
Efficacy And Tolerability Of The Neuraminidase Inhibitor Zanamivir

M Iozzo

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Abstract

Until recently, management options for influenza were limited to vaccination and use of the M2 inhibitors amantadine or rimantadine. Increased insight into the mechanisms of influenza virus replication combined with advances in the science of rational drug design have resulted in the development of the neuraminidase inhibitors, a new class of medicines that promise significantly to impact the management of influenza. The neuraminidase inhibitor zanamivir is the first antiviral specifically developed to combat both influenza A and influenza B viruses. The efficacy and tolerability of zanamivir have been established in an extensive program of double-blind, placebo-controlled trials conducted at study sites throughout the world. Zanamivir rapidly and effectively alleviated influenza symptoms regardless of patients' age or clinical characteristics. In clinical trials involving more than 4000 patients and in usual clinical practice involving tens of thousands more to date, no zanamivir-resistant viruses have been isolated. Adverse event data collected during Phase II and Phase III clinical trials of zanamivir in the treatment of influenza show that it has favorable tolerability, a feature that distinguishes it from other antiviral therapies for influenza. An important tool for the management of influenza, zanamivir will help health care practitioners to reduce the clinical, economic, and humanistic impacts of this disease.

INTRODUCTION

In the spring of 1997, an infant boy in Hong Kong died 12 days after contracting a respiratory illness. The illness was later identified as influenza and traced to a variant of Influenza A virus H5N1, previously known to infect only birds.^{1,2} Influenza caused by the H5N1 variant eventually spread to at least 18 Hong Kong residents and caused 6 deaths. The means by which it infected humans remains unknown, although direct transmission of the virus from birds to humans is suggested by the finding that all but one of the human cases had been exposed to live chickens during the days before their illness. H5N1 did not appear to spread efficiently from person to person, and no additional cases of human infection were reported after the authorities mandated the destruction of all 1.6 million birds in Hong Kong.

The infection of humans with the highly pathogenic H5N1 virus variant served as a reminder of the ever-present threat of emergence in human populations of new influenza virus subtypes to which there is little or no pre-existing immunity. Fortunately, the H5N1 variant was not capable of efficient person-to-person transmission. Had it been highly contagious, it may have sparked an influenza pandemic.

Influenza pandemics, which have occurred approximately every 15 years over the last century, cause significant morbidity and mortality. A shift in the predominant circulating virus subtype from H1N1 to H2N2 in 1957, for example, ignited a pandemic that resulted in approximately 70,000 excess deaths (that is, deaths exceeding the number expected when an epidemic is not present) in the United States alone.³

Even in nonpandemic years and in years when less pathogenic strains predominate, the influenza virus is a major cause of death and debilitation. The excess mortality associated with influenza epidemics occurring every one to three years has increased during the last 15 years to approximately 30,000 persons per year in the United States.⁴

Influenza epidemics typically have an abrupt onset and end separated by a 2- to 3-week upsurge in the frequency of new cases and a 2- to 3-month plateau.³ Community outbreaks are often heralded by an increase in medical visits from children suffering from fever and respiratory illness. This increase in the incidence of pediatric visits is followed by more respiratory consultations from adults and the elderly, who may present or develop life-threatening complications,

such as pneumonia or exacerbations of chronic pulmonary or cardiovascular diseases.

Cough and fever, usually accompanied by myalgia, headache, and sore throat, are the characteristic symptoms of influenza.^{3,5} The suddenness with which these symptoms develop distinguishes influenza from other respiratory infections such as the common cold, in which symptoms develop more gradually. Even an uncomplicated case of influenza is likely to require days of bed rest and is associated with general malaise and weakness that may persist weeks beyond the cessation of other symptoms.

Influenza may exacerbate other chronic conditions, particularly asthma. In one longitudinal study⁶ of 138 asthmatic adults, 44% of asthma exacerbations with mean decreases in mean peak expiratory flow rate of at least 50 L/min were associated with laboratory-confirmed infections with pathogens such as influenza B, rhinoviruses, and coronaviruses. The well-established role of influenza in promoting exacerbations of asthma has led experts to recommend that asthmatics receive an annual influenza vaccination.⁷

The influenza virus is transmitted primarily via inhalation of virus-containing aerosol particles originating from an infected person.^{3,8} The infection rates vary from one epidemic to another, but typically at least one in 10 of a community population is infected during an outbreak.³ The incidence of infection among those occupying closed environments such as nursing homes and military bases and among families of infected persons is much higher, ranging from 24% to 87% across studies conducted in the United States.⁹

