The use of antiviral agents for the management of severe influenza

James R. Smith, PhD; Robert E. Ariano, PharmD, BCPS, FCCM;
Stephen Toovey, MBBCh, PhD, FFTM, RCPS(Glas), FACTM, FFTM, ACTM

The clinical course of pandemic H1N1 2009 influenza can be severe, particularly in the very young and patients with comorbidities. Pandemic H1N1 2009 is sensitive to the antiviral agents oseltamivir and zanamivir but is resistant to adamantine. Although few clinical data are yet available, treatment of pandemic H1N1 2009 influenza in hospital settings with oseltamivir or zanamivir appears to be beneficial. In hospitalized patients with severe influenza treated with oseltamivir, mortality and length of stay are significantly reduced, and viral load is reduced more quickly than in untreated patients. In patients at high risk treated with oseltamivir or zanamivir, reductions in the risk of complications and mortality after treatment have been demonstrated with oseltamivir and zanamivir, although there are fewer data on the latter. There is no evidence yet that other antiviral agents are effective in severe or pandemic H1N1 2009 influenza. Current World Health Organization guidance strongly recommends the use of oseltamivir for severe or progressive infection with pandemic H1N1 2009, with zanamivir as an alternative if the infecting virus is oseltamivir-resistant. Very little resistance to oseltamivir has been found to date. (Crit Care Med 2010; 38[Suppl.]:S000–S000)

KEY WORDS: influenza; H1N1; hospitalized; intensive care; antiviral; oseltamivir; zanamivir; neuraminidase inhibitor; treatment

There has been a considerable sense of public relief in the realization that the current influenza pandemic caused by pandemic H1N1 (pH1N1) 2009 is unlikely to result in the catastrophic levels of morbidity and mortality associated with the 1918 "Spanish flu" pandemic. Most infected persons continue to experience mild and uncomplicated influenza-like illness, but a proportion go on to having severe disease that often involves rapid progressive pneumonia, leading to respiratory failure, refractory shock, and death in some cases (1). Severe disease appears more common in young children and those with underlying medical conditions (including asthma, obesity, and pregnancy) or immunosuppression, although individuals without obvious risk factors have also been affected (1–8). Treatment of these patients is difficult and demanding, strongly suggesting that emergency rooms and ICU will experience the heaviest burden of patient care. Experience from the winter months in New Zealand, where 972 of 3179 recorded cases (30.6%) through late August 2009 were hospitalized and 114 were admitted to ICU (9), could presage an increase in disease severity in northern hemisphere countries later in 2009.

Antiviral drugs have already proved their worth in the treatment and prevention of seasonal influenza, but most of this experience has been in the management of infections in primary care. The challenges posed by the current pandemic are to determine whether these drugs can be used to treat severe cases of influenza and what benefit they might offer to those populations of patients who are at higher risk for a more complicated disease course with attendant elevations in the risk of hospital admission and mortality. This article reviews the current evidence on these topics.

MATERIALS AND METHODS

Treatment Guidelines for Pandemic H1N1 2009 Influenza

The pH1N1 2009 is now the predominant influenza virus in the temperate zones of the northern and southern hemispheres, although infection rates in the latter have returned to below baseline levels (10). The World Health Organization (WHO) has confirmed that the circulating pH1N1 2009 viruses are sensitive to both oseltamivir and zanamivir (11) and that their susceptibility to neuraminidase inhibition is very similar to that of drug-sensitive seasonal viruses (12). The circulating seasonal H1N1 strains are still resistant to oseltamivir. In August 2009, the WHO issued updated guidelines on drug treatment and prophylaxis of influenza caused by pH1N1 2009 and other viruses (11). This guidance made the specific and strong recommendation that all patients with severe or progressive pH1N1 2009 illness should be treated with oseltamivir, including children aged younger than 5 yrs, neonates, and pregnant women, and that treatment should be started as soon as possible (11). In patients whose response is inadequate, the dosage of oseltamivir can be increased to 150 mg twice daily, and the treatment duration is prolonged. In reaching this recommendation, the WHO acknowledged that an orally administered drug is easier to use than one administered by inhalation. If oseltamivir is not available or if the virus is resistant to it, patients should be treated with zanamivir (11). Similarly, in its updated guidance on antiviral use for the 2009 to 2010 season, the US Centers for Disease Control and Prevention recommends that any patient admitted to hospital with influenza, whether suspected or confirmed, should be treated with a neuraminidase inhibitor (13).

