Review article

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Management of influenza in patients with asthma or chronic obstructive pulmonary disease

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Objective: To review the prevention and treatment of influenza in patients with asthma and/or chronic obstructive pulmonary disease (COPD).

Data sources: Computer-assisted MEDLINE searches for article and manual searches of conference proceedings on influenza, influenza vaccination, rimantadine, amantadine, oseltamivir, zanamivir, asthma, and/or COPD.

Study selection: Published articles and pertinent conference abstracts in the areas mentioned in Data sources were selected. Articles included for review were studies conducted on humans.

Results: Annual vaccination against influenza is the currently accepted practice for influenza management in patients with asthma and/or COPD. However, despite the availability and use of vaccination, influenza continues to cause serious morbidity and increased mortality. The management of influenza in at-risk patients with the older antivirals such as amantadine or rimantadine has not been widely accepted because of the rapid emergence of resistant variants, their lack of effect against influenza B, and poor adverse event profile. A new class of influenza antivirals, the neuraminidase inhibitors, has recently become available for the management of influenza. The currently marketed neuraminidase inhibitors are zanamivir and oseltamivir. Clinical studies have shown that these neuraminidase inhibitors are effective for the treatment and chemoprophylaxis of influenza A and B.

Conclusions: Vaccination against influenza remains the gold standard for the prevention of influenza in patients with asthma and/or COPD. The neuraminidase inhibitors zanamivir and oseltamivir are useful adjuncts to influenza vaccines for the management of influenza in these patients who are at high-risk of developing influenza related complications.

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INTRODUCTION

Influenza is the acute febrile illness caused by a respiratory tract infection with influenza A and B viruses. Influenza is a highly contagious infection that is transmitted by virus-laden respiratory aerosols, which are expelled during coughing and sneezing. It is a seasonal illness that affects all age groups, with epidemics occurring mainly during the winter months. The seasonality of influenza infections may be related to behavioral factors influencing exposure, including indoor crowding because of bad weather and possibly the prolonged survival of the virus in aerosol at lower temperatures.

Although the bronchial epithelium is the primary site of viral replication, the spectrum of influenza infections can vary widely, from asymptomatic to serious respiratory tract illness with systemic symptoms as a result of the host response to infection. In uncomplicated influenza, the systemic signs of illness include fever, malaise, chills, headache, myalgia, dizziness, and loss of appetite. Acute respiratory symptoms include unproductive cough, sore throat, and nasal congestion.

People with underlying diseases such as asthma and/or chronic obstructive pulmonary disease (COPD), cardiovascular disease, diabetes, the elderly, and the very young are considered to be at higher risk for complications of influenza. In these individuals influenza may exacerbate an underlying condition or predispose them to secondary bacterial infections and pneumonia. Influenza epidemics are normally accompanied by increased hospitalizations and mortality rates with concomitant increases in demands on healthcare resources.

The control of influenza and its associated complications is therefore an important public health and economic goal. This review will concentrate on the strategies used for the management of influenza in patients with asthma or COPD. This group of patients is considered at greater risk of developing influenza-related complications because their airways are already compromised.

EPIDEMIOLOGY OF INFLUENZA-RELATED MORBIDITY AND MORTALITY

A review of the US national data on influenza suggests that an average of

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approximately 114,000 hospitalizations and 20,000 deaths per year are related to influenza.[1] During the 1978 to 1981 influenza epidemics, the rate of hospitalization for acute respiratory disease in Houston, Texas was shown to be approximately 93 in 100,000 for otherwise healthy persons compared with 197 in 100,000 for persons with high-risk conditions, including those with chronic pulmonary disorders.[2] Those older than 65 years with pulmonary disease had the highest rates of hospitalization (875 in 100,000), and the rate was 275 in 100,000 for people 45 to 64 years.[2] Only 23% of the patients hospitalized for acute respiratory disease were >65 years; however, this age group accounted for 60 to 70% of persons who died during influenza epidemics.[3] During two other epidemics, 1968 to 1969 and 1972 to 1973, influenza-related mortality in Portland, Oregon, was low in otherwise healthy adults between 45 and 64 years (approximately 2 in 100,000), but increased to 870 in 100,000 in those older than 45 years with underlying cardiovascular and pulmonary disease.[4]