Influenza epidemics exact large humanistic and economic tolls. Direct costs for medical care of influenza are estimated at \$1 billion to \$3 billion annually in the United States; annual indirect costs of work and school absenteeism and reduced productivity range from \$10 billion to \$15 billion.^{3,8} Direct medical costs are highest in the elderly, who are at increased risk for hospitalization due to influenza-associated pneumonia or exacerbation of chronic medical conditions. Excess hospitalization rates of 800 per 100,000 have been reported during recent epidemics among patients with high-risk medical conditions.³ The elderly compared with younger patients are also at heightened risk of dying from influenza; approximately 90% of deaths attributed to influenza occur in patients more than 65 years of age.³

Until recently, management options for influenza were limited to vaccination and treatment or prophylaxis with the M2 inhibitors amantadine or rimantadine. The Centers for Disease Control and Prevention recommends vaccination for patients at high risk of developing complications of influenza (such as the elderly and the immunocompromised) and health care workers.¹⁰ Limitations of the vaccine include the need to administer it annually, relatively poor efficacy in patient groups with weakened immune responses, lack of compliance attributed primarily to fear of side effects, and lack of protection when the inactivated viruses in the vaccine do not correspond with viruses circulating in the community.^{10,11,12,13,14} Like the vaccine, the M2 inhibitors have significant shortcomings, including narrow therapeutic coverage, treatment-limiting neurological side effects, and the ability to foster development of resistant viruses.¹⁵

ZANAMIVIR IN THE TREATMENT AND PREVENTION OF INFLUENZA

The substantial personal, social, and economic costs of influenza have continued to increase despite the availability of the influenza vaccine and the M2 inhibitors. Recent insights into the mechanisms of influenza virus replication combined with advances in the science of rational drug design have resulted in the development of the neuraminidase inhibitors, a new class of medicines that promise significantly to impact the management of influenza. Introduced in the United States in 1999, the neuraminidase inhibitor zanamivir is the only antiviral therapy to combine potent efficacy at the source of infection with favorable, no drug interactions, and minimum risk of viral resistance. Oseltamivir, the second neuraminidase inhibitor to be approved, will not be addressed in this review.

INDICATION

Zanamivir is indicated for the treatment of uncomplicated acute illness due to influenza virus in patients who have been symptomatic for up to 2 days. Zanamivir has been thoroughly studied in children as well as adults. With proven efficacy in children and its favorable tolerability profile, zanamivir is the only neuraminidase inhibitor to be approved for patients as young as 7 years of age. Zanamivir is also being evaluated for the prevention of influenza.

DOSING AND ADMINISTRATION

Nonsystemic administration of influenza medication is desirable because influenza is not a systemic infection; the virus is confined to the respiratory tract.³ Systemic influenza

symptoms such as fever and myalgia arise from the activity of inflammatory mediators (cytokines) that respiratory cells release into the bloodstream.¹⁶ To maximize its antiviral potency and tolerability, zanamivir was developed for administration by oral inhalation. The topical mode of delivery of zanamivir via the Diskhaler(r) device allows the medication to be delivered directly to the site of infection in the respiratory tract with minimal systemic drug exposure. The extremely low systemic exposure with zanamivir contributes to its favorable tolerability (see below).

Data from a survey¹⁷ of more than 1400 patients using zanamivir during the 1999-2000 influenza season demonstrate that topical administration of zanamivir via the Diskhaler(r) device is well accepted and does not deter them from using the medication. Ninety percent (90%) of patients indicated that they found the instructions for using the device easy to understand; the same proportion found the device easy or very easy to use.

The recommended dose of zanamivir for the treatment of influenza is two inhalations for a total dose of 10mg twice daily for 5 days. Patients should be advised to complete the 5-day course of therapy even if they begin to improve within 5 days. The finding that the compliance rate across the zanamivir treatment studies exceeded 90%¹⁸ suggests that the length of the recommended regimen does not hinder completion of the course of treatment.

