CONTEXT AND POLICY ISSUES:

Pandemic H1N1 (also referred to as swine flu) is a strain of influenza A virus that was initially identified in pigs and subsequently found to circulate among humans.\(^1\) The H1N1 virus can be spread between humans via respiratory droplets, but contaminated surfaces can also be a source of viral transmission.\(^1\) Like other influenza viruses, H1N1 causes fever, cough, sore throat, headache, and muscle pain in uncomplicated cases.\(^1\) In more complicated cases, symptoms such as shortness of breath, central nervous system complications (drowsiness, altered mental state), secondary involvement of organs such as the kidneys and heart, and dehydration can occur.\(^1\)

While vaccination is the preferred means of reducing the spread of pandemic H1N1 infection, antiviral medications can also prevent H1N1 related illness from developing in individuals who have been exposed.\(^2\) Antiviral medications can also be used to treat individuals who have already developed symptoms.\(^2\) Oseltamivir is a neuraminidase inhibitor.\(^3\) Drugs in this class exert their effects by inhibiting viral neuraminidase, an enzyme that enables the virus to enter host cells and to release newly formed viral particles that then spread the virus to other cells.\(^3\) Oseltamivir is taken orally within two days of the onset of symptoms to reduce symptom duration in adults and children over one year of age with acute uncomplicated illness due to influenza viruses.\(^3\) Oseltamivir can also be used to prevent the development of influenza in those who have been exposed to an individual infected with an influenza virus.\(^3\) Zanamivir is also a neuraminidase inhibitor used for treatment and prevention of influenza, but is approved for use in adults and children age seven and older and is administered via inhalation.\(^4\) Like oseltamivir, zanamivir is to be used within two days of symptom onset.\(^4\) H1N1 is resistant to the anti-viral amantadine.\(^1\)

A mutation of the H1N1 virus (referred to as the H274Y mutation) has been associated with resistance to oseltamivir.\(^5\) In 2009 in Japan, 97% of circulating strains of H1N1 had this
mutation. This report will review the evidence of comparative clinical and cost-effectiveness of oseltamivir and zanamivir in the prophylactic and post-exposure treatment of H1N1. This information could be useful in informing policy decisions about the use and coverage of these medications.

RESEARCH QUESTIONS:

1. What is the comparative clinical effectiveness of oseltamivir versus zanamivir or amantadine for the prophylactic and post-exposure treatment of H1N1?

2. What is the comparative cost-effectiveness of oseltamivir versus zanamivir or amantadine for the prophylactic and post-exposure treatment of H1N1?

METHODS:

A limited literature search was conducted on key health technology assessment resources, including PubMed, OVID Medline, OVID Embase, The Cochrane Library (Issue 5, 2010), University of York Centre for Reviews and Dissemination (CRD) databases, ECRI (Health Devices Gold), EuroScan, international health technology agencies, and a focused Internet search. The search was limited to English language articles published between January 1, 2005 and May 20, 2010. Filters were applied to limit the retrieval to health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, controlled clinical trials, observational studies, and economic studies.

SUMMARY OF FINDINGS:

One relevant RCT and two relevant observational studies were identified from the literature search. No relevant health technology assessments, systematic reviews, meta-analyses, controlled clinical trials, or economic studies were identified that compared the clinical or cost-effectiveness of antiviral agents in prophylactic and post-exposure treatment of H1N1.

Randomized controlled trials

In a 2010 study reported by Sugaya et al., the clinical effectiveness of a long-acting neuraminidase inhibitor (laninamivir octanoate) was compared to oseltamivir in children 9 years of age or younger with influenza infection. This was a double-blind RCT with three treatment arms: laninamivir 40 mg single inhaled dose, laninamivir 20 mg single inhaled dose, and oseltamivir 2 mg/kg orally twice daily for five days. A double-dummy technique was used to maintain the blinding of patients and investigators since one medication was inhaled and the other was administered orally. The study was carried out in 43 centers in Japan, and children were included if they had flu-like symptoms for 36 hours or less with a temperature of at least 38.0°C. The children also had to be able to take the study drug by inhalation. Patients with comorbidities and those who had taken antiviral medication in the previous four weeks were excluded. A diagnosis of influenza was made using a rapid test kit and then a throat swab with culture, and sensitivity to neuraminidase inhibitors was also assessed. All viruses identified as the H1N1 subtype were then tested for the presence of the H274Y mutation. Study enrollment was not restricted to patients with H1N1, but data for this subgroup were presented. The
primary endpoint of the study was the time to alleviation of flu-like symptoms, and the secondary endpoint was the duration of fever.