In a situation update in late September 2009, the WHO reported that the majority of >10,000 isolates of pH1N1 2009 tested for resistance were sensitive to oseltamivir, concluding that the 28 resistant isolates found so far did not indicate the development of widespread antiviral resistance (14). The WHO also confirmed that 12 of the resistant viruses were isolated from patients who had received osel-

From F. Hoffmann-La Roche Ltd (JRS), Basel, Switzerland; St Boniface General Hospital and University of Manitoba (REA), Winnipeg, MB, Canada; University College London (ST), London, UK.

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For information regarding this article, E-mail: james.smith.js1@roche.com

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tamivir as prophylaxis (14), and that it was withdrawing its earlier support for the use of antiviral drugs for prophylactic purposes (11, 14). The WHO now recommends close monitoring for symptoms in those exposed to infected persons and those at high risk for severe or complicated illness, followed by early antiviral treatment (14). The WHO has confirmed that the pandemic virus is resistant to the M2 inhibitors amantadine and rimantadine (15). For this reason, neither agent is discussed in detail here.

Oseltamivir

Oseltamivir (Tamiflu; F. Hoffmann-La Roche Ltd, Basel, Switzerland) is a neuraminidase inhibitor used for the treatment and prophylaxis of influenza A and B infections in humans. After systemic absorption of an oral dose, oseltamivir, a pro-drug, is rapidly converted to the active metabolite, oseltamivir carboxylate (OC), which distributes widely to potential sites of influenza infection (bioavailability of ≈80%) (16). The product is approved for use in adults and children aged 1 yr or older with seasonal influenza, but authorization has recently been granted in the US and Europe for use in infants aged younger than 1 yr and pregnant women infected with pH1N1 2009 (17–21). When used for influenza treatment, oseltamivir is administered twice daily for 5 days in a dose of 75 mg for adults and adolescents and 30 to 75 mg for children aged 12 yrs or younger, according to body weight (17); for infants, a dosage of 2 to 3 mg/kg of body weight twice daily is recommended (17–21). When influenza is circulating and the risk of infection is high, oseltamivir also can be administered prophylactically for up to 42 days as a once-daily regimen that delivers half of the recommended treatment dose.

Because oseltamivir and its carboxylate are excreted primarily via the kidney, systemic exposure increases if renal function is impaired and to a marked degree in individuals with creatinine clearance rates of <30 mL/min (16). The recommended treatment dosage for adults with clearance rates of >10 to 30 mL/min is 75 mg once daily (Table 1) (17). Data on the use of oseltamivir in individuals with creatinine clearance rates of <10 mL/min are limited. Pharmacokinetic and tolerability data have been collected from 24 patients with end-stage renal disease undergoing maintenance hemodialysis or continuous ambulatory peritoneal dialysis (22). In this open-label study, patients received multiple doses of 30 mg oseltamivir over the course of 6.5 wks in the form of an oral suspension. Hemodialysis patients received nine doses in total, given 1 hr after the completion of every other session (patients underwent dialysis three times each week). Continuous ambulatory peritoneal dialysis patients received six doses in total, administered on a once-weekly schedule, immediately after a dialysate exchange. Both regimens were well-tolerated and provided exposure levels to OC that were safe and sufficient for treatment and prophylaxis (22). Dose regimens for patients with renal failure and those on dialysis are suggested (Table 1), based on the available data, guidance from the Public Health Agency of Canada, and calculations predicated on pharmacokinetic principles (by author REA) (17, 23). No dose adjustment is necessary in patients with mild to moderate hepatic impairment (17), suggesting that hepatic carboxylesterase capacity is adequate to convert oseltamivir to its active metabolite (24).

Table 1. Recommended dosages for oseltamivir treatment in patients with renal impairment or failure

Creatinine Clearance	Treatment
>30 mL/min	75 mg twice daily
>10–30 mL/min	75 mg once daily or 30-mg suspension twice daily or 30-mg capsule twice daily
≤10 mL/min (renal failure)*	Single 75-mg dose for the duration of illness
Dialysis patients*	Low-flux HD: 30 mg after alternate dialysis sessions
	High-flux HD: 75 mg after each dialysis session
	CAPD dialysis: 30 mg once weekly
	CRRT high-flux dialysis: 30 mg daily or 75 mg every 48 hrs

*Oseltamivir does not have regulatory approval for patients with renal failure; dosing regimens have been suggested based on the available data (17, 23).

CAPD, continuous ambulatory peritoneal dialysis; CRRT, continuous renal replacement therapy; HD, hemodialysis.

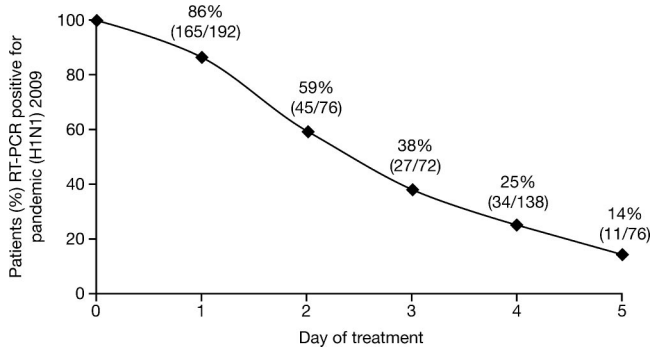

Figure 1. Patients (%) positive via reverse-transcriptase polymerase chain reaction for pH1N1 2009 after the initiation of oseltamivir treatment (75 mg twice daily for at least 5 days). After treatment day 5, only 12 of 179 patients (7%) tested positive via reverse-transcriptase polymerase chain reaction for pH1N1 2009 and no viable (infectious) virus could be isolated from any patient (26).

Experience in Treatment of Pandemic H1N1 2009

Very few published data are available on the effectiveness of the neuraminidase inhibitors in treating patients infected with pH1N1 2009. A series of 49 patients (mostly adolescents) admitted to the hospital in Kobe City, Japan, with pH1N1 2009 were treated with either oseltamivir (n = 22) or zanamivir (n = 26) (25). No complications occurred, both antivirals were well-tolerated, and most patients were discharged soon after admission. The duration of fever appeared to be less in patients who started neuraminidase inhibitor therapy sooner after symptom onset (25). Findings from 292 patients with pH1N1 2009 influenza who started oseltamivir treatment (75 mg twice daily for at least 5 days) on hospital admission indicate that treatment induces a rapid decline in viral shedding (Fig. 1) (26). By day 5 of treatment, only 11 of 76 patients (14%) tested positive for the pandemic virus on reverse-transcriptase polymerase chain reaction, and no viable (infectious) virus could be isolated from any patient after day 5. After 24 hrs of treatment, 228 of 292 patients (78%) had a normal body temperature and all patients had a mild illness course. In another study, multivariable analysis of 272 hospitalized patients with severe pH1N1 2009 revealed that receipt of antiviral drugs (188 of 200 using oseltamivir) within 2 days of the onset of illness was significantly associated with a positive outcome (8).

Experience in Severe Influenza: Human Infection With Avian Influenza

Despite the predominance of information on the current H1N1 influenza pandemic,

close attention is still given to human cases of H5N1 avian influenza, which have been reported mainly in Southeast Asia but have also affected people in other parts of Asia and in Africa (27). Human H5N1 infections generally have been much more severe than seasonal influenza, characterized by progressive pneumonia and respiratory distress (28, 29) that frequently require patients to be mechanically ventilated (29, 30). Thus far, infections have resulted in death in approximately 60% of reported cases (27). Oseltamivir seems to have been effective in treating human H5N1 infections to date; a synopsis of published and unpublished data from 10 uncontrolled studies suggests that it improves survival markedly, but that early initiation of therapy is important (28). A case series report (31) from Indonesia found that although initiation later than the second day of onset was effective in many cases, initiation within 2 days of onset was associated with significantly lower mortality. Recently presented data from a registry database of avian influenza cases confirm that early treatment with oseltamivir increases the survival likelihood and that treatment is beneficial if started ≤8 days from symptom onset (32).

Recent reviews of experience with oseltamivir in human H5N1 influenza have suggested that increasing the dose could be more effective (29, 30). A recent case series report described clinical and pharmacokinetic findings in three seriously ill Vietnamese patients administered oseltamivir 150 mg twice daily via nasogastric tube (33). A young man and a pregnant woman infected with influenza A (H5N1) and an elderly woman with influenza A (H3N2) were admitted with fever, cough, and dyspnea between 6 and 8 days after symptom onset and were mechanically ventilated. After administration of oseltamivir starting no later than the second day after ICU admission, steady-state systemic exposure to OC was higher in all patients than levels achieved in healthy volunteers and patients with mild influenza after an oral dose of 150 mg twice daily. The concentration of OC that produced inhibition in 50% of the sample (IC_{50}) of H5N1 virus isolated from the female patient was 0.69 ng/mL, and trough OC concentrations in the H5N1-infected patients exceeded this value by a factor of >500. Trough OC concentrations in the H3N2-infected patient exceeded typical published IC_{50} values for this strain by a factor of >3000. However, despite achievement of adequate levels of active metabolite, which led to clearance of all virus after 5 days of oseltamivir treatment in the male H5N1-infected patient and the H3N2-infected patient, only the man survived; both women died of respiratory failure (33).