MECHANISM OF ACTION

Zanamivir is the first antiviral specifically developed to combat both influenza A and influenza B viruses, responsible for approximately 65% and 35% of influenza infections, respectively.¹⁹ This activity against both virus types differentiates zanamivir from the only other class of anti-influenza medicines, the M2 inhibitors, which are only active against influenza A. Whereas zanamivir inhibits viral replication and proliferation by inhibiting neuraminidase, an enzyme present in both influenza A and influenza B viruses, the M2 inhibitors inhibit viral replication and proliferation by blocking an M2 ion channel present only on influenza A viruses. Thus, while the M2 inhibitors are ineffective in inhibiting influenza B viruses, zanamivir potently inhibits their growth in vitro. In addition, zanamivir was more potent than the M2 inhibitors amantadine and rimantadine at inhibiting growth of influenza A virus in in vitro tests.²⁰

Zanamivir's dual activity against influenza A and B is particularly important from the practical standpoint that the viral pathogens responsible for illness attributed to influenza

are often unknown when antivirals are prescribed for a patient. Because of the time and high cost requirements of rapid diagnostic tests, influenza is nearly always diagnosed clinically on the basis of symptoms, a necessary practice if antiviral therapy is to be initiated early enough to be helpful. Influenza A and B cannot be distinguished clinically, and they often co-circulate. When influenza is clinically diagnosed and the responsible pathogens have not been isolated, it is most prudent to prescribe zanamivir to ensure coverage against influenza B as well as influenza A.

Although neuraminidases are found in other viruses such as parainfluenza or mumps, zanamivir is selective for the neuraminidase of influenza A and B.^{15,20} Also, zanamivir does not affect viruses such as rhinovirus and adenovirus, devoid of neuraminidase.^{15,20}

DRUG RESISTANCE

In clinical trials involving more than 4000 patients and in normal clinical practice involving tens of thousands more, no zanamivir-resistant viruses have been isolated after use of inhaled zanamivir.²¹ This finding is attributed to zanamivir's selective action at a site on viral neuraminidase that, unlike many other portions of influenza viruses, is highly conserved. A resistant strain of influenza B virus was identified in the atypical case of an immunocompromised 18-month female after a course of zanamivir treatment (16mg to 32mg every 6 hours for 2 weeks) with an investigational nebulized solution.²²

The lack of association of zanamivir with the development of viral resistance distinguishes it from the M2 inhibitors, which act at portions of the influenza virus that readily mutate to engender resistant viral strains.²³ Cross-resistance occurs, so that viruses resistant to one M2 inhibitor are resistant to the other. Across studies, one-quarter to one-half of patients treated with rimantadine shed resistant virus as early as 2 days after initiation of therapy.²³ One study conducted in a nursing home²⁴ determined that amantadine-resistant viruses were found in all patients from whom viral isolates could be obtained who had received amantadine at the onset of influenza symptoms. Three individuals residing in adjacent rooms who had not received amantadine also became infected with identical resistant viruses, a finding that suggests that amantadine-resistant viruses are contagious. Similar transmission of resistant viruses to family members has also been observed with rimantadine.²³

CLINICAL EFFICACY IN THE TREATMENT OF INFLUENZA

The efficacy of inhaled zanamivir (10mg inhaled twice daily for 5 days) was established in a series of double-blind, placebo-controlled trials^{25,26,27,28,29} conducted at study sites throughout the world (Table 1). Most studies enrolled patients as young as 12 years of age, and some enrolled patients at high risk of developing complications of influenza (Table 1). Patients participating in the studies were required to be feverish or to have a fever and to be suffering from at least two symptoms including headache, myalgia, cough, or sore throat.

Figure 1

Table 1. Phase II and III Parallel-Group, Placebo-Controlled Trials with Inhaled Zanamivir

Study	N	Location	Time between onset of symptoms and treatment	Patient Age	High-Risk Patients Included?	Time to symptom alleviation** (Placebo-Zanamivir)
Study 1 ²⁵ (NAIB3001)	455	Australia, New Zealand, South Africa	336 hours	<12 years	Yes	1.5 days [†]
Study 2 ²⁶ (NAIA2005)	197	Europe	348 hours	<18 years	No	1.3 days [†] (results combined with Study 3)
Study 3 ²⁶ (NAIB2005)	220	North America	348 hours	<13 years	No	1.3 days [†] (results combined with Study 2)
Study 4 ²⁷ (NAIA3002)	777	North America	348 hours	<12 years	Yes	0.5 days
Study 5 ²⁸ (NAIB3002)	356	Europe	348 hours	<12 years	Yes	2.5 days [†]
Study 6 ²⁹ (NAIB2007)	116	Europe	348 hours	<13 years	Yes	1 day

*p<0.05 vs placebo

^Numbers are for the intent-to-treat population.