In the Netherlands, data from influenza epidemics from 1967 to 1991 showed that influenza was responsible for an average of 2,360 deaths per year. The average incidence of excess influenza-related mortality increased with age: 0.7 in 100,000 for age group 0 to 59 years, 18 in 100,000 for ages 60 to 69 years, 58.2 in 100,000 for ages 70 to 79 years, and 206.6 in 100,000 in those older than 80. Of those yearly influenza-related deaths (2,360), 17% had lung disease (pneumonia, asthma, and/or COPD) registered as the primary cause of death. Approximately 95% of these deaths occurred in the elderly (older than 60 years).[5]

A retrospective study of children younger than 15 years of age with asthma and other medical conditions was performed to evaluate the rates of hospitalization for acute cardiopulmonary disease, outpatient visits and antibiotic courses from 1937 to 1993.[6] In this study, influenza accounted for a mean of 19, 8, and 2 excess hospitalizations for cardiopulmonary disease yearly per 1,000 high-risk children aged <1 year, 1 to 3 years, and 3 to <15 years, respectively. For every 1,000 children, an annual estimate of 120 to 200 outpatient visits and 65 to 140 antibiotic courses were attributed to influenza.[6]

INFLUENZA IN PATIENTS WITH ASTHMA AND/OR COPD

Asthma and COPD are complex respiratory conditions, associated with airflow limitation in affected individuals. The pathology of both conditions is characterized by chronic inflammation of the bronchial mucosa (although the inflammatory cell profiles associated with this inflammation are not the same), and as such, can be exacerbated by allergens, irritants, or infections of the airways. COPD is an umbrella term encompassing airway disease, usually as a consequence of tobacco smoking and including chronic bronchitis, emphysema, and small airway disease. These conditions may be present independently or together, to variable degrees, in an individual patient. The progressive and irreversible (or less reversible) nature of the airflow limitation in COPD is in marked contrast to the impaired airflow in asthma that is at least partly reversible either spontaneously or with treatment.

The cause of most asthma and COPD exacerbations remains controversial despite numerous studies. However, respiratory viruses including influenza have been detected in up to 80 to 85% of wheezing episodes in children[7] and approximately 50% of asthma exacerbations in adults.[8] Further, there are concerns that influenza can consistently precipitate exacerbations of asthma or COPD in children and adults. A longitudinal prospective study by Roldaan and Masural[9] in 32 children (9 to 16 years) with atopic disease requiring regular or maintenance treatment with oral corticosteroids showed that of the 58 (18 of proven viral origin) clinical episodes of symptomatic respiratory infections studied, 39 resulted in an asthma exacerbation. Influenza A was the most frequently detected virus, accounting for 13 of 18 (72%) of the symptomatic respiratory viral infections. All influenza A infections caused asthma exacerbation, some of which were severe with decreases in forced expiratory volume in 1 second (FEV_1) of >50%.[9]

Similarly in adults, Teichtal et al[10] found that influenza A and B viruses accounted for 61% of all viral organisms detected by nasopharyngeal aspirates culture and viral serology in adults hospitalized because of their asthma. Overall, influenza infection accounted for 19% of all respiratory tract infections detected. In another study of 47 patients hospitalized because of an asthma or COPD exacerbation, Philit et al[11] reported that the influenza virus (26%) was the most frequently discovered respiratory infection. Consistent with this, data collected from several studies show influenza A and B infection rates up to 28% in COPD exacerbations.[12]

Pulmonary function is most compromised during the acute stage of influenza illness, the first 5 days.[9,13] The time-course of the fall in FEV_1 in children with asthma during influenza A or B infection, from preinfection to convalescence, is shown in Figure 1 (adapted from Kondo and Abe[13]). The reduction seen in FEV_1 is greatest during the first 2 days of illness, with improvements occurring thereafter. Kondo and Abe[13] showed that 15 of 20 children hospitalized because of uncontrollable asthma at home experienced a decrease in FEV_1 >20% from baseline during the acute stage. The mean maximum decrease in FEV_1 on the second day of illness was 30.3 ± 10.9% for the total influenza positive group; subgroup analysis showed similar declines in FEV_1 of 28.9 ± 10.3% and 32.0 ± 12.2% for influenza A and B groups, respectively.[13] The time-course for the decline in FEV_1 was similar to that reported by Roldaan and Masural,[9] but the observed declines were greater, ranging from 55 to 75% in three asthmatic children with influenza A.

In patients with COPD, Smith et al[14] expressed concerns that infections with influenza viruses produce the greatest

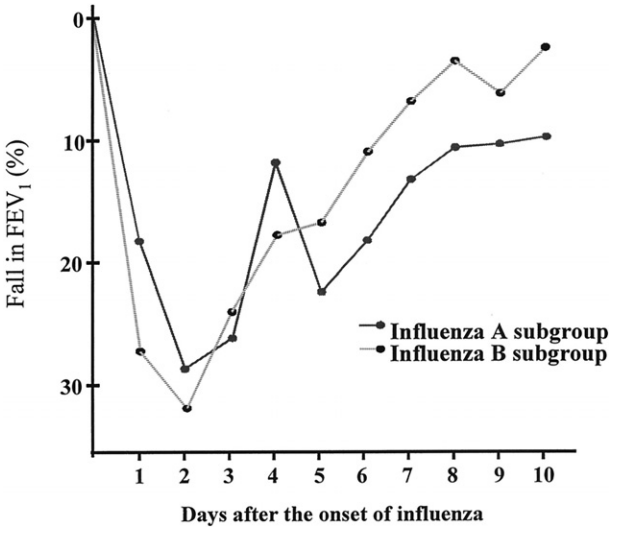

Figure 1. Time-course for the changes in FEV_1 in children with influenza.[13]

decreases in pulmonary function when compared with other respiratory infections. The mean decrease in FEV_1 observed after influenza infections was 118.5 mL compared with 15.2 mL for other respiratory infections and was detectable up to 90 days after infection.[14]

In a retrospective patient survey done in Holland and Norway, Bohnen et al[15] compared the impact of influenza on subjects with asthma and/or COPD to otherwise healthy subjects. Two hundred thirty questionnaires were completed and returned, and of these, 151 were from asthma and/or COPD subjects. For individuals who consulted their doctors, cough was reported to be the most troublesome symptom with 60% of asthma/COPD subjects and 34% of otherwise healthy subjects visiting their doctors as a result. Of interest was that asthma/COPD patients were more likely to receive prescribed medication for their influenza-like illness compared with those who were otherwise healthy (34% vs 23%, respectively; $P = 0.024$).[15]

VACCINATION AGAINST INFLUENZA

Annual influenza vaccination is recommended in most developed countries for all at-risk individuals, including those with persistent asthma or COPD.[16,17] In the general population, when there is a good antigenic match between vaccine and circulating strains, influenza vaccines are 70 to 90% effective in preventing influenza-like illness in otherwise healthy persons <65 years old.[18] The effectiveness of vaccination decreases in the elderly (those >65 years) and in persons with reduced immunocompetence. In a meta-analysis of 20 observational studies, the efficacy of the influenza vaccine for preventing illness in the elderly (>65 years) was estimated to be 56% (95% confidence interval [CI], 39 to 68%).[19]

The number of studies investigating the efficacy of influenza vaccination in patients with asthma or COPD is limited. A study in children (6 to 16 years) with chronic asthma showed significant decreases in the mean days hospitalized per 100 days at risk for influenza-like illness (0.7 vs 2.2 days for vaccinated and nonvaccinated, respectively; $P < 0.01$) and influenza-like illness accompanied with asthma ($P < 0.05$) during subsequent epidemics. However, hospitalization for asthma alone was not affected.[20] In a prospective survey of acute respiratory illness in immunized and nonimmunized high-risk patients, vaccination significantly reduced the incidence of febrile illness by 64% ($P < 0.05$) and total respiratory illnesses by 77% ($P < 0.05$) in patients with chronic pulmonary disease during influenza A seasons.[21]

Sugaya et al[22] conducted a vaccine efficacy study in Japanese children aged 2 to 14 years with moderate to severe asthma (most required regular inhalation of cromolyn sodium and oral ingestion of theophylline). In these patients, vaccine efficacy was 67.5% ($P < 0.01$) against influenza A (H3N2) and 43.7% ($P < 0.01$) against influenza B.[22] However, no difference in the severity or frequency of asthma attacks was noted between the two groups.

