no treatment, and studies comparing the antivirals with one another or early administration of a particular antiviral (<48 hours) compared with later administration of the same antiviral (>48 hours) were included. Investigators independently screened all citations by title and abstract and by full text (920 articles) for inclusion. Several patient-important outcomes were assessed, including patient death, hospitalisation, duration of signs and symptoms, complications and adverse effects (see original report for full list of outcomes).²

Two investigators independently extracted data from the included studies using a pretested electronic form. Established methods to assess the risk of bias were used. The quality of evidence was assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach.³ Following GRADE guidelines, confidence in the effect estimates were categorised into four levels from very low to high.

Meta-analyses were conducted by using either the odds ratio (dichotomous outcomes) or mean differences or standardised mean differences (continuous outcomes). Whenever possible, studies were pooled for analysis according to whether or not results were adjusted for confounding. Although greater emphasis should be placed on data from the adjusted meta-analyses, the pooled results from unadjusted studies were also reported to provide a comprehensive view of the available evidence. Studies and other unpublished observational data that could not be pooled were synthesised narratively. When data were available, subgroup analyses were performed by age, risk of complications, laboratory-confirmed influenza versus influenza-like illness as well as other variables.

Results

Twelve thousand one hundred and eighty-eight database citations and 27 articles from the grey literature were identified, and 74 articles met the eligibility criteria. The majority of studies reported comparisons of oral oseltamivir with no antiviral therapy. Table 1 summarises the effects of oseltamivir over no treatment and the quality of evidence for each of the outcomes. Additional tables summarising the effects of the other antivirals are in the original publication.⁷

The evidence suggests that oseltamivir may reduce mortality in high-risk populations, such as hospitalised patients, compared with no antiviral treatment, but this effect is less pronounced when pooling data from unadjusted studies.⁴–¹⁴ Meta-analyses indicate that oseltamivir may also reduce both hospitalisation in outpatients¹⁵–¹⁸ as well as duration of symptoms.¹⁹–²⁴ Data from several studies also suggest that oseltamivir may reduce complications such as pneumonia,¹⁵,¹⁷,¹⁸ otitis media¹⁵,¹⁸ or any recurrent cardiovascular outcome.²⁵,²⁶ Pre-planned subgroup analyses showed statistically significant effects in children compared with adults for both pneumonia and otitis media.

When comparing zanamivir to no treatment, there was moderate quality evidence that zanamivir reduced the duration of symptoms²⁴,²⁷,²⁸ (23 hours, CI 95% 17–28 hours; SMD –0.94, CI 95% –1.21 to –0.66); and very low-quality evidence that hospitalisations may be reduced¹¹,²⁹ (OR 0.66, CI 95% 0.37–1.18). However, patients with influenza-like illness may experience more complications with inhaled zanamivir, including otitis media, respiratory disease or other complications.²⁹

In direct comparisons of oseltamivir with zanamivir, inconsistent evidence suggests that zanamivir may have a slight advantage in reducing the duration of symptoms²⁰,²³,²⁸,³⁰,³¹ (by 7 hours, CI 95% 2–12 hours; SMD 0.26, CI 95% 0.07–0.45). Very low to low-quality evidence showed that the two treatments may not differ with respect to mortality, hospitalisation, ICU admission, critical adverse events or viral shedding (as measured 5 days after treatment).¹¹,²⁰,²⁴

Results from studies evaluating the effects of initiating treatment with oral oseltamivir within 48 hours of symptom onset versus initiation of treatment after 48 hours of symptoms suggest that mortality (OR 0.33, CI 95% 0.12–0.86), hospitalisations (OR 0.52, CI 95% 0.33–0.81) and ICU admission (OR 0.22, CI 95% 0.15–0.33) may be reduced when oseltamivir treatment is initiated earlier.³²–³⁹ Similarly, there was low-quality evidence showing a reduction in symptom duration⁴⁰ and risk of complications,⁴¹,⁴² when treatment was initiated earlier rather than later with amantadine or rimantadine, respectively.