Data were available from 184 of the 186 patients who were randomized. Of the patients with available data, 112 were infected with H1N1 (n=40 for laninamivir 40mg, n=40 for laninamivir 20mg, and n=32 for oseltamivir). The H274Y mutation was found in 96% of H1N1 strains. In patients with the H1N1 strain, the median time in hours to alleviation of symptoms was 49.6 (95% CI: 39.7–62.1; p=0.007) for laninamivir 40 mg, 44.3 (95% CI: 24.3–58.9; p=0.001) for laninamivir 20 mg, and 110.5 (95% CI: 68.8–141.9) for oseltamivir. The median duration of fever in hours was 30.5 (95% CI: 21.4–41.6; p=0.034) for laninamivir 40 mg, 23.8 (95% CI: 20.1–38.3; p=0.006) for laninamivir 20 mg, and 49.3 (95% CI: 33.5–62.8) for oseltamivir. The p-values presented here in parentheses refer to the comparison of each laninamivir group to oseltamivir. Diarrhea, nausea, and vomiting were the most common adverse effects with both drugs. The authors concluded that laninamivir octanoate was effective for treating oseltamivir-resistant H1N1 infection, that the drug was well-tolerated, and that laninamivir octanoate had the advantage of requiring a single inhalation per treatment course. The results of this study may not be generalizable to strains of H1N1 without the H274Y mutation, children with comorbidities, adults with H1N1 infection, a non-Japanese population, or patients who present more than 36 hours following onset of symptoms. Further, laninamivir is not yet available in Canada.

Observational Studies

In a 2009 study reported by Kawai et al., the clinical effectiveness of oseltamivir and zanamivir was compared for the 2007-2008 and the 2008-2009 influenza seasons. The study was carried out in 15 clinics in Japan, and both adults and children were enrolled. Data from 291 patients who had been treated with neuraminidase inhibitors were used in the analysis, 232 of whom had the H1N1 strain. Patients were included if they reported to one of the clinics with flu-like symptoms and a diagnosis of influenza virus infection was confirmed by a commercial antigen detection kit. Only those patients who were treated with oseltamivir or zanamivir within 48 hours of symptom onset were enrolled in the study, and patients were excluded if they had severe underlying diseases. Patients were administered oseltamivir or zanamivir at the clinician’s discretion, in consideration of treatment guidelines and patient preference. An assay was used to determine influenza virus subtype, and status of the H274Y mutation was also assessed and found to be present in 49 samples, all of which were from the 2008-2009 season. Oseltamivir was administered orally at a dose of 75 mg twice daily for five days in adults and children who weighed at least 37.5 kg, and 2 mg/kg twice daily for five days in children who weighed less than 37.5 kg. Zanamivir was administered at a dose of 10 mg inhaled twice daily for five days for adults and children aged five years and older. Outcome measures included the duration of fever following the initial dose of antiviral medication and the rate of prolonged fever (defined as a fever lasting 48 hours or 72 hours after initiating drug therapy). The statistical analysis was not adjusted for any patient characteristics; however, the oseltamivir and zanamivir groups were described as being clinically similar.

For those with H1N1 infection in the 2007-2008 season, the duration of fever (mean ± SD, hours) following the first dose of medication was 32.0 ± 18.9 in the oseltamivir group compared to 31.5 ± 14.9 in the zanamivir group (p value >0.05). For those with H1N1 infection in the 2008-2009 season, the duration of fever (mean ± SD, hours) following the first dose of medication was 49.1 ± 30.2 in the oseltamivir group compared to 27.5 ± 18.5 in the zanamivir group.
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(p<0.001). In the 2008-2009 season, the percentage of patients with H1N1 who remained febrile 48 hours after initiating treatment was higher in those treated with oseltamivir compared to zanamivir (37.7% versus 12.6%, p<0.001). The percentage of patients with H1N1 who remained febrile 72 hours after initiating treatment was also higher in those treated with oseltamivir compared to zanamivir (23.4% versus 1.1%, p<0.001). The authors concluded that the clinical effectiveness of oseltamivir in treating H1N1 infection was reduced during the 2008–2009 season, likely due to the H274Y mutation, but that the same was not true for zanamivir. This study may be limited by its non-randomized design, which could lead to bias in the assignment of treatments which was at the discretion of the clinician. Furthermore, the results of this study may not be generalizable to populations where the prevalence of the H274Y mutation in H1N1 strains is low, to patients with comorbidities, to a non-Japanese population, or to patients who present more than 48 hours after onset of symptoms.