Severe Seasonal Influenza

The results of five studies in a hospital inpatient setting give some indications of the possible effectiveness of oseltamivir in more severely ill patients with influenza. The largest of these was an analysis of the effect of oseltamivir treatment on mortality in 327 Canadian adults who required hospital treatment for laboratory-confirmed type A or B influenza (34). Most (69%) were elderly (i.e., aged ≥65 yrs), and 52 (16%) of the patients were ill enough to need admission to ICU for periods of between 1 and 22 days (median, 5 days). In the primary analysis of 26 patients who died within 15 days of symptom onset, 4 of 103 (4%) deaths were in patients treated with oseltamivir (75 mg twice daily for 5 days), and 22 of 219 (10%) were not given any antiviral treatment, representing a significant treatment-related reduction in mortality (odds ratio, 0.21; 95% confidence interval [CI], 0.06–0.80; $p = .03$). Analysis of elderly patients alone also showed a significant difference in mortality risk (odds ratio, 0.24; 95% CI, .06–.92). In a preliminary report of another study by this group that examined outcomes specifically in adult patients admitted to ICU with confirmed influenza (35), 54 of 238 patients (24%) died within 15 days of diagnosis, and treatment with oseltamivir was a significant predictor of longer survival in multivariate analysis (odds ratio, 3.2; 95% CI, 1.5–7.0).

Although the median length of stay in the Canadian hospital study was shorter for the treated patients (6 vs. 8 days), this difference did not reach statistical significance ($p = .07$) (34). A significant shortening of length of stay in treated patients, however, was reported in the first of two studies in hospitalized adults at a Hong Kong hospital (36). Like the Canadian study, the retrospective cohort study of 356 adults with laboratory-confirmed influenza included mostly patients aged older than 65 yrs and/or with comorbidities. Only patients who presented within 48 hrs of symptom onset received oseltamivir (75 mg twice daily for 5 days), and these patients were discharged earlier than untreated patients (median length of stay of 4 and 6 days, respectively), producing an adjusted hazard ratio for discharge of 1.54 (95% CI, 1.23–1.92; $p < .0001$). The study also found that longer length of stay was significantly and independently associated with prolonged viral shedding (continuing after day 4) (36). Viral shedding was examined more specifically in a subsequent observational study by the same group, this time using a prospective design (37). In 147 hospitalized adult influenza patients (75.5% aged >65 yrs), those who started treatment with oseltamivir (75 mg twice daily for 5 days) within the first 4 days of symptoms had significantly faster reduction of viral load than those who were untreated. One week after symptom onset, 26% of treated patients and 57% of untreated patients still had detectable viral RNA. Absence of detectable viral RNA 5 days after symptom onset was a significant independent predictor of shorter hospital stay (37). The initial report (38) of a prospective study by the Hong Kong group in a group of 760 hospitalized influenza patients, 37 (4.9%) of whom died, confirms the survival benefits shown by the Canadian group: treatment with oseltamivir was associated with lower in-hospital mortality when adjusted for time to presentation and complications (hazard ratio, .38; 95% CI, .19–.78).

Several outpatient studies have shown that oseltamivir treatment is more effective when started within 48 hrs of the onset of influenza symptoms (39–41). The experience with the more severely ill patients described is consistent with this observation; although treatment started during the first 4 days after symptom onset was still beneficial with respect to reducing viral load (37), patients starting treatment on days 1 or 2 of the viral load study had significantly faster clearance than those who started on days 3 or 4 (14.3% and 35.3%, respectively, had detectable viral RNA at symptom day 7; Table 2). In the Canadian study (34), only 29% of treated patients started within 48 hrs of onset and 49% did not start oseltamivir until day 4 or afterward; the multivariate analysis showed that in patients who started treatment later than 48 hrs, the difference in mortality risk compared with untreated patients was not significant (odds ratio, .24; 95% CI, .05–1.14). In the first Hong Kong study (36), no patients received oseltamivir after 48 hrs.