Despite the recognition of the importance of vaccination as the gold standard for the prevention of influenza, many persons still become infected during annual epidemics. Several factors such as the patient's age and immunocompetence, the timing of vaccination, and the degree of similarity between the vaccine and the circulating influenza strains may limit the efficacy of vaccination in preventing influenza illness. Further, repeated annual vaccinations are necessary because of the changing antigenic properties of the influenza virus and decline in blood antibody levels. As such, outbreaks of influenza A and B infections do still occur in places such as nursing homes, despite the high resident vaccination rates and a good vaccine-to-circulating-strain match.[23] A recent study, which recruited asthma and COPD patients with influenza-like illness, showed at least 50% of those vaccinated developed laboratory-confirmed influenza infection.[24] Of particular concern, however, are the low vaccination rates in patients with asthma and/or COPD.[25,26] Approximately 15% or less of at-risk patients are vaccinated[25]; an increase to a vaccination rate of approximately 30% can be achieved if patients are reminded when to be vaccinated.[25] Therefore, effective treatments for influenza A and B that are complementary to vaccination are required to prevent influenza-related respiratory illness.

TREATMENT OF INFLUENZA

The antiviral M2 protein inhibitors, amantadine and rimantadine, have

been available in some countries for more than 20 years for the prophylaxis and treatment of influenza A. Both antiviral drugs are available in tablet or syrup form and their recommended dosing regimen is summarized elsewhere.[27] A reduction in the dose is recommended for patients with hepatic or renal dysfunction; such patients should be observed carefully for adverse events.

Placebo-controlled trials have reported efficacy of 50 to 90% in preventing influenza illness for both amantadine and rimantadine against naturally occurring outbreaks of influenza A attributable to H1N1, H2N2, and H3N2 subtypes.[28] Both agents are similarly efficacious for the treatment of acute uncomplicated influenza when treatment is started within 2 days of illness onset; therapeutic benefits include reducing the duration of influenza symptoms such as fever, and more rapid overall functional improvement.[28–32] However, the efficacy for both amantadine and rimantadine is limited by the rapid emergence of drug-resistant variants,[33–35] their ineffectiveness against influenza B, and their poor adverse event profile.[36] Importantly, their effectiveness against severe influenza or in patients at high risk for serious complications of influenza has not been reported in controlled clinical trials.[37]

Because the availability of rapid diagnostic tests for influenza viruses is limited, any new therapeutic drug for the treatment or prophylaxis of influenza needs to be effective against both influenza A and B. A new class of antiviral agents for the management of influenza, the neuraminidase inhibitors, has recently become available. Unlike amantadine and rimantadine, these are potent inhibitors of both influenza A and B virus replication.[38,39] The currently marketed neuraminidase inhibitors are zanamivir (Relenza, GlaxoSmithKline, Uxbridge, UK) and oseltamivir (Tamiflu, Roche Pharmaceuticals, Nutley, NJ). Both these inhibitors have shown efficacy in shortening the duration of illness in patients with confirmed influenza infection.[40–44]

Zanamivir is available as a dry powder inhalation from a Diskhaler device (GlaxoSmithKline). The recommended treatment dose is two inhalations, 5 mg per inhalation for a total dose of 10 mg, twice daily for 5 days. In patients with renal impairment, no dosage modification is required because of its low systemic exposure.[45,46] In contrast, oseltamivir is an oral medication with the recommended dose of one 75 mg capsule taken twice daily for 5 days. The oseltamivir dosage should be reduced to 75 mg once daily in patients with creatinine clearance of <30 mL/minute, and caution is advised when administering to those with creatinine clearance of <10 mL/minute.[47]

The influenza antivirals including zanamivir and oseltamivir should not be considered substitutes for vaccination, but as valuable adjuncts in the prevention and control of influenza.