Sugaya et al. (2008)\(^7\) compared the clinical effectiveness of oseltamivir and zanamivir in children with influenza infections in a hospital-based outpatient clinic in Japan during the 2005-2006 and 2006-2007 seasons. The selection of neuraminidase inhibitors was generally based on patient or parent preference and clinical presentation. Results for the H1N1 strain were reported separately, and included data from 24 patients who were treated with oseltamivir and 12 patients who were treated with zanamivir. The patients included in the analysis arrived at the hospital within 48 hours of the onset of a fever. A diagnosis of influenza was determined from a rapid diagnostic test which was performed prior to starting oseltamivir or zanamivir. The dosage of oseltamivir was based on weight, and it was administered orally in two divided daily doses for 5 days. Zanamivir was administered via inhalation of 10mg twice per day for 5 days. Outcome measures included the total febrile period and the duration of fever after the first dose of antiviral medication. The statistical analysis was not adjusted for any differences in patient demographics. The mean age (± SD) zanamivir group was greater than the oseltamivir group (8.1 ± 2.1 years compared to 6.4 ± 2.2 years).

The total febrile period in days (mean ± SD) for the children with H1N1 who were treated with oseltamivir was 2.60 ± 0.81 and 2.46 ± 0.72 for zanamivir (p-value >0.05). The durations of fever in days following initiation of therapy (mean ± SD) in children with H1N1 who were treated with oseltamivir and zanamivir were 1.79 ± 0.79 and 1.54 ± 0.62, respectively (p-value >0.05). The authors concluded that the clinical effectiveness of oseltamivir and zanamivir for H1N1 infection in children with influenza was the same. However, in the presence of limited sample size and statistical power, findings from this study remain inconclusive. This study was limited by its non-randomized design, which creates the potential for bias. The results of this study may not be generalizable to a non-Japanese population, adults, or patients who present more than 48 hours following onset of symptoms. Furthermore, the results may not be generalizable to geographic regions where the H274Y mutation is commonly encountered.

Limitations

Three studies were identified that compared neuraminidase inhibitors for the treatment of flu-like symptoms in individuals with H1N1 infection.\(^5\-7\) Two of these studies had non-randomized designs\(^5,7\), which carries an increased risk of potential residual confounding and bias relative to a randomized design. No attempt was made to adjust for confounding variables in the statistical analyses. One of the two neuraminidase inhibitors compared in the RCT has not yet received marketing approval in Canada.\(^6\) Thus, these results are not applicable to Canada at this time.
No studies of the comparative efficacy of neuraminidase inhibitors for the post-exposure prophylaxis of H1N1 infection were identified by the search, nor were any studies of the cost-effectiveness of this class of antiviral agents in the treatment or prevention of viral illness from H1N1.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING:

In summary, based on the limited clinical evidence identified, oseltamivir appears to be less effective than other neuraminidase inhibitors for the treatment of H1N1 infection due to strains that have the H274Y mutation. Data from two Japanese studies suggest that, in the absence of the H274Y mutation, the clinical effectiveness of oseltamivir and zanamivir was comparable for the treatment of influenza due to H1N1 infection. The relevance of these observations to clinical practice or policy decisions about the use of oseltamivir and zanamivir for post-exposure treatment of H1N1 infection may be influenced by the prevalence of H274Y mutation in H1N1 strains circulating in a particular area. H1N1 is resistant to the anti-viral amantadine. No literature was identified from which to draw conclusions about the comparative clinical effectiveness of antiviral agents for post-exposure prophylaxis of H1N1 or about their cost-effectiveness in the prophylactic and post-exposure treatment of H1N1.

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