Zanamivir for the prevention of influenza in adults and children age 5 years and older

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Abstract: On a yearly basis there are 3–5 million severe cases and 250,000–500,000 deaths worldwide attributed to influenza. Four antiviral medications are currently available on the market; however, resistance has resulted in the armamentarium being shrunk to two remaining active treatment options for influenza. These two neuraminidase inhibitors, oseltamivir and zanamivir, are recommended for the treatment and prophylaxis of influenza A and B in children and adults. Zanamivir, which is the focus of this review, is an inhaled antiviral that has shown benefit in the community, household, and nursing home population for post-exposure prophylaxis. Zanamivir protection rates range from 67%–84% in clinical trials of adults and children. Although the influenza vaccine remains the best modality to combat the disease, zanamivir may also assist in decreasing morbidity associated with influenza A and B.

Keywords: flu, prophylaxis, neuraminidase inhibitors, Relenza, community, household, nursing home

Influenza is responsible for 3–5 million severe cases and 250,000–500,000 deaths worldwide annually (WHO 2003). Influenza produces a seasonal epidemic in both developed and developing countries. Death and hospitalizations mainly occur in the high-risk populations such as the elderly and those with chronic illnesses. Humans are affected by influenza type A and B resulting in an upper respiratory tract infection. Vaccination against the influenza virus serves as the best prevention when combating the virus. However, the vaccine does not protect all due to the antigenic shift of the virus strains as it travels the world. Though antiviral medications do not replace the vaccine, they are utilized for prophylaxis and relief of symptoms associated with influenza.

Two classes of antiviral agents have demonstrated efficacy against the influenza virus: M2 ion channel inhibitors (adamantanes derivatives: amantadine and rimantadine) and neuraminidase inhibitors (oseltamivir and zanamivir). The adamantanes have efficacy against influenza type A, where as the neuraminidase inhibitors are effective for both type A and B. All antiviral agents can be used for prophylaxis or treatment of influenza. Yet, over the past three years the influenza virus has shown increased resistance to the adamantanes worldwide with an associated increase from 1.9% to 12.3% (CDC 2006). Due to this growth in resistance and specific isolates identified in 2005–2006, the treatment and prophylaxis with these therapeutic agents are no longer recommended in the US. Therefore, the neuraminidase inhibitors may see increased use worldwide during subsequent flu seasons.

This review will focus on zanamivir, a neuraminidase inhibitor, for the prophylaxis of influenza in children and adults. Zanamivir is a micronized, dry powder inhaled antiviral agent that inhibits the neuraminidase molecule active site on the surface of the influenza virus. This is thought to prevent infection and distribution of the virus

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to uninfected cells. Zanamivir is indicated for prophylaxis of influenza type A and B in children 5 years of age and older. It is only commercially available in an inhaled form due to poor oral bioavailability and should be used with a diskhaler® (Glaxo Wellcome UK Ltd, Middlesex, UK) device, which is provided with the medication. The medication is provided in foil blister packs (rotadisks) which are inserted individually and replaced in the diskhaler®. Each rotadisk contains 4 doses and provides 5 mg per dose. Five rotadisks are packaged with the diskhaler®. The prophylaxis dose for all ages of zanamivir is 10 mg (two 5 mg blisters) inhaled once daily, at the same time each day, for 10 days of therapy. Zanamivir should be initiated within 1.5 days of symptom onset for the index case in a household setting. For a community outbreak, zanamivir should be initiated within 5 days of identification and be administered for a total of 28 days of therapy. Data is not available regarding the use of zanamivir if the recommended initiation time frame has past.

Intranasal zanamivir has been evaluated but provided no greater efficacy than placebo or when added to the inhaled formulation; thus, intranasal administration is not currently recommended and a dosage formulation is not available (Kaiser et al 2000). An IV formulation of zanamivir was studied in one trial (Calfee et al 1999); however, this dosage form is not marketed.

Zanamivir has low protein binding and is excreted primarily unchanged in the urine. No adjustment is needed for renal dysfunction as zanamivir has limited systemic absorption. Zanamivir appears to be well tolerated as adverse effects are reported as being similar to placebo and difficult to distinguish from the influenza virus. The most common adverse effects seen are headache, throat, and tonsil pain, and cough and nasal symptoms. Zanamivir lacks drug interactions and does not affect cytochrome P450 enzymes. Administering the live intranasal flu vaccine concurrently with zanamivir may inhibit the vaccine replication. It is recommended to administer the vaccine at least 24 hours after zanamivir cessation and to not provide zanamivir until 2 weeks following the vaccine. Caution should be utilized in patients with milk allergy considering that each blister contains 20 mg of lactose or milk protein. Zanamivir has not been studied in pregnancy and should only be used if the benefit outweighs the risk to the fetus and mother. However, its low systemic absorption may be a possible benefit for use considering this pharmacodynamic parameter.