The efficacy and safety of oseltamivir has been evaluated in patients with chronic cardiac and/or respiratory disease. Martin et al[48] recruited 404 chronic cardiac and/or respiratory disease patients with influenza-like symptoms of $\leq$36 hours duration and randomized to either oseltamivir or placebo. Of these, 251 (62%) had laboratory-confirmed influenza. Treatment with oseltamivir reduced the median time to afebrile state by 1 day compared with placebo (42.8 hours [95% CI: 37.0 to 53.4] vs 67.9 hours [95% CI: 61.1 to 72.0]).[48]

In another study, Murphy et al[24] evaluated the efficacy and safety of zanamivir specifically in patients with asthma and/or COPD. In this study, 525 asthma or COPD patients (aged $\geq$12 years) with influenza-like symptoms of $\leq$36-hour duration were recruited and randomized to either zanamivir or placebo treatment. Of these, 313 (60%) had laboratory-confirmed influenza. Treatment with zanamivir reduced the median time to alleviation of influenza symptoms by 1.5 days compared with placebo in influenza-positive patients (7.0 vs 5.5 days; 95% CI 0.50 to 3.25 days; $P = 0.009$). Importantly, the efficacy of zanamivir in reducing time to alleviation of influenza symptoms was not affected by the patients' age, severity of illness, or underlying asthma/COPD status.[24]

Zanamivir also reduced the mean overall influenza assessment score compared with placebo ($P = 0.004$) over days 1 to 5. Although the study did not have sufficient power to demonstrate a reduction in complications, the use of zanamivir was associated with a trend toward fewer influenza-related complications requiring antibiotic use and a change in respiratory medication. Further, pulmonary function tests suggest that zanamivir more rapidly improves lung function compared with placebo during the acute stage of illness (Fig 2).[24]

In a phase III study,[42] zanamivir shortened the median duration of influenza symptoms by 2.5 days ($P = 0.048$) in high-risk patients, which included mainly (57 of 76, or 75%) patients with respiratory disorders.

A pooled analysis of data on 321 high-risk patients, 222 (69%) of whom had respiratory disease, recruited to zanamivir trials completed before or during the 1998 to 1999 winter season showed a 2.5-day benefit of zanamivir in reducing the median time to alleviation of symptoms in patients with confirmed influenza (7.5 vs 5.0 days; $P = 0.015$). The high-risk patients who were treated with zanamivir returned to normal activities 3 days earlier (7.0 vs 10.0 days; $P = 0.022$) and had an 11% reduction in the median total symptom score over 1 to 5 days ($P = 0.039$) compared with placebo. Further, the incidence of complications requiring antibiotic use was reduced by 43% (relative risk, 0.57; 95% CI, 0.33 to 0.99; $P = 0.045$) in the zanamivir group compared with placebo.[49]

SAFETY OF NEURAMINIDASE INHIBITORS IN ASTHMA AND/OR COPD

In otherwise healthy patients, the use of oseltamivir has been associated with an increase in the incidence of nausea and vomiting compared with placebo

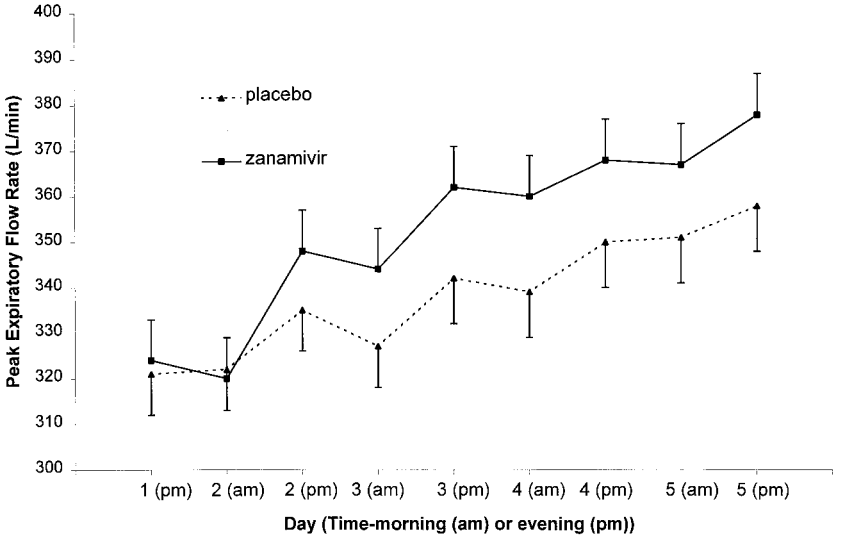

Figure 2. Course of PEFR from days 1 to 5 in patients with influenza, n = 160 for zanamivir group and n = 153 for the placebo group. Data shown are the mean ± standard error of readings taken in the morning (AM) and evening (PM).[24]

(18% vs 7.4%, respectively).[50] Gastrointestinal tolerability of oseltamivir may be improved if taken with food. In clinical studies of otherwise healthy patients (including some high-risk), the safety profile of zanamivir was similar to placebo, with the most commonly reported adverse events being consistent with the symptoms of influenza.[51] In general, the adverse events reported with zanamivir and oseltamivir were mild to moderate in nature and not treatment limiting.

Inhaled zanamivir is well tolerated and in clinical studies of predominantly young adults, it has a safety profile similar to inhaled placebo lactose powder in patients with underlying asthma and/or COPD.[24,42] Similarly, oseltamivir is well tolerated in patients with chronic cardiac and/or respiratory disease.[48]

There have been concerns expressed after postmarketing reports that zanamivir may reduce lung function and induce bronchospasm in patients with asthma and/or COPD. However, Zanamivir is not precluded for treatment of patients with underlying airway disease, but it is recommended that these patients should have a fast-acting inhaled bronchodilator available when inhaling zanamivir and to discontinue treatment if their respiratory symptoms worsen.[45,46] The National Institute of Clinical Excellence in the United Kingdom specifically recommends that patients with chronic respiratory disease, including asthma and/or COPD, who require regular medication may be treated with zanamivir within 48 hours of onset of symptoms during periods when influenza is known to be circulating.[52]

In an earlier study, Cass et al[52] administered zanamivir or placebo to 13 otherwise healthy patients with mild or moderate asthma and found that inhaled zanamivir did not significantly affect pulmonary function or airway responsiveness. Inhaled zanamivir was considered clinically equivalent to inhaled lactose placebo in terms of airway responsiveness, evaluated by comparison of the concentration of methacholine producing a 20% fall in FEV_1 from the postsaline value during methacholine challenge before treatment and after 14 days of continuous administration. Further, zanamivir did not interfere with other concomitant medications that these patients were prescribed for control of their asthma.[53]

The study by Murphy et al[24] in asthma and/or COPD patients with influenza-like symptoms showed that inhaled zanamivir was well tolerated and had an adverse event profile similar to inhaled lactose placebo. Most of the adverse events reported were mild or moderate in nature and typical of influenza illness. There was no evidence to suggest that zanamivir had a deleterious effect on pulmonary function. In fact, zanamivir produced modest improvements in pulmonary function as measured by morning (increase of 13 L/minute, $P = 0.011$) and evening (increase of 13 L/minute, $P = 0.007$) peak expiratory flow rate (PEFR) during the acute stage of illness, days 1 to 5 (Fig 2).[24] Although the increases in PEFR were small, the important observation was that zanamivir did not have an adverse effect on lung function, especially during the first few days of illness when pulmonary function is at its most compromised. There was no difference in the proportion of patients who had a decline (from baseline) in FEV_1 and PEFR of >20% at anytime posttreatment between the zanamivir and placebo groups (13% vs 14%, respectively). Further, larger declines in FEV_1 of >40% from baseline were uncommon (<1% in each treatment group) in patients without laboratory-confirmed influenza, suggesting that marked decreases in pulmonary function are strongly associated with influenza virus infection.[24]

The impact of any influenza management strategy can also be judged by its ability to reduce influenza-related complications. An appropriately designed and powered study with this as the primary endpoint has not been performed, but in patients with asthma and/or COPD, Murphy et al[24] showed a trend for zanamivir to be associated with fewer ($P = 0.064$) influenza-related complications requiring antibiotic use and a change in respiratory medication. The association with fewer influenza-related complications requiring antibiotic use in zanamivir-treated patients is consistent with that observed in otherwise healthy patients.[54] A pooled analysis of high-risk patients (321 patients, 69% with respiratory disease) treated with inhaled zanamivir showed a 43% ($P = 0.045$) reduction for influenza-related compli-

cations requiring antibiotic use without increased risk for asthma exacerbation or increased asthma symptoms.[49]

ACCEPTABILITY OF ZANAMIVIR AND OSELTAMIVIR TREATMENTS

The efficacy and tolerability of zanamivir and oseltamivir treatment have been established in clinical trials. Whereas one study in 73 elderly patients comparing the Turbohaler with the Diskhaler device suggested that most of the patients recruited had some difficulty with the Diskhaler device,[55] >90% compliance to inhaled zanamivir regimen has been observed across all other clinical studies. The results of these studies, in which over 1,500 patients have been randomized, suggest that patients find the topical administration and the Diskhaler device acceptable. Similarly high adherence rates to oseltamivir treatment have been reported. Murphy et al[24] reported good compliance to zanamivir treatment in patients with asthma/COPD, with 94% patients successfully completing at least 4 days of treatment (eight doses). Further, 90% of patients felt that the Diskhaler device was easy or very easy to use.

Information gained from outpatient settings using zanamivir or oseltamivir during the course of typical clinical practice are useful adjuncts to monitor acceptability of treatment to that obtained in clinical trials. However, the use of oseltamivir outside the clinical trial setting has not been reported. For zanamivir, an Australian survey[56] designed to evaluate patients' perception of treatment in clinical practice reported that zanamivir was associated with an early return to normal activities and confirmed the benefits observed in controlled clinical trials. Symptom relief was reported by 77% of patients within 48 hours and approximately two-thirds returned to normal activities within 72 hours. Importantly, no differences were seen between the total population (2,238 responses) and the respiratory disease subgroup (362 responses, 16%) in terms of perceived response to treatment and device use. Patients found the Diskhaler device easy to use irrespective of age; overall compliance was good, with 76% reporting completing 80 to 100% of their treatment, and 90% found the device easy or very easy to use,[56] consistent with clinical study observations.[24]

CONCLUSION

The effective prevention and treatment of influenza in asthma/COPD remains an important goal. Until recently, the management of influenza was limited to vaccination and the use of the M2 inhibitors, amantadine or rimantadine. Vaccination remains the gold standard for prophylaxis against influenza and its use is recommended in patients with asthma and/or COPD. The clinical efficacy of amantadine or rimantadine in patients with asthma and/or COPD has not been specifically studied. In addition, amantadine and rimantadine have not gained wide acceptance because of their poor adverse events profile, the rapid emergence of resistant strains, and their ineffectiveness against influenza B. The development of the neuraminidase inhibitors, zanamivir and oseltamivir, has revolutionized the management options of influenza. Clinical studies have shown that early treatment with zanamivir significantly shortens the duration of influenza illness by 1.5 days in patients with asthma and/or COPD compared with placebo. Similarly for oseltamivir a 1-day benefit to attain afebrile state has been reported for patients with chronic cardiac and/or respiratory disease compared with placebo. Inhaled zanamivir is a well tolerated drug with a safety profile similar to inhaled lactose placebo. Oseltamivir has been associated with increased nausea and vomiting when compared with placebo, but is otherwise well tolerated. Clinical studies have shown both zanamivir and oseltamivir to be acceptable forms of treatment with high compliance rates. Additional patient surveys have shown that zanamivir is also an acceptable treatment in routine clinical practice for the management of influenza in patients with asthma and/or COPD. The neuraminidase inhibitors zanamivir and oseltamivir are useful adjuncts to vaccine for the management of influenza in patients with asthma and/or COPD.

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CME Examination

1–5, Nathan RA, Geddes D, and Woodhead M. 2001;87:447-454.

CME Test Questions

1. What is the primary site of replication of the influenza virus?
   a. Nasal mucosa.
   b. Bronchial epithelium.
   c. Blood.
   d. Muscular epithelium.
2. How many deaths per year are related to influenza in the United States?
   a. 10,000.
   b. 20,000.
   c. 30,000.
   d. 40,000.
3. What is the effectiveness of influenza vaccines that have good antigenic match to the circulating stain in persons <65 years old?
   a. 20 to 30%.
   b. 30 to 50%.
   c. 70 to 90%.
   d. 90 to 100%.
4. What is the mechanism of action of zanamivir?
   a. Neuraminidase inhibitor.
   b. M2 protein inhibitor.
   c. Hemagglutinin inhibitor.
   d. Nucleoside analog.
5. For how many days were influenza symptoms alleviated in a study of zanamivir versus placebo in patients with asthma and/or COPD?
   a. 1.0.
   b. 1.5.
   c. 2.0.
   d. 2.5.

Answers found on page 487.