Study 1,²⁵ which enrolled 455 patients within 36 hours of onset of influenza symptoms, was conducted in the Southern hemisphere during the 1997-1998 flu season. Zanamivir alleviated symptoms of influenza a median 1.5 days sooner than placebo in both the intent-to-treat population and in patients with laboratory-confirmed influenza in this trial (Table 2). The response to zanamivir was similarly robust regardless of whether patients were infected with influenza A or influenza B (Table 2). The benefits of zanamivir were most pronounced in high-risk patients (for example, those older than 65 years), whose symptoms were alleviated a median 2.5 days earlier than with placebo (Table 2). High-risk patients treated with zanamivir compared with placebo patients experienced significantly fewer complications (14% vs 46% of patients; p<0.01) and used significantly fewer antibiotics for complications (14% vs 38% of patients;

p<0.05).

Figure 2

Table 2. Symptom Alleviation Data from Study 125

	N		Time to Symptom Alleviation	
	Zanamivir	Placebo	Placebo-Zanamivir Difference in Median Days	Placebo-Zanamivir Difference in %
Intention-to-treat	227	228	1.5*	23
Influenza-positive	161	160	1.5*	25
Influenza A	105	109	2.0*	31
Influenza B	56	51	1.5	25
Not confirmed positive	66	68	0.25	4
Febrile	128	123	2.0*	31
Febrile, influenza-positive	97	106	2.0*	31
Afebrile	99	105	-0.5	-9
High-risk	37	39	2.5*	31
High-risk, influenza-positive	24	28	3.25	39

*p<0.05 zanamivir vs placebo

These data are corroborated by results of a European study (Study 5),²⁸ which enrolled 356 patients within 48 hours of onset of symptoms. Zanamivir alleviated symptoms of influenza a median 2.5 days sooner than placebo in both the intent-to-treat population and in patients with laboratory-confirmed influenza (Table 3). Zanamivir relieved the range of influenza symptoms in this study: median symptom scores over 2 weeks were reduced with zanamivir compared with placebo for headache (33%), sore throat (33%), feverishness (20%), myalgia (25%), cough (44%), and weakness (25%). Statistically significant (p<0.05) benefits of zanamivir over placebo were observed beginning 24 hours after initiation of therapy for cough, feverishness, and myalgia. Data from the four other placebo-controlled studies, including one conducted in Japan, are consistent with those from Studies 1 and 5 (Table 1).

Figure 3

Table 3. Median Time to Alleviation of Influenza Symptoms in Study 528

	Median days (n)		Placebo Minus Zanamivir	
	Placebo	Zanamivir	Difference (95% CI)	Hazard Ratio (95% CI)
Intention-to-treat	7.5 (n=182)	5.0 (n=174)	2.5*	23
Influenza-positive	7.5 (n=141)	5.0 (n=136)	2.5*	25

*p<0.05 zanamivir vs placebo

Zanamivir rapidly and effectively alleviated the symptoms of influenza regardless of patients’ age or clinical characteristics, but a pooled analysis¹⁸ across the six placebo-controlled trials demonstrates that its benefits were especially evident in older patients and in patients with more severe illness (Table 4). In addition, although zanamivir administered as late as 2 days after onset of influenza symptoms was effective, it was most effective in patients administering it within 30 to 36 hours of symptom onset. Patients using zanamivir in Studies 2 and 3²⁶ had their symptoms alleviated in about half the time of placebo patients (median 4 days versus 7 days), an advantage that was less robust among patients using zanamivir more than 30 hours after symptom onset. The latter data underscore the importance of efficient clinical diagnosis of influenza, so that therapy can be initiated promptly for maximum benefit.

Figure 4

Table 4. Median Time to Alleviation of Influenza Symptoms Across Six Placebo-Controlled Studies¹⁸

	Median days (n)		Difference in days
	Placebo	Zanamivir	
Intention-to-treat	6.0(1102)	5.0(1133)	1.0*
Influenza-positive	6.0(765)	5.0(807)	1.0*
Febrile	6.5(595)	5.0(630)	1.5*
Afebrile	5.5(161)	5.0(161)	0.5
Symptoms not severe	5.5(543)	4.5(555)	1.0*
Symptoms severe	8.0(222)	5.0(252)	3.0*
Age less than 50 years	6.0(619)	5.0(690)	1.0*
Age at least 50 years	7.5(146)	4.5(117)	3.0*

*p<0.05 zanamivir vs placebo

CLINICAL EFFICACY IN THE PREVENTION OF INFLUENZA

Zanamivir has also been shown to be effective in the prevention of influenza although the drug has not been approved for this indication. Zanamivir (10mg once daily for 10 days) given as prophylaxis to families in which one member had developed influenza showed significant protective efficacy versus placebo in one recent study.³⁰ While 1 in 5 (19%) of families treated with placebo developed symptomatic, laboratory-confirmed influenza, only 1 in 25 (4%) of families treated with zanamivir developed influenza.

