New Treatments For Influenza

By Richard Ward, MD, CCFP, FCFP

Case 1

The Jones family presents to your office late one Friday afternoon. They are fit-in appointments, arriving in the midst of a busy office. It is the middle of “flu season” on a cold March day. Mrs. Jones informs you the family will be leaving the next day for a much-anticipated trip to Florida. Their eight-year-old son, Jamie, has been sick for three days with “this bug that’s been going around.” His symptoms began with a high fever and body aches. He now has a persistent dry cough, although his fever is “starting to let up.” She is looking for an antibiotic for Jamie so he can recover quickly and enjoy the holiday.

Question:
What is the most likely diagnosis?

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Influenza

Influenza is a significant and common illness that family physicians are faced with on an annual basis. It results in morbidity and mortality in both the “healthy population” and the “high-risk” population. Immunization, the cornerstone of management of influenza A, is a familiar fall ritual to most family physicians.

Influenza circulates predictably once a year during the winter months. The flu usually circulates extensively in a community over a six-week period, and then remains sporadic throughout the year. The timing of this local outbreak varies across the country. