Summary of Evidence for Benefits and Harms of the Use of Influenza Antiviral Agents against Pandemic Influenza A H1N1 (2009) Infections - November 2010 Update

Foreword

This document provides a brief review of recent published literature that covers use of antivirals in treatment of H1N1 (2009) infections. Most of these papers have been published since the development in February 2010 of (revised) WHO guidelines for pharmacological management of pandemic A (H1N1) 2009 and other influenza viruses. At this time there is no evaluation of these published clinical reports, nor any conclusion. WHO has commissioned a full systematic review of the relevant evidence, and any conclusions on the benefit of antivirals in treatment or prevention of severe influenza disease will come from this work. The outcome of this work will be made available to the Expert Committee for their 18th meeting in march 2011.

Background

This summary will focus on the use of the influenza neuraminidase inhibitors (NAIs) against influenza A H1N1 (2009) infections, with the majority of clinical data obtained from the use of the oral inhibitor oseltamivir, and limited use of the inhaled inhibitor zanamivir. The influenza A H1N1 (2009) viruses circulating globally are resistant to the adamantanes (M2 ion-channel inhibitors), so these have had very limited use. Investigational intravenously administered NAIs (intravenous (IV) zanamivir and IV peramivir) have occasionally been used in the treatment of life-threatening disease. Where oseltamivir resistance (H275Y mutation) has been detected, zanamivir (inhaled or IV) has often been the treatment method of choice.

There are no randomized controlled trials assessing the efficacy and safety of NAIs (or other antivirals) for influenza A H1N1 (2009) infections. There are, however, a growing number of observational studies assessing efficacy and other outcomes; in particular, efficacy in relation to time from symptom onset to treatment. Data from early studies have been included in the WHO Guidance Document for Management of Pandemic A (H1N1) 2009 and other influenza viruses, Updated February 2010, Part II, Review of Evidence. Here, publications released since the distribution of this WHO document are reviewed, including 41 case series, 29 case reports, 1 antiviral treatment review and 4 public health publications.

Case Series and Reviews

Studies involving mainly severely-ill hospitalized patients (1 review, 14 case series)

One review (Falagas et al., 2010) evaluated published evidence on the treatment strategies used for influenza H1N1 (2009) and covered pooled data from 22 studies, including 15 cohort studies with more than 10 patients, 5 cohort studies with less than 10 patients, and 2 case reports. Studies from 8 different countries worldwide were included with a total of 3020 patients. 1622 (53.7%) of these patients received antivirals, of whom 661 (40.8%) received oseltamivir monotherapy, 95 (5.9%) received zanamivir, 8 (0.5%) amantadine, 1 (0.06%) rimantadine and 44 (2.7%) received a combination of two of these antivirals. Attempts to evaluate these pooled data looking at the impact of antiviral treatment and early administration of antivirals on mortality were hampered by the scarcity of comparative data. However, re-analysis of one large study from the U.S. (Louie et al.,
2009) in 1088 hospitalized patients indicated that administration of antivirals within 2 days from symptom onset was significantly associated with reduced mortality (p<0.001).\(^4\)

At least 14 further observational studies have been published studying mainly severely-ill hospitalized patients. Of these studies, nine reported positive trends or beneficial effects of antiviral therapy. Five studies have shown a statistically significant effect of antiviral treatment,\(^4,5,6,7,8\) while 4 have shown trends that early treatment may have been beneficial,\(^9,10,11,12\) and 5 studies have not shown a clear benefit.\(^13,14,15,16,17\)

Studies demonstrating statistical significance of antiviral use particularly highlighted the importance of early treatment. In a study from Taiwan, Chien et al. present data suggesting that a duration from symptom onset to initiation of oseltamivir treatment of greater than 48 hours was significantly associated with development of respiratory failure among patients infected with H1N1 (2009) influenza virus (p=0.011).\(^4\) In the U.S., Lee et al. noted that fatal cases among hospitalized patients (28/123) were less likely to have received oseltamivir within 2 days of hospitalization than those who survived (61% vs. 96% p<0.01).\(^5\) Chinese surveillance data identified lack of antiviral treatment within 48 hours after symptom onset as a significant risk factor when comparing severe to mild (OR=0.1, p<0.001) and fatal to severe disease (OR=3.0, p=0.01).\(^7\) Similarly, a surveillance system for hospitalized cases of severe H1N1 (2009) in Spain demonstrated worse outcomes (ICU or death) when treatment was started after 48 hours (OR=2.39, p<0.001) and a significant difference in interval between illness onset and antiviral treatment [median (hospitalized vs. ICU/death) = 3 vs. 5 days (p<0.001)].

In a study by Fuhrman et al., the impact of antiviral treatment on the likelihood of severe outcomes varied depending upon other risk factors.\(^8\) In those ICU patients with other identified risk factors, late antiviral administration (>48 hours) was significantly associated with severe outcomes (OR=2.0, 95% CI: 1.4-3.0); whereas those without risk factors demonstrated a trend towards antivirals as a protective factor, but the results were not significant (OR=1.9, 95% CI: 0.8-4.8), though this may be a result of lack of power within the study.

Another publication by Fuhrman et al. also demonstrated a non-significant treatment benefit trend.\(^12\) 244 ICU and 514 hospitalized patients were included in this study. Antiviral treatment was initiated less than 48 hours after symptom onset for 74% of non-severe hospital cases, but in only 39% of severe cases. To et al. noted that in 74 hospitalized patients in Hong Kong, including 23 with Acute Respiratory Distress Syndrome (ARDS), that the median time for initiation of oseltamivir therapy was 5 days after symptom onset in the group with ARDS and a fatal outcome, 4 days in the survival-without-ARDS group and 2 days in the mild disease group.\(^9\) In a U.K. study, Nguyen-Van-Tam et al. reported that cases receiving antiviral treatment before hospital admission were less likely to require high dependency or ICU care and were 50% less likely to die in hospital.\(^11\) Finally, a Swiss study by Bertisch et al. of 15 pandemic H1N1 (2009) hospitalized patients noted that, despite having given oseltamivir treatment later than recommended, no patients died.\(^10\)

One of the studies reporting no antiviral efficacy (N=68) may have been confounded by time to treatment, as the median treatment delay after symptom onset was 7 days.\(^13\) Another study reporting no antiviral efficacy was undertaken in Argentina in severely ill patients on mechanical ventilation (N=377) with 60% of participants on high dose 300mg oseltamivir.\(^14\) It was reported that the frequency of oseltamivir use was similar in survivors and non-survivors. A large study of hospitalized patients (N=1348), included 92 severe cases, of which 88 were treated in an ICU.\(^15\) Amongst these severe cases, there was no statistical difference in survival between those given oseltamivir less than 48 hours and more than 48 hours after the onset of illness (p= 0.8250). In a comparison of influenza H1N1 (2009) survivors and non-survivors, a study by Xi et al. demonstrated no impact of antiviral treatment nor antiviral treatment within 48hours on mortality.\(^16\) One Japanese study compared delays in antiviral treatment for fatal and severe cases, but reported no significant
difference. This may be a reflection of the ease of accessibility of antivirals in Japan, leading to a high proportion of influenza patients receiving early treatment. However, the authors also note that the impact of early treatment observed in other health care systems may be due to confounding by simultaneous access to antivirals and other hospital care.

**Studies in Pregnant women (5 Case Series)**

Data indicate that pregnant women are at increased risk of hospitalization and death from pandemic influenza H1N1 (2009), particularly in the third trimester, in addition to an increased risk of adverse neonatal outcomes. Three large studies of H1N1 (2009) infection in pregnancy have indicated strong protective value of early oseltamivir treatment.

A strong association between treatment delay of >3 or >5 days and severe outcomes was documented in a French study of 315 hospitalized pregnant women (Adjusted OR(>3d) = 4.8, 95% CI: 1.9–12.1; and aOR(>5d) = 61.2, 95% CI: 14.4–261.3). Only 55% of those entering the ICU received antivirals within 48 hours, whereas this percentage was 88% and 80% for mild and moderate outcomes (severe vs. mild/moderate p=0.001).

In a New York study comparing 62 pregnant women and 74 non-pregnant women, a significant treatment benefit was observed. Only 3.3% (N=30) of pregnant women receiving oseltamivir treatment within 2 days of symptom onset experienced severe illness, compared with 21.4% (3/14) and 44.4% (4/9) of those starting treatment 3-4 and ≥5 days after symptom onset, respectively (p=0.002). A further large U.S. study included 788 pregnant women infected with pandemic influenza H1N1 (2009) reported to the CDC. Extensive analysis has shown that with an antiviral treatment delay of more than 4 days after symptom onset, patients were more likely to be admitted to the ICU (37/65, 56.9%) than those treated within 2 days (13/138, 9.4%) (Relative risk 6.0, 95% CI, 3.5–10.6, p<0.001). Only one death (1/198, 0.5%) occurred in a patient receiving antiviral treatment within 2 days of symptom onset, compared with 20/74 (27%) in those with treatment delayed for more than 4 days [relative risk, 53.5 (95% CI, 7.3-391.70, p<0.001)].

A Brazilian cross-sectional study of 57 pregnant women hospitalized for H1N1 (2009) infection reported no maternal deaths. Although no direct comparison was available, a comparison made by the authors with two other studies suggested more complete and faster antiviral coverage in this report, and these were given as possible explanations for the lack of fatalities. Similarly, a prospective study of influenza-infected pregnant women on Réunion Island suggested that the 86% coverage and median delay of less than 2 days to oseltamivir treatment may have influenced patient outcomes. Although not significant at the 95% level, the delay in treatment for severe H1N1 (2009) patients was 62.7 hours, as opposed to only 41.3 hours in mild cases.

**Studies in Paediatrics including Neonates (9 Case Series)**

Three retrospective studies, encompassing a total of 153 oseltamivir-treated children, have examined pandemic H1N1 (2009) infections and their treatment, of which many cases had known risk factors and included at least 14 neonates below 6 months. Disease severity in children was described as similar to that observed in seasonal influenza. Of these three, only Lockman et al. discussed antiviral efficacy, stating that ICU length of stay did not differ between an early (within 48 hours) oseltamivir treatment group, (n=5, length of stay 4.2 ±6.6 days, mechanical ventilation 4.0±4.2days) versus a late treatment group (n= 6, length of stay, 6.8± 8.8 days, mechanical ventilation 7.8±6.5days), with all patients surviving to hospital discharge.

In a Japanese case series of 21 paediatric (≤15 years) hospitalized patients, the 100% survival rate was in-part attributed to the administration of antivirals to all patients, of which 20/21 were within
48 hours.28 Although there was no comparison group within the study, an indirect comparison with mortality and time to treatment data from studies in other countries suggested that those countries providing early antivirals may have experienced better patient outcomes.29 A paediatric H1N1 (2009) mortality study in the UK indicated that only 64% (45/70) of fatal cases received antivirals, of which only 16% (7/45) received oseltamivir within 48 hours.29

Very few data are available for the use of oseltamivir in very young and preterm infants. A study of 10 paediatric ICU patients, of which 3 were preterm and the average age at admission was 24.5 days, provides important information demonstrating a full recovery of all infants with no residual deficits or side effects resulting from oseltamivir treatment (2-3mg/kg bid).30 In another prospective study of 147 pICU H1N1 (2009) cases (median age 10 months), a significant protective effect against mortality due to oseltamivir administration within 24 hours was observed (OR 0.2, 95% CI: 0.07-0.54).31

Another study followed oseltamivir prophylaxis (1mg/kg dose BID) in 32 neonates accidentally exposed to pandemic H1N1 (2009) virus.32 No pandemic H1N1 (2009) infections were reported and oseltamivir carboxylate (OC) plasma levels were comparable to those observed in children administered 3mg/kg/dose BID. In a study by Wildschut et al., OC plasma concentrations were followed in three H1N1 (2009)-infected paediatric patients on ECMO administered a double dose of oseltamivir suspension (age range 6-15 years).33 High OC plasma levels were observed in 2 patients, potentially due to the increased dose and, in one patient, reduced kidney function. However, concentrations in the third patient were suboptimal, potentially attributable to impaired absorption due to gastric bleeding and decreased gastric motility. This was the first paediatric study to demonstrate the ability to achieve adequate OC levels in critically-ill ECMO patients, and highlights both the approximate doses required and also indicates possible failings of nasogastric administration in patients with gastric problems.

Studies in Other Higher Risk Groups (1 Case series)

HIV co-infection is both a risk factor for severe influenza disease and for development of antiviral resistance. Feiterna-Sperling et al. provide data from an outbreak of mild H1N1 (2009) infections amongst 15 HIV-infected school children.34 Those showing more severe initial fever were supplied with oseltamivir, and when these were compared with the untreated cases, the duration of viral shedding was significantly reduced (H1N1 RNA detected 4 vs. 8 days, p=0.005).

Studies of Mild Disease (8 Case Series)

A number of observational studies were undertaken using RT-PCR to screen for infected patients, for example, at airports, and those self-reporting with illness. These studies were non-randomised and therefore bias in the composition of the patient population may act as a confounder. Several of these studies showed a significant outcome of antiviral treatment with oseltamivir. Li et al. undertook a retrospective cohort study involving 145 RT-PCR positive patients in Hong Kong and compared outcomes between treated and non-treated patients.35 Viral load in nasopharyngeal aspirates (NPA) was significantly lower in treated patients (within 48 hours) versus untreated patients at day 5 after symptom onset (p=0.04). In addition, the rate of viral load reduction in NPA samples was greater in those treated within 48 hours than non-treated [Rate of viral load reduction (treatment <2days)= -0.638log₁₀ copies/ml/day, 95%CI -0.809 to -0.466, versus rate of viral load reduction (no treatment)= -0.409 log₁₀ copies/ml/day, 95%CI -0.663 to -0.185], however a similar rate was observed between patients treated within 48 hours and more than 48 hours after symptom onset. Virus was undetectable by day 6 after initiation of treatment, which was 1 day earlier than those initiating treatment more than 2 days after symptom onset. In the non-treated patients, resolution of fever was 1.4 days later than in the treated patient group (p= 0.012).
Ling et al. undertook a prospective observational study in Singapore with 70 hospitalized patients PCR-positive for pandemic H1N1 (2009) and treated with oseltamivir for 5 days. Mean time from illness onset to hospitalization was 3±2 days. Influenza-like illness, as defined by the CDC and WHO, was observed in 44/70 (63%) and 34 (49%) of patients, respectively. Mean virus shedding duration was 6±2 days, with 26/70 (37%) having virus signal persisting beyond 7 days. When oseltamivir was given within 1-3 days of illness there was significantly shorter virus shedding than in those commencing treatment at 4 days or later after onset (p<0.05).

Hien et al. recruited 200 PCR-positive travellers and 121 PCR-positive non-travellers in Vietnam and reported a rapid therapeutic response to oseltamivir. Shen et al. reported on a retrospective study in Chinese hospitalized patients, 236 treated with oseltamivir, of which 78.5% were within 48 hours of symptom onset. All the patients had mild disease and no mortality was associated with antiviral use. Ou et al. reported on 145 imported cases to China, that all patients recovered fully upon treatment within 5-11 days.

The "first few hundred" study in the UK followed up 392 cases of confirmed influenza, of which most were mild cases managed in the community. 92% of patients were treated with oseltamivir and 12% experienced adverse effects, mostly described as moderate. Only 27% received antiviral treatment within 48 hours, but duration of fever was significantly shorter in those treated early (median 5 vs. 9 days, p=0.01).

A retrospective study (Yu et al.) of medical charts from 1291 patients with confirmed H1N1 (2009) infection in China provides data on 983 oseltamivir-treated patients with mild influenza. Most patients received a standard course, though 11% received prolonged treatment for persistent viral RNA. Multivariable analysis suggests that oseltamivir treatment within 48 hours of symptom onset reduces duration of fever and shedding of viral RNA, in addition to an association of treatment with a reduced risk of radiographically confirmed pneumonia.