Zanamivir also protects against community-borne influenza. A short, 5-day course of zanamivir prophylaxis reduced the risk of development of influenza after close contact with individuals with influenza-like illness by a third compared with placebo in one study.³¹ A 28-day course of zanamivir prophylaxis had a protective efficacy compared with placebo of 67% and 84% for laboratory-confirmed influenza and laboratory-confirmed influenza with fever, respectively, in a study³² conducted in a community setting during an influenza outbreak.

SIDE EFFECT PROFILE

Adverse event data collected during Phase II and Phase III clinical trials of zanamivir in the treatment of influenza show that it has favorable tolerability, a feature that distinguishes it from other antiviral therapies for influenza. Unlike the M2 inhibitors, which may cause side effects such as jitteriness, nervousness, and anxiety in approximately 10% of patients,^{3,10} zanamivir is not associated with significant neurological side effects. Furthermore, zanamivir does not provoke nausea and vomiting, which are common side effects (10% to 20% incidence) of the neuraminidase tablet oseltamivir, the only other marketed neuraminidase inhibitor.³³ Even during long-term therapy in the 28-day prophylaxis study described above,³² zanamivir’s tolerability profile was similar to that of placebo.

The most common adverse events reported with zanamivir and placebo in the influenza treatment studies are listed in Table 5. Most of these adverse events, such as headache, cough, and nasal signs and symptoms, probably occurred as symptoms of influenza rather than side effects of study medication. Adverse events were reported in zanamivir clinical trials regardless of their suspected cause.

Figure 5

Table 5. Adverse Events* in Phase II and Phase III Placebo-Controlled Clinical Trials with Inhaled Zanamivir

Event	Zanamivir 10mg BID (n=1132)	Placebo (n=1520)
Diarrhea	3%	4%
Nausea	3%	3%
Headaches	2%	3%
Vomiting	1%	2%
Nasal Signs and Symptoms	2%	3%
Bronchitis	2%	3%
Cough	2%	3%
Sinusitis	3%	2%
Ear, Nose, and Throat Infection	2%	2%
Dizziness	2%	<1%

*Adverse events were reported regardless of their suspected cause.

Zanamivir should be prescribed cautiously in patients with chronic obstructive pulmonary disease or asthma because of the potential for bronchospasm or decline in lung function. Although not observed in clinical trials, bronchospasm has been noted in clinical practice in zanamivir-treated patients, the majority of whom had underlying respiratory disease.³⁴ The CDC recommends caution in using zanamivir in this population and states that patients with chronic obstructive pulmonary disease or asthma should have a fast-acting inhaled bronchodilator available when using the drug.³⁵

DRUG INTERACTIONS

Zanamivir appears on the basis of in vitro and in vivo studies conducted and clinical experience accumulated to date to be devoid of drug interactions.³⁶ This advantage of zanamivir is attributed to its topical route of administration, which delivers the drug directly to the site of viral replication and minimizes systemic exposure. This lack of interaction with other medications is an especially important advantage of zanamivir because anti-influenza therapies are likely to be used in patient groups using other concomitant medications.

CONCLUSIONS

The neuraminidase inhibitor zanamivir offers unique advantages compared with other antivirals. First, it is distinguished from the M2 inhibitors in its potent efficacy against all known subtypes of both influenza A and influenza B. In addition, unlike the M2 inhibitors, which rapidly and frequently foster viral resistance, zanamivir does not select for resistant viruses. No zanamivir-resistant

isolates have been recovered from patients using inhaled zanamivir in clinical trials or normal clinical practice to date. Zanamivir has a favorable tolerability profile, a feature that differentiates it from other antiviral therapies. In addition, its topical mode of administration targets the site of infections while minimizing systemic exposure. Zanamivir, an important new tool for the management of influenza, will help health care practitioners to reduce the clinical, economic, and humanistic impacts of this disease.

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Author Information

Mike Iozzo, BS, PA-C

Hartford Hospital Emergency Trauma Center