DISCUSSION

Treatment of High-Risk Populations

Several population groups are recognized to be at higher risk for severe disease after becoming infected with influenza, and priorities for vaccination and other disease prevention measures are higher as well. These include children aged younger than 5 yrs, adults older than 65 yrs, those with chronic comorbidities or suppressed immune function, and pregnant women. Although all the published data on influenza treatment with oseltamivir in these groups have been generated in outpatient settings rather than in hospitalized patients, they illustrate the potential for influenza to be avoided or the severity of the disease course to be reduced in vulnerable individuals receiving treatment.

Table 2. Factors associated with persistent viral RNA detection at 1 wk and persistent virus isolation after 4 days of illness in patients hospitalized with influenza A infection

Variable	Patients With Viral RNA Detected at Symptom Day 7, %	*p*	Patients With Virus Isolated on Symptom Day ≥4, %	*p*
Influenza virus				
A	32.7	.001	17.2	**<.001**
B	69.6		56.0	
Age				
>65 yrs	39.0	.011	17.0	.921
≤65 yrs	9.5		17.9	
Comorbidity, major				
Yes	45.7	.040	22.7	.221
No	25.4		13.9	
Systemic corticosteroid use				
Yes	53.8	.007	24.1	.256
No	25.0		14.9	
Oseltamivir initiation time				
Day 1–2	14.3	.004	2.3	**<.001**
Day 3–4	35.3		18.2	
Not received	57.1		38.5	

See (36).

Immunosuppressed Patients

As noted, no randomized controlled studies of oseltamivir in patients with severe influenza have yet been published, and this is also true for patients with impaired immune function. Despite this, several retrospective studies suggest that treatment or prophylaxis with oseltamivir is beneficial in preventing or controlling influenza infections in immunocompromised patients. Many of these have been performed in patients who have undergone bone marrow transplantation to treat hematologic cancers. In a retrospective study of respiratory virus infections in adults who had undergone hematopoietic stem cell transplantation, 72 and 40 patients were infected with influenza A and B, respectively. The incidence of pneumonia was significantly lower in influenza A patients treated with oseltamivir, occurring in 3 of 26 (12%) treated patients and in 22 of 46 (48%) using no antiviral therapy ($p < .05$). A similar pattern was seen with influenza B infections: pneumonia occurred in 1 of 15 (7%) patients treated with oseltamivir or ribavirin compared with 8 of 25 (32%) using no antiviral ($p = .06$) (42). A second smaller study by the same group compared 25 leukemia patients with laboratory-confirmed influenza who received neuraminidase inhibitor therapy (oseltamivir in 21 cases), with eight who received no antiviral therapy. Fourteen treated patients presented with upper respiratory tract infection, one (7%) of whom subsequently had pneumonia develop, and 11 (79%) presented with pneumonia. None of the treated patients died, whereas three of eight (38%) untreated patients died of influenza pneumonia (43). An uncontrolled study in which oseltamivir treatment was started within 48 hrs of the onset of influenza symptoms in 39 bone marrow transplantation patients found that only two patients had pneumonia, and no patient died (44). In another smaller retrospective analysis of 18 hematopoietic stem cell transplantation patients with influenza who had lower respiratory tract infection develop, 3 of 10 (30%) patients who received no antiviral treatment died in the 30 days after treatment, compared with two of five (40%) who received rimantadine and none of three (0%) using oseltamivir (45).

Other High-Risk Populations

The effects of oseltamivir treatment in patients aged older than 65 yrs and those with co-existing cardiac or respiratory diseases have been demonstrated in several studies. Subgroup analysis of a large placebo-controlled study showed that oseltamivir treatment reduced both the rate of lower respiratory tract complications and risk of hospitalization (46). Other studies assessed efficacy in these two risk groups by pooling data from more than one placebo-controlled trial, finding that treatment reduced the duration of acute febrile illness, viral shedding rate, and the rate of respiratory complications (47, 48). A randomized study of influenza treatment in 118 adults with chronic heart or lung disease found that oseltamivir was associated with significant reductions in disease severity and duration, as well as in the incidence of complications and antibiotic use, compared with symptomatic treatment alone (49).

A study in 5355 children and adolescents aged 1 to 17 yrs with co-existing illnesses that put them at increased risk for influenza complications found that oseltamivir reduced the risk of otitis media and respiratory illness (other than pneumonia) compared with no antiviral treatment (50). This study, which used a retrospective analysis of insurance claims data, showed that some of the benefits seen in the full study population also applied to younger children; in children aged 1 to 2 yrs, the risk of respiratory illness other than pneumonia was 37% lower in those who received oseltamivir than in those using no antiviral treatment, and in those aged 3 to 5 yrs, the risk of otitis media and associated complications was 60% lower in those who were treated (50). The first major study to evaluate the effect of oseltamivir as an influenza treatment in otherwise healthy children showed that the benefits of reduced illness duration seen in adult studies are also achieved in children, including those aged 1 to 5 yrs (51), although pneumonia risk was not significantly reduced by oseltamivir in children aged 1 to 5 yrs in a later retrospective study of insurance claims data (52). Although use in infants aged younger than 1 yr is not approved for seasonal influenza treatment (although an exception has been made by regulatory authorities in the case of pH1N1 2009), two studies of this age group have been published. In Japanese children treated with oseltamivir, 4 mg/kg per day for 5 days, the mean duration of fever in those aged younger than 1 yr was very similar to that in the older children (1–15 yrs) at approximately 2.5 days, whereas fever in untreated older children lasted for a mean of 4.2 days (53). Additionally, in a cohort of 157 German infants aged younger than 1 yr hospitalized with influenza, body temperature declined to <37°C in 82% of infants within 36 hrs of starting oseltamivir treatment (54).

A high-risk group that has recently attracted more attention is pregnant women. Although pregnant women have for some time been a priority for vaccination programs, data are scarce on the use of oseltamivir during pregnancy. However, a recent report of unexpectedly

high rates of mortality and hospitalization in pregnant women infected with pH1N1 2009 in the US (55) has prompted a change in guidance, based on review of both published evidence and manufacturers' data on pregnant or breast-feeding women (17–19, 21). A recent article that reviewed the incidence of birth defects in Japanese women who used oseltamivir for at least 1 day during the first trimester of pregnancy, together with postmarketing surveillance data in pregnant women, concluded that oseltamivir is not a major teratogen (56). An *ex vivo* modeling study has also demonstrated little transfer of oseltamivir or OC across the human placenta (57). No studies have been published that report efficacy outcomes in pregnant women using oseltamivir.

Safety and Tolerability

Oseltamivir is generally well-tolerated at the recommended doses (58). Gastrointestinal events are the only adverse effects consistently reported with a higher frequency than placebo, but this rarely result in treatment withdrawal (up to 1%) (58). Neuropsychiatric events have also been reported in influenza patients receiving oseltamivir, but a comprehensive review of the available data revealed no increased risk vs. those using no antiviral and no plausible mechanism by which oseltamivir or OC could cause or worsen these events (59). Oseltamivir is well-tolerated at high doses; in a randomized, placebo-controlled study, no significant safety concerns were identified with dosages of 225 mg and 450 mg twice daily for 5 days (60). Headache was the most frequent adverse event but was not significantly higher than placebo (20.0% for placebo vs. 23.7% for 225 mg and 23.2% for 450 mg). Other commonly reported effects were nausea (8.0% vs. 25.8% and 31.3%, respectively), vomiting (2.0% vs. 7.2% and 16.2%, respectively), and dizziness (4.0% vs. 11.3 and 10.1%, respectively). No withdrawals or serious adverse effects were reported in the 450-mg arm, and no evidence of cardiac toxicity was seen. Oseltamivir also has a low potential for clinically relevant drug interactions (16). Co-administration with paracetamol or aspirin had no effect on the pharmacokinetics of either drug (16, 61), and administration with the immunosuppressants cyclosporine, mycophenolate mofetil, and tacrolimus (62), the antibiotic amoxicillin (63), or the anticoagulant warfarin had no effect (64).

Zanamivir

The other neuraminidase inhibitor approved for influenza treatment and prophylaxis is zanamivir (Relenza; GlaxoSmithKline, Research Triangle Park, NC). In contrast to oseltamivir, the drug is not orally bioavailable and so it is administered by inhalation via a dry powder inhaler (Diskhaler or Rotahaler; GlaxoSmithKline); this delivery device severely limits zanamivir's role in critical illness, especially for those with respiratory failure who are receiving mechanical ventilation. Only 10% to 20% of an inhaled dose is absorbed systemically, so distribution of the drug to extrapulmonary sites of influenza infection is minimal. Zanamivir is not metabolized, so no dosage adjustment is needed in individuals with impaired hepatic function. Clearance is primarily through glomerular filtration, thus renal impairment would be anticipated to reduce drug clearance (65). In a small study of intravenous zanamivir in volunteers with various degrees of renal dysfunction, those with severe renal impairment had a dose-equivalent sevenfold higher exposure to zanamivir than those with normal renal function. In this subset of five subjects, no adverse clinical effects were noted. Although stated otherwise by Cass et al (65), it is premature to comment on the lack of a need for dosing adjustment in those with renal function impairment.

Zanamivir is indicated for the treatment and postexposure prophylaxis of influenza in adults and in children 5 yrs or older (except in the US, where it is approved only in children aged $\geq$7 yrs) (66). The standard dosages are 10 mg twice daily (two inhalations of 5 mg each) for treatment and 10 mg once daily for prophylaxis. Emergency authorization has been given in Europe and the US for use in pregnant women infected with pH1N1 2009 (18, 67). Phase I clinical trials are examining the feasibility of intravenous zanamivir administration (68).

Experience in Pandemic H1N1 2009 Influenza and Severe Influenza

As noted earlier, the only published data (25) on the use of zanamivir in treating pH1N1 2009 influenza are from the report of 26 hospitalized Japanese patients who responded well to therapy. No published data exist on the efficacy of inhaled zanamivir in patients with severe influenza caused by avian (H5N1) or seasonal strains, except for an incomplete study of a zanamivir plus rimantadine combination (69), which is discussed later. The results of a pooled analysis by Monto et al (70) examining seven outpatient treatment studies found that patients whose symptoms were categorized by the investigator as severe at the start of therapy obtained greater benefit with zanamivir relative to placebo (measured by time to alleviation of symptoms) (70).

In seriously ill patients, the need to administer zanamivir by inhalation is a disadvantage, particularly in those with severe cough or dyspnea. The delivery device requires the patient to inspire enough to deagglomerate the powder formulation and to achieve adequate pulmonary deposition of drug, and it requires a breath-hold after inspiration (71). Authors of a case report on a bone marrow transplantation recipient whose influenza did not respond to zanamivir treatment attributed the failure to poor penetration of inhaled drug to the peripheral lung region (72). Dosing by oral inhalation also presents practical challenges; in a hospital-based study (73), 50% (19 of 38) of patients aged 71 yrs or older were unable to load and prime the delivery device despite previous training, and 65% (24 of 37) were unable to do so 24 hrs later.

Treatment of High-Risk Patients

The earlier clinical trials of zanamivir in outpatient settings showed that treatment efficacy in certain high-risk groups was as good as in healthy adults and children. Zanamivir treatment was associated with significantly fewer influenza complications and significantly less associated antibiotic use than placebo in a subgroup of 76 patients at high-risk who had respiratory, metabolic, or cardiovascular disorders, and/or were aged older than 65 yrs (74). When those data were subsequently pooled with data on high-risk patients (adults and children) from five other randomized, placebo-controlled trials to produce a larger data set (n = 321), similar benefits were demonstrated, with zanamivir producing a 43% reduction in the relative risk of complications needing antibiotic treatment, relative to placebo (75). In other high-risk groups, however, there are few published reports of zana-

mivir treatment. A small Spanish study of an influenza outbreak in patients whose immune function was compromised by hematologic disease found zanamivir to be effective as a treatment for seven patients with influenza symptoms and as prophylaxis for three nonsymptomatic high-risk patients (76). A Japanese group reported that zanamivir effectively relieved influenza symptoms in two immunocompromised children being treated for acute lymphoblastic leukemia (77). Zanamivir is moderately effective in treating children aged 4 to 12 yrs, as shown by lower frequencies of complications and antibiotic use relative to placebo recipients in a randomized controlled trial (78). No data have been published on experience in children younger than 4 yrs old, however, and zanamivir is not approved for use in children younger than 5 yrs of age, a group at elevated risk of more severe and complicated disease. In a recent review of the use of neuraminidase inhibitors in pregnant women, reports on the use of zanamivir were too few to allow any inferences on safety to be drawn (56).

Other Antiviral Agents: Other Neuraminidase Inhibitors

The neuraminidase inhibitors peramivir and laninamivir (CS-8958) are nearing the end of their clinical development programs for the indications of influenza treatment and prophylaxis, and applications for regulatory approval should be filed in late 2009 or early 2010. Peramivir has been developed in an injectable form because of poor bioavailability when administered orally; this should be a more practical way to deliver antivirals to ICU patients than oral or inhaled dosing. For this reason, peramivir is the subject of an ongoing pre-emergency use authorization review in the US that may permit its use in critically ill patients with pandemic influenza. Trials are also underway to assess a nasogastric dosage form of oseltamivir and an intravenous injection of zanamivir. A comparison of peramivir and oseltamivir in acute serious influenza has been completed (79), but results are not yet published. The other phase III clinical trials on peramivir and laninamivir, also unpublished as yet, have been performed in patients with uncomplicated seasonal influenza.

Ribavirin

Ribavirin is indicated for the treatment of infant bronchiolitis caused by respiratory syncytial virus and in combination with interferon or peginterferon for hepatitis C. The ability to inhibit influenza virus replication was first reported in the 1970s; however, despite early clinical studies that showed encouraging results when the drug was administered by inhalation (80, 81), no large clinical trials were performed. In general, ribavirin is less active against influenza viruses than the adamantines or neuraminidase inhibitors (68), but its unique inhibitory activity against the viral RNA polymerase may confer a reduced potential for the development of drug resistance (82). The drug must be used with care because of its teratogenic properties and its hematologic, gastrointestinal, and hepatic toxicities, as well as exposure risk to healthcare workers when aerosolized. Ribavirin has attracted renewed interest, however, as a co-therapy for influenza treatment. When combined with oseltamivir and amantadine, ribavirin was active against influenza A (H1N1), A (H3N2), and A (H5N1) *in vitro* (83), and double combinations with oseltamivir or amantadine were effective in mouse models of influenza A and B (84–86). Such combinations may be particularly useful in treatment of influenza viruses resistant to one or more antivirals, but further clinical investigation is required.

Other Combinations of Antivirals

Antiviral monotherapy has the potential to exert selective pressure for the development of drug resistance (82). By combining agents with different modes of action, this potential may be reduced. The only report of the use of a combination of antivirals to treat influenza in a hospital setting was a trial comparing zanamivir plus rimantadine with rimantadine alone (69). The two treatments appeared to have similar efficacy and tolerability, but the trial's early termination severely limits what can be inferred from these results. The potential for combining oseltamivir and rimantadine to improve efficacy in influenza A infections has been shown in preclinical studies (87, 88), and the tolerability and pharmacokinetics of this combination are being assessed. Combination therapy with oseltamivir and amantadine also appears safe and without pharmacokinetic consequences in healthy subjects (89), but it is too soon to recommend these combinations as empirical therapy for severe illness.

Interferon

Interferon exerts its activity against influenza viruses indirectly by stimulating the host's immune response, but it has not been reported effective against pH1N1 2009 influenza or severe seasonal influenza. Nevertheless, the potential new oral form of interferon-α for influenza prophylaxis is being investigated in Australia (90).

CONCLUSIONS

Because most antiviral administration takes place in the outpatient setting rather than in serious or complicated disease cases, relatively few reports have appeared on the effectiveness of the licensed neuraminidase inhibitors oseltamivir and zanamivir in pH1N1 2009 or severe seasonal influenza. Most experience in these settings is with oseltamivir, and preliminary evidence suggests that this agent is as beneficial in the seriously ill patient as in the typical patient with uncomplicated influenza, with faster resolution of infection and a reduction in mortality risk. Oseltamivir has been widely studied in patients at higher risk for complicated or serious illness. In young children, elderly patients, and patients with immune compromise and/or comorbidities, antiviral treatment can reduce the risk of influenza-related complications and mortality.

The August 2009 update to the WHO's guidelines on pharmacotherapy of pH1N1 2009 reflects the greater extent of experience with oseltamivir relative to zanamivir, strongly recommending treatment with the former in patients with severe or progressive infection, and recommending the latter when the virus is known to be oseltamivir-resistant or in the absence of oseltamivir. Other neuraminidase inhibitors due to be approved in the near future may have a role to play in managing seriously ill patients, and new dosage forms will increase suitability for use in a critical care setting. Combinations of antivirals are likely to have an advantage in cases in which viruses of different susceptibilities are circulating. However, as with all other aspects of management of pH1N1 2009 and serious seasonal influenza, further investigation is essential.

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