Conclusions

The results of this review underscore the need for additional, high-quality studies to inform guidelines about the use of antiviral treatments for influenza. Many of the studies indentified in this review had a high risk of bias resulting from the lack of control for confounding variables and possible selection bias. In addition, meta-analysis was limited by the fact that few studies reported appropriately adjusted effect measures. These limitations make it difficult to draw firm conclusions from the studies, and care must be used when using this information to make healthcare decisions. Based on this evidence, however, oral oseltamivir and inhaled zanamivir may
| Quality assessment | Summary of findings | Anticipated absolute effects |
|--------------------|---------------------|-----------------------------|
| **Participants (studies)** | **Overall quality of evidence** | **Study event rates (%)** | **Relative effect (95% CI)** | **Risk with no antiviral treatment** | **Absolute effect with Oseltamivir (95% CI)** |
| Follow-up to 30 days | | | With no antiviral treatment | With oseltamivir | |
| Mortality | ⚫⚫⚫ LOW* | 59/242 (24.4%) | 31/439 (7.1%) | Adjusted OR 0.23 (0.13–0.43) | 240 deaths per 1000 | 172 fewer deaths per 1000 (from 120 to 201 fewer) |
| (681 (three studies)) | | | | OR 0.51 (0.23–1.14)** | 240 deaths per 1000 | 101 fewer deaths per 1000 (from 172 fewer to 25 more) |
| Hospitalisation | ⚫⚫⚫ VERY LOW** due to risk of bias | 61/320 (19.1%) | 228/1237 (18.4%) | Adjusted OR 0.75 (0.66–0.86) | 12 hospitalisations per 1000 | 3 fewer hospitalisations per 1000 (from 1 to 4 fewer) |
| (1557 (nine studies)) | | | | OR 0.75 (0.66–0.86) | 12 hospitalisations per 1000 | 3 fewer hospitalisations per 1000 (from 2 to 4 fewer) |
| ICU admission/mechanical ventilation/respiratory failure | ⚫⚫⚫ LOW†due to risk of bias, inconsistency | 1238/100585 (1.2%) | 431/50125 (0.86%) | Adjusted OR 0.75 (0.66–0.86) | 12 hospitalisations per 1000 | 3 fewer hospitalisations per 1000 (from 2 to 4 fewer) |
| (150710 (four studies)) | | | | OR 0.75 (0.66–0.86) | 12 hospitalisations per 1000 | 3 fewer hospitalisations per 1000 (from 2 to 4 fewer) |
| Duration of hospitalisation (days) | ⚫⚫⚫ VERY LOW** due to risk of bias, inconsistency | – | 200/1032 (19.4%) | The mean duration of hospital stay was 5.16 days (5.02–5.29) |
| (832 (five studies)) | | | | Pooled Risk 13.0% (95% CI 11–15%) | \[\] |
| Duration of signs and symptoms (measured from onset of symptoms or treatment) (time to return to normal activity was not measured) | ⚫⚫⚫ VERY LOW** due to risk of bias, inconsistency | – | 832 | – | – |
| (5842 (six studies)) | | | | | |
| Complications – Pneumonia | ⚫⚫⚫ VERY LOW** due to inconsistency | 449 | 5393 | – | – |
| (150466 (three studies)) | | | | | The mean time was 0.91 standard deviations lower (1.25–0.57 lower)‡ |
| | | | | | |
| (265276 (six studies)) | | | | | |

∗denotes high risk of bias due to attrition.
**denotes very low quality of evidence.
†††denotes inconsistency.
‡denotes risk of bias.

Pooled Risk 13.0% (95% CI 11–15%).
Table 1. (Continued)

| Quality assessment | Summary of findings | Anticipated absolute effects |
|--------------------|---------------------|-----------------------------|
| **Participants (studies)** | **Study event rates (%)** | **Relative effect (95% CI)** | **Risk with no antiviral treatment** | **Absolute effect with Oseltamivir (95% CI)** |
| **Follow-up to 30 days** | **With no antiviral treatment** | **With oseltamivir** | **Risk with no antiviral treatment** | **Absolute effect with Oseltamivir (95% CI)** |
| **Overall quality of evidence** | **to risk of bias, inconsistency** | **Adjusted OR** | **14 otitis media per 1000** | **3 fewer otitis media per 1000 (from 2 to 5 fewer)** |
| **Complications – Otitis media** | | | **19 otitis media per 1000** | **4 fewer otitis media per 1000 (from 1 to 7 fewer)** |
| 78407 (two studies) | 546/40022 (1.4%) | 285/38385 (0.74%) | **OR 0.75 (0.64–0.87)** | **14 otitis media per 1000** |
| 193105 (four studies) | 2053/105758 (1.9%) | 1381/87347 (1.6%) | **OR 0.77 (0.63–0.94)** | **19 otitis media per 1000** |
| **Complications – Cardiovascular outcomes** | | | | |
| 100830 (two studies) | 62385 | 38445 | **Adjusted OR** | **200 cardiac events per 1000** |
| 60678 (two studies) | 6814/50696 (13.4%) | 606/9982 (6.1%) | **OR 0.45 (0.25–0.81)** | **73 fewer cardiac events per 1000 (from 128 fewer to 16 more)** |
| **Critical Adverse Events** | | | | |
| 104930 (five studies) | 60817 | 44113 | **Rate Ratio** | **420 adverse events per 1000 patient years** |

*Although we did not downgrade, publication bias cannot be excluded.
**Studies not adjusted for potential confounding factors.
***Significant differences in effect for pandemic versus seasonal influenza (see subgroup analyses table).
†Publication bias a concern because large studies had for-profit funding and weighed heavily in analyses.
††No independent comparison group.
†††High heterogeneity among studies.
‡This translates to reduced symptom duration of approximately 33 hours (95% CI 21–45 hours). Despite the large effect, we did not upgrade because there was important inconsistency across studies.

Note: Information linking specific studies to each of the analyses above may be found in the original publication.
provide net benefit over no treatment, although treatment with zanamivir may result in more complications than no treatment. In direct comparisons, zanamivir may be slightly more effective in reducing the duration of symptoms than oseltamivir. The evidence further suggests that administering antivirals within 48 hours of symptoms may be of greater benefit than initiating treatment at a later time.

Although the overall confidence in the effect estimates is low to very low, this review has nevertheless provided important evidence supporting a role for antivirals in the treatment of influenza and must be viewed in the context of the information available from RCTs and the substantial burden of influenza worldwide. There remains a need for high-quality evidence from RCTs that address patient-important outcomes and include hospitalised patients with influenza. Observational studies can continue to supplement this evidence by contributing data about special populations, adverse effects and rare harms.

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Conflict of interest

Ms. Santesso; Drs. Mustafa, Brozek, Hopkins, Flottorp, and Schünemann; Mr. Chen; Ms. Cheung; Mr. Wong; and Mr. Tian report the following: Grant (money to institution): World Health Organization.

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