Several publications have documented the use of antivirals in school outbreaks. Strong et al. documented the use of oseltamivir for treatment and prophylaxis in 53 staff and 273 pupils, of which 47% and 41% reported adverse effects, respectively. No adverse events were life threatening in nature, but the authors question whether the benefits of antivirals in this group outweighed the harms caused due to prophylaxis or treatment with oseltamivir.

**Resistance Development to Oseltamivir (H275Y) (4 Case Series)**

Four case series documented development of resistance (H275Y), mainly in the immunocompromised, in 3/25 patients (12%), 10/1608 (0.006%) patients, 4/187 (2.1%) patients, and 4/30 (13.3%) patients.

**Case Reports**

A number of case reports have been published, most relating to complex or prolonged cases, including some cases where resistance to antivirals was observed.

**Oseltamivir (17 Case Reports)**

One case report described the successful treatment, with dose adjusted oseltamivir (2mg/kg/day), of a newborn girl. Her mother had died from respiratory failure 7 days after a caesarean section, and the newborn presented with respiratory distress and was PCR-positive for pandemic H1N1(2009) virus. A 6 day-old 32 week preterm low birth-weight male with H1N1 (2009) infection was treated with 4mg/kg BID, however this case resulted in a fatal outcome.
Similarly to the report on ECMO in pediatric patients by Wildschut et al., a case report of oseltamivir use in a 24 year old patient on ECMO and haemofiltration indicated that the usual double dose given to ECMO patients may be unnecessarily high.\textsuperscript{49} Although drug accumulation was comparable to studies in healthy volunteers, clearance was significantly slower leading to an increased elimination half life.

Two case reports described neurological side effects in 2 patients infected with pandemic H1N1 (2009) virus and were treated with oseltamivir (75mg or 150mg).\textsuperscript{50,51} A total of 5 case reports documented development of resistance to oseltamivir in immunocompromised patients during oseltamivir treatment,\textsuperscript{52,53,54,55,56} and one report in a child with cystic fibrosis.\textsuperscript{57} One case of human-to-human transmission of oseltamivir resistant H1N1 (2009) has been reported.\textsuperscript{58} Three case reports document resistance development during treatment with oseltamivir in immunocompetent patients.\textsuperscript{59,60,61} Evidence in one of these immunocompetent patient reports suggested development of resistance within 48 hours of treatment.\textsuperscript{61} One publication reported prolonged replication in 2 patients for 14 and 28 days with oseltamivir treatment, without development of resistance.\textsuperscript{62}

One report (Nguyen et al.) of multidrug resistance upon prolonged oseltamivir treatment has been reported. Elevated \( I_{50} \) values were reported for oseltamivir, peramivir and zanamivir in this fatal case of a 14 year old girl with dual H275Y and I223R virus mutations.\textsuperscript{63}

**Zanamivir Treatment (IV or Inhaled) (10 Case Reports)**

Five case reports describe the use of IV zanamivir in critically ill patients. Harter et al. reported on 2 patients with pneumonitis and ARDS due to pandemic H1N1 (2009) virus; both were treated with IV zanamivir and achieved a favourable outcome.\textsuperscript{64} Dulek et al. described an immunocompromised child with oseltamivir resistant pandemic H1N1 (2009) pneumonia.\textsuperscript{65} The child was treated with IV zanamivir, which was well tolerated and associated with a decrease in viral load. In addition, Speers et al. described a severely ill patient with oseltamivir-resistant virus; the patient improved with IV zanamivir, but subsequently died of non-respiratory complications.\textsuperscript{55} Couturier et al. described in detail several cases of oseltamivir resistant H1N1 (2009) in which zanamivir was administered.\textsuperscript{45} In one patient IV zanamivir was administered after failure of a 10 day 150mg BID oseltamivir course, but died several days later from cerebral infarction; the second patient received several high-dose oseltamivir courses followed by IV zanamivir, during which the patient recovered, but returned to hospital and received a further 4 days of inhaled zanamivir, followed by IV zanamivir before dying on hospital day 12 of this second admission.

Similarly to the Nguyen et al. report above, one fatal case of infection with dual mutation (H275Y and I223R) virus due to prolonged treatment with IV zanamivir in a 5 year old patient has been reported.\textsuperscript{66} Paediatric oseltamivir dose followed by IV zanamivir led to temporary recovery, but a treatment interlude allowed viral rebound and the patient required further IV zanamivir then triple therapy before death on day 118. Resistant virus isolated gave \( I_{50} \) values for oseltamivir, zanamivir and peramivir elevated by a factor of 45, 10 and 7, respectively, compared to wild type values.

Three case reports describe the successful clearance of oseltamivir resistant virus using inhaled zanamivir: Esposito et al., from a child with cystic fibrosis without any adverse event,\textsuperscript{57} and Memoli et al. and Anton et al. in immunocompromised patients.\textsuperscript{54,56}

One report described a fatal respiratory event following nebulization of the lactose-containing zanamivir formulation, which, due to the presence of lactose, blocked the ventilator.\textsuperscript{57} Use of the inhaled formulation of zanamivir is not recommended for nebulisation.\textsuperscript{68} An aqueous saline solution can be made available for nebulisation on compassionate grounds and was used in the case of long duration moderate disease in a 3 year old immunocompromised child with oseltamivir resistant
H1N1 (2009) virus. A 10-day treatment course was pursued and fever and respiratory symptoms resolved after 6 days. The patient made a full recovery with no severe side effects from treatment.

**IV Peramivir Treatment (2 Case Reports)**

Two case reports describe the use of IV peramivir. Campbell et al. described the successful use of a 10 day treatment with IV peramivir and oral oseltamivir. This treatment regime cleared extrapulmonary virus in a haematopoietic stem-cell transplant recipient after previous failure to clear virus with oral combination therapy and IV immunoglobulin over 10 days. Memoli et al. reported the failure of a 10 day course of IV peramivir to clear an oseltamivir resistant pandemic H1N1 (2009) virus, which is consistent with the cross-resistance reported in vitro with the H275Y mutation.

**Public Health Publications (4 publications)**

Several publications consider the use of antivirals in the public health context and examine the potential links between national-level practices and outcomes. Goldstein and Lipsitch have compared guidelines for antiviral usage adopted by different countries during the 2009 pandemic. For example, in Chile there was an active antiviral usage policy with almost 650,000 courses distributed. In contrast in Argentina treatment was reserved for hospitalized patients until after the peak of the epidemic. Deaths were higher in Argentina (580/9119 confirmed cases or 1.44 per 100,000 inhabitants) compared with Chile (136/12,257 confirmed cases or 0.8 deaths per 100,000). Further evidence for the benefits of early treatment came from Argentina’s change in policy during the 2009 pandemic to include treatment of non-hospitalized high risk groups including pregnant women. Deaths in pregnant women before the policy change were 31/174 (17.8%) compared with 4/69 (5.8%) after the change in policy, which is a significant reduction (Odds Ratio 95% CI: 0.07, 0.85; p= 0.015).

An understanding of national prescribing practices is key to understanding the results of two Japanese studies described earlier in this document. Both articles compare these practices in Japan (ease of antiviral access and widespread early treatment) with other countries and cite these differences as possible explanations for differences in patient outcomes.

Ease of antiviral access and prescribing practices were compared with mortality at the national level between five European countries in a letter by Hernandez et al. Those countries prescribing more antivirals reported significantly less mortality (e.g. Germany vs. Spain: oseltamivir retail per 100,000 = 405.3 vs. 40.9; mortality per million = 1.6 vs. 5.82). Therefore, these comparisons of public health practices at a population level can provide insight into the potential impact of oseltamivir treatment.
References


45. Couturier BA, Bender JM, Schwarz MA, Pavia AT, Hanson KE, She RC. Oseltamivir-resistant influenza A 2009 H1N1 virus in immunocompromised patients. Influenza Other Respi Viruses 2010;4:199-204.