In addition, patients with chronic airway disease such as asthma or chronic obstructive pulmonary disease (COPD) should avoid zanamivir due to bronchospasm concerns. Although previous data found pulmonary function not significantly affected by zanamivir (Cass et al 2000), post marketing reports led to the warning. If a patient routinely takes bronchodilators, it is recommended that the patient administer the bronchodilator prior to the zanamivir dose. However, if bronchospasms or a decline in respiratory function occurs after utilization, it is recommended to discontinue the product and seek treatment if warranted.

Concerns exist regarding the patient administration technique and use of the inhaler. Although the diskhaler® does not require coordination with releasing the dose and inspiration, the device may be difficult to use for some patient populations. In the pediatric population, it is challenging to have a young child inhale appropriately and obtain the desired quantity of drug. A parent may place zanamivir into the end of a straw prior to blowing through the straw forcing the medication into the child's throat which has been shown to be efficacious (Imuta et al 2003). Thirty-eight elderly patients were assessed on their use of the device (Diggory et al 2001). After a 15 minute education period, these patients demonstrated use of the device. Patients could receive up to five additional minutes of education after the initial period. Ten patients achieved perfect scores regarding the demonstration. After 24 hours, the patients were again asked to show how to use the device. Only five patients had perfect scores and in general most patients scores decreased, $p < 0.001$. In this study, the elderly had trouble primarily with loading the disk in the device and priming the device. The straw technique may be useful in the elderly population as well.

Prophylaxis studies

Zanamivir has several studies evaluating its use as a prophylactic agent for influenza in children and adults. The first double-blind trial randomized 1107 adults (18–64 years) to zanamivir (10 mg daily) or placebo for 4 weeks at the start of the 1997 influenza season (Monto et al 1999). The most prominent virus of 2006 was A/Sydney/5/97 (H3N2) which was not in the annual vaccine. The primary outcome was the number of individuals who had symptomatic, laboratory-confirmed influenza. This was defined as a rise in titers and/or isolation of the influenza virus, and two or more of the following on three concurrent diary cards: cough, headache, sore throat, myalgia, feverishness, or temperature $\geq$37.8 ºC. Patients recorded symptoms and temperatures twice daily on the diary cards that were checked weekly and were asked

to contact the study center if any respiratory symptoms developed. Only 14% of patients in the study received the influenza vaccine. Symptomatic, laboratory-confirmed clinical influenza occurred in 2% and 6.1% of the zanamivir group versus placebo, respectively. Zanamivir provided a 67% efficacy in prevention laboratory-confirmed clinical influenza versus placebo, $p < 0.001$. It also provided 84% efficacy against laboratory-confirmed influenza with fever, $p = 0.001$. Zanamivir was 43% efficacious against all febrile illnesses, $p = 0.009$ and 31% efficacious against influenza infection, with or without symptoms, $p = 0.03$. In the subset of unvaccinated patients, zanamivir decreased symptomatic, laboratory-confirmed influenza by 60% ($p = 0.009$) and confirmed influenza with fever by 81% ($p = 0.004$). Overall, no difference in adverse effects was found between groups and compliance was high in both groups. A severe adverse effect was found in 1 patient in each group. Four patients in the zanamivir group and seven patients in the placebo group discontinued the medication due to drug-related events, specifics were not stated.

Another study evaluated zanamivir for a community outbreak in high-risk patients 12 years of age or older. (Data on File, Relenza 2000) This multi-center, double-blind study randomized patients from various countries to zanamivir 10 mg daily or placebo for 28 days during December 2000–April 2001. Therapy was initiated within 5 days of identifying the community outbreak. There were 1678 patients randomized to the zanamivir group and 1685 patients in the placebo group. Patient ages ranged from 12–94 years of age, mean 60 years. Fifty-six percent of the patients were over 65 years of age. Sixty-seven percent and 68% of the zanamivir and placebo group, respectively, had received the flu vaccine for the season. This intention-to-treat analysis determined only 4 patients (0.2%) in the zanamivir group developed symptomatic influenza with confirmed serology/culture versus 23 patients (1.4%) in the placebo group, $p < 0.001$. Symptomatic influenza was defined as two of the following symptoms reported for 3 consecutive days on diary cards: feverish or temperature $\geqslant$37.8 ºC, headache, cough, sore throat, or muscle/joint aches and pains. Only 4 patients in the zanamivir group and 21 patients in the placebo group were diagnosed with symptomatic influenza with culture/serology positive results on Day 2–28 (95% confidence interval [CI] 0.07, 0.49). This was similar for Day 3–28 as well (95% CI 0.07, 0.52). Adverse effects were similar between both groups. Five percent of patients in each group withdrew from the study for similar reasons, specifics were not provided in the study.

Kaiser and colleagues (2000) randomized 575 patients (age 13–65 years) to inhaled zanamivir, intranasal zanamivir, inhaled and intranasal zanamivir, or placebo after close contact with people who had influenza-like illnesses for no longer than 4 days. Close contact was defined as living in the same home, sleeping in the same room, or confined in the same room for extended periods of time. This was a multicenter trial conducted during the 1995–1996 influenza season. Unstable chronic illness, influenza vaccination, or anti-influenza medications during the previous days were trial exclusions. Treatment medication or placebo was administered for 5 days. No significant difference was found between the four groups for patients developing proven influenza after exposure; however, the trial did not reach its power as 840 patients were not enrolled. The inhaled zanamivir appeared to prevent more infections than the intranasal zanamivir or placebo; however, this was not statistically significant. Intranasal zanamivir produced results similar to those of the placebo group. The authors determined that intranasal route was not effective and acknowledged that five days of prophylactic therapy may not be sufficient, thus studies of longer duration are warranted.

The Zanamivir Family Study Group conducted a multicenter, double-blind, parallel, placebo controlled study of zanamivir for prophylaxis in a family setting from December 1998 to April 1999 (Hayden et al 2000). Families with 2–5 people, one being an adult and at least one a child, age 5–17 years, were enrolled once one person developed influenza-like illness. All eligible family members began taking zanamivir or placebo within 36 hours of symptom onset in the index case. Patients who were immunocompromised, pregnant, breast feeding, were taking an antiviral medication, or less than 5 years of age were excluded from the study. The index case was administered the treatment regimen of zanamivir or placebo. Three hundred thirty-seven families (1158 participants) were randomized to treatment or placebo. Both influenza A and B were confirmed in the study. The primary end point was the proportion of families who had one or more family members (household contacts) that developed symptomatic, laboratory-confirmed influenza. Symptomatic was defined as possessing at least two of the following: temperature $\geqslant$37.8 ºC, feverishness, cough, headache, sore throat, or myalgia on three consecutive diary card entries. This occurred in 4.1% of families in the zanamivir group versus 19% of families in the placebo group, $p < 0.001$. Families with laboratory-confirmed influenza in the index case experienced a proportionally higher incidence

of influenza, 8% for the zanamivir group versus 29% in the placebo group, $p < 0.001$. Overall, zanamivir provided a 79% protection rate from influenza among families. Based on examining symptom onset ≥1 day after prophylaxis initiation, zanamivir's protection rate increased to 84%, $p < 0.001$. No development of resistance to zanamivir was seen in the study via viral sequencing. Three patients discontinued zanamivir due to adverse effects. One stopped the medication due to gastrointestinal pain and discomfort and the other two patients stopped due to headaches. Of those patients with asthma requiring medication, 11% of the placebo group had an exacerbation versus 6% in the zanamivir group.

In the previous study, protection could occur from treating the index case, thus decreasing viral shedding; therefore, Monto and colleagues (2002) evaluated zanamivir prophylaxis in 487 families in which the index case was not treated. This multicenter, double-blind, parallel, placebo-controlled trial randomized families (1291 contacts) to zanamivir or placebo for 10 days. Index patients were only tested for the influenza virus, but not treated. Family inclusions were the same as the above study and subjects had to start therapy within 36 hours of symptom onset in the index patient. One hundred and thirty-two contacts had been vaccinated for influenza. The zanamivir and placebo group were similar regarding vaccination. The primary end point was laboratory–confirmed influenza in families during the period of prophylaxis, day 1–11. This study was conducted from June 2000–April 2001 and both influenza type A and B were documented. Zanamivir reduced the occurrence of symptomatic, laboratory-confirmed influenza by 81% in households, $p < 0.001$. A similar reduction was also seen when evaluating individual contacts versus families. No evidence of resistance was found in clinical isolates. Influenza-like illness was the common adverse effect seen in the study, yet zanamivir was well tolerated in all. Fifty-eight patients were classified to have an underlying respiratory condition, mostly asthma. Two of these patients had bronchospasms and both were in the placebo group.

Three studies have specifically evaluated zanamivir efficacy in the nursing home population for prophylaxis. The first pilot study randomized patients to zanamivir 10 mg inhaled and 4.4 mg intranasal twice daily or rimantadine 100 mg once daily for 14 days for influenza A outbreaks (Schilling et al 1998). For influenza B outbreaks, patients received zanamivir as stated or no medication. Study nurses administered the medications for the pilot. Sixty-five patients received zanamivir and 23 received rimantadine for an influenza A outbreak. No patients in the zanamivir group developed laboratory-confirmed influenza A; although, one patient in the rimantadine group was positive. Eight patients versus one in the zanamivir group developed a respiratory illness versus placebo, respectively. Thirty-five patients received zanamivir versus 17 who received nothing for an influenza B outbreak. Again, no patients had laboratory-confirmed influenza B in the zanamivir group. One patient who did not receive the medication was influenza B positive. Only one patient in the zanamivir group had a respiratory illness, versus three who did not receive zanamivir. No serious adverse effects were reported with zanamivir. Most patients complained of nasal symptoms (16%), gastrointestinal symptoms (8%), and throat irritation (7%). Forty patients with mild to moderate COPD did not have a difference in severity or incidence of adverse effects.

A larger multicenter, double-blind trial randomized 489 asymptomatic nursing home patients to zanamivir (10 mg inhaled daily) or placebo for 14 days after an influenza outbreak was recognized (Ambrozaitis et al 2005). The study occurred over three influenza seasons, thus a few patients ($n = 5$) were randomized twice. Twice weekly evaluation for respiratory illness was conducted. Only 9% of patients were vaccinated. Approximately 85% of patients were considered high-risk (age ⩾65 years, diabetes, respiratory, or cardiac condition). Symptomatic, laboratory-confirmed influenza occurred in 6% and 9% of the zanamivir and placebo patients, respectively, $p = 0.355$. All cases occurred in a site where no one had the vaccination and more than half of the failures occurred within 2 days of the outbreak. Collectively, zanamivir provided a 32% protection versus placebo. Laboratory-confirmed influenza with fever occurred in 2% of the zanamivir and 6% of the placebo group, $p = 0.043$. This equates to zanamivir providing 70% protection against febrile influenza. Complications of the influenza illness and adverse effects of zanamivir were not significantly different between groups. No evidence of zanamivir resistance was found in isolates.

A similar study was conducted in the US at multiple sites over the same three year period (Gravenstein et al 2005). There were 375 patients were randomized to inhaled zanamivir (10 mg daily) or placebo for 14 days. For influenza A outbreaks, rimantadine (100 mg daily) or placebo tablets was also administered. Overall, 482 randomizations occurred as some patients were randomized twice or three times (zanamivir: 238, rimantadine: 231, placebo: 13). Almost all patients were vaccinated for the current influenza season and 96% of patients were considered high-risk (as

stated previously). Symptoms were assessed in each patient throughout the study. Only 3% of patients in the zanamivir group versus 8% of the rimantadine group developed symptomatic, laboratory-confirmed influenza A, $p = 0.038$. This results in 61% additional protection using zanamivir versus rimantadine. Almost half of the failures occurred within the first two days. When evaluating days 2–15, 2% versus 7% of patients developed symptomatic, laboratory positive influenza with zanamivir or rimantadine, respectively, $p = 0.024$. Zanamivir showed an additional 68% efficacy over rimantadine. When examining days 3–15, zanamivir provided an additional 77% efficacy. Only 1% of zanamivir versus 6% of rimantadine patients developed symptomatic, laboratory confirmed influenza, $p = 0.02$. No significant differences were seen between the groups in regards to adverse effects. Complications occurred in 3% of patients on rimantadine versus 1% of patients on zanamivir, $p = 0.109$. No resistance was identified with zanamivir in the isolates; however, 38% were resistant to rimantadine.

Intravenous formulation

An intravenous formulation of zanamivir was studied in 16 healthy males who were inoculated with the virus (Calfee et al 1999). This double-blind study randomized patients to zanamivir 600 mg IV over 30 minutes twice daily for 5 days or placebo. The medication was provided 4 hours prior to an H1N1 virus exposure. Symptoms were assessed twice daily throughout the period. Serologic infection was identified in one patient in the zanamivir group, $p < 0.005$; however, no viral shedding was found, $p < 0.005$. One patient in the zanamivir group versus seven in the placebo group had fever, $p < 0.05$. Prophylactic intravenous zanamivir was found to be well-tolerated and protected against the influenza A virus.

Conclusion

Although the influenza vaccine remains the optimal intervention for prevention, zanamivir has proven efficacy and safety for post-exposure prophylaxis of influenza A and B viruses in adults and children. Zanamivir has been evaluated in the community, home, and nursing home setting. Caution should be used in patients with underlying airway diseases. Education on the appropriate use of the device is warranted in all patient populations.

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