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Antiviral Therapy for Pandemic Influenza A (H1N1) Infection: Dosing, Combination Therapy, and Resistance

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Key Points

- Neuraminidase inhibitors, oseltamivir and zanamivir, were the drug of choice for pandemic influenza A (H1N1) (pH1N1) infection.
- The standard recommended dose of oseltamivir for adults with pH1N1 infection is 75 mg orally twice daily.
- The bioavailability of oseltamivir in critically ill patients with pH1N1 infection was shown to be comparable to that of healthy ambulatory patients, suggesting that optimal viral suppression could be achieved and that doses higher than 75 mg twice daily were unlikely to be of any additional benefit.
- The volume of distribution for oseltamivir carboxylate was similar between morbidly obese patients and non-obese control patients with pH1N1 infection, indicating that no dose adjustment was needed.
- Although oseltamivir carboxylate levels were 30% lower in pregnant patients than in non-pregnant women, the active drug levels were well above those required to inhibit viral replication.
- Combination therapy with multiple antivirals, depending on the combination used, may have synergistic effect against pH1N1.
- Oseltamivir resistance in influenza A viruses is conferred by a mutation in the neuraminidase gene causing an amino acid change in the protein. To date, the prevalence of resistant pH1N1 remains low.

Introduction

In the review "Antiviral Therapy for Pandemic Influenza A (H1N1) Infection: A Meta-Analysis", the evidence behind the efficacy of antiviral therapy and prophylaxis for pandemic influenza A (H1N1) (pH1N1) infection was addressed. A number of other ancillary issues arose with regard to therapy for adults during the 2009 influenza A (H1N1) pandemic. These include route of drug administration, appropriate antiviral dosing, the use of combination therapy, and the development of antiviral resistance. This review will focus on the evidence that emerged during the 2009 pandemic on these topics.

Route of Administration, Dosing and Combination Therapy

Currently available antiviral agents active against influenza infection include the adamantanes and the neuraminidase inhibitors. Since adamantanes were inactive against pH1N1, this review will limit discussion to the neuraminidase inhibitors. Oseltamivir and zanamivir have traditionally been the two

neuraminidase inhibitors available for use, whereas peramivir remains in clinical trials and was only approved for emergency authorization during the pandemic. Laninamivir, a long-acting parenteral agent, was recently approved for use in Japan.

Oseltamivir is available in an oral formulation as a prodrug (oseltamivir phosphate), which is then metabolized to its active form, oseltamivir carboxylate. It was the preferred agent for therapy during the 2009 influenza A (H1N1) pandemic due to its systemic distribution (around 80% bioavailable) and excellent safety profile (1). The inhaled formulation of zanamivir is approved for use in uncomplicated pH1N1 infection. However, given that less than 2% of the dose enters systemic circulation it is not recommended for complicated infections (2-4). Furthermore, nebulized zanamivir is known to clog ventilator tubing and is therefore problematic in intubated patients (4). Two investigational agents were available as parenteral formulations during the H1N1 pandemic, zanamivir and peramivir. The main indications for their use included treatment failure with oseltamivir, suspected oseltamivir resistance, and in patients where gastrointestinal absorption was a major concern (2). A surveillance study of hospitalized patients with pH1N1 infection in the United States identified eight patients (0.1%) who were treated with intravenous (IV) zanamivir and 33 patients (0.4%) who were treated with IV peramivir, compared to 99% of patients who were treated with oseltamivir (5). The vast majority of patients treated with parenteral antivirals were those admitted to the intensive care unit (93%). Unfortunately there are no large scale efficacy or safety data to date on these agents and therefore their utility remains unclear.

The standard recommended dose of oseltamivir for adults with pH1N1 infection is 75 mg orally twice daily. During the H1N1 pandemic, concerns arose that patients who were critically ill may be underdosed with oseltamivir due to impaired gastric absorption and overall burden of disease. The World Health Organization recommended considering a dose of 150 mg twice daily in severe illness, although there was no evidence to support this recommendation (3). This question was addressed by Ariano *et al.* in a study where 44 critically ill patients with suspected or confirmed pH1N1 infection were treated with standard dosing at 75 mg twice daily (6). They found that oseltamivir carboxylate median, trough and area under the curve levels were similar in their patients compared to previous efficacy studies with healthy ambulatory patients. These levels were well above the suggested 50% maximal inhibitory concentrations suggested for optimal viral suppression, and therefore they concluded that doses higher than 75 mg twice daily are unlikely to be of any additional benefit.

The issue of under-dosing has also been suggested in patients who are morbidly obese. The study by Ariano *et al.* also provided some insight into this, finding no association between body mass and volume of distribution (6). A more recent pharmacokinetic study identified that the volume of distribution for oseltamivir carboxylate is similar between morbidly obese patients and non-obese control patients with pH1N1 infection, indicating that no dose adjustment is needed (7). Conversely, it has been shown that oseltamivir carboxylate levels are 30% lower in pregnant patients, likely related to their increased creatinine clearance (8). Regardless, this study still showed that oseltamivir carboxylate levels were well above those required to inhibit viral replication.

An argument for increased dosing of oseltamivir is its excellent safety profile. Doses as high as 450 mg twice

daily are well-tolerated (9), with the most common side effects being headache, nausea and vomiting. Birth outcomes have also recently been studied in pregnant patients using oseltamivir: while there were increased rates of late transient hypoglycemia, there were no differences in other adverse birth outcomes among infants who were exposed to neuraminidase inhibitors in the womb compared with those who were not (10). Therefore, although pharmacokinetic data have yet to support increased dosing or longer durations of therapy, this approach may be considered in some patients.

Given the uncertainty around dosing and route of administration in patients with severe pH1N1 infection, as well as concerns about developing resistance, it has been suggested that combination therapy with two neuraminidase inhibitors may be of benefit. In a murine model it has been shown that oseltamivir and peramivir have additive effects despite acting on the same binding site (11). One case series of 21 patients with severe pH1N1 infection who received both oral oseltamivir and inhaled zanamivir did not show any additional benefit, with a mortality rate of 23.8% (12), compared to a mortality rate of 17%-46% in large scale studies of patients with severe pH1N1 infection who received oseltamivir monotherapy (13-15). Of note, there was a randomized control trial comparing oral oseltamivir, inhaled zanamivir, and the combination of the two in ambulatory patients with seasonal influenza (16). The investigators found that combination therapy was inferior to oseltamivir monotherapy in terms of both virological and clinical response. In another study examining a triple combination regimen of oseltamivir, ribavirin and amantadine, it was demonstrated that this combination of drugs provided synergistic effects *in vitro*, and it was even effective against pH1N1 viruses that are resistant to oseltamivir (17, 18). While there is little theoretical basis for synergy, there is some empirical evidence and further clinical trials are needed to evaluate this approach.

Resistance

Traditionally all strains of influenza A and B have remained susceptible to neuraminidase inhibitors. Oseltamivir resistance was first reported to be significant during the 2008-2009 influenza season, where seasonal influenza A (H1N1) in particular was implicated; however at that time the prevalence of resistant H1N1 viruses was low (19). Resistance was conferred by a mutation in the neuraminidase (NA) gene causing an amino acid change from histidine to tyrosine in position 275 (H275Y). A meta-analysis performed in September 2010 (which included pH1N1 studies to that point) estimated the overall incidence of resistance to oseltamivir to be 2.6%; however there was significant heterogeneity between studies (20).

There is particular concern that antiviral resistance will develop in patients with hematologic malignancies due to their inability to reduce viral loads.

More recent cohort studies have generated insight into the epidemiology of antiviral resistance during the pandemic. In Japan, where up to 70% of the world's oseltamivir consumption occurs, the rate of resistance was estimated to be low at 1.4% (21). Of the 61 cases of resistance, there were only two instances where an epidemiological link was possible, with the vast majority of cases arising sporadically on therapy with no further evidence of transmission. To date, only three case reports have identified transmission of oseltamivir-resistant strains of pH1N1. The first two involved immunocompromised patients on hematology/oncology wards in the United Kingdom and the United States (22, 23). The third study from Vietnam is of particular concern, as it documented the transmission of an oseltamivir-resistant strain to seven healthy subjects aboard a train (20). While zanamivir resistance has been documented in seasonal H1N1 strains, only mildly reduced susceptibility has so far been reported in pH1N1 (24).

There is particular concern that antiviral resistance will develop in patients with hematologic malignancies due to their inability to reduce viral loads. A large surveillance study from the Netherlands noted that of 18 cases of oseltamivir resistance, 11 were patients with hematologic disorders (25). A cohort study in Seattle tested for oseltamivir resistance in 33 hematology-oncology patients, identifying resistance in one patient before the initiation of therapy and eight patients after initiating therapy (26). In an Australian study of 10 hematology patients who had repeat nucleic acid test for pH1N1, 7 continued to test positive after at least 4 days of oseltamivir therapy, among whom the H275Y NA mutation

was identified in 4 patients (27). The hypothesis is that high viral loads are more conducive to the emergence of resistance; however further studies with larger cohorts are needed to provide a definitive answer.

The H275Y mutation has become established in circulating seasonal influenza A (H1N1) in the presence of oseltamivir use, with little apparent effect on viral fitness[1] (28). This is likely attributable to a secondary mutation that confers stability of the neuraminidase protein. Some *in vitro* evidence also suggests that the H275Y mutation may be a secondary event following spontaneous mutations that occur in cell culture (29, 30). Why pH1N1 has not yet acquired a secondary mutation spontaneously or through reassortment with seasonal H1N1 remains unclear, although the picture may be changing. A recent communication from Australia identified a cohort of patients where 14% of the pH1N1 isolates carried the H275Y mutation, and none of these patients had received prior antivirals (31). The story of adamantane resistance can serve as a cautionary tale, demonstrating that the emergence of resistance is random in nature, depending on the predominant clade incorporating the mutation (32). Given that oseltamivir was the workhorse antiviral during the pandemic, it is fortunate that widespread resistance has not yet occurred. Furthermore, resistance to other neuraminidase inhibitors has not yet been documented, thus sparing these treatment options should widespread oseltamivir resistance arise.

1. Viral fitness is the replicative adaptation of a virus to its environment and is related to the capacity of the virus to replicate in a given setting, its capability to be transmitted to a new host and its ability to cause disease.

Conclusions

The 2009 pandemic demonstrated the difficulty in developing therapeutic guidelines quickly with little supporting evidence. A large body of literature has now been generated, which will allow for the reassessment of a number of controversies that arose during the 2009 pandemic. Oseltamivir and zanamivir remain the drugs of choice for pH1N1 infections, with oseltamivir being favoured in complicated cases. Increased doses of oseltamivir do not appear to be necessary in any situation, including the critically ill, obese and pregnant patients; however higher doses also appear to be well-tolerated. Alternative parenteral agents are promising. However, further clinical studies are still needed to validate their efficacy and safety. There are scant data on the utility of combination therapy and this practice requires further investigation. Oseltamivir resistance was identified during the pandemic, predominantly in hematology-oncology patients; however widespread transmission of oseltamivir-resistant pH1N1 did not occur, and to date no outright resistance to zanamivir has been observed. These findings should be interpreted with caution, as seasonal influenza has demonstrated that antiviral resistance can be acquired without a compromise in viral fitness, leading to widespread prevalence. Lessons learned from this pandemic can be applied to the future management of seasonal as well as pandemic influenza.

The story of adamantane resistance can serve as a cautionary tale, demonstrating that the emergence of resistance is random in nature, depending on the predominant clade incorporating the mutation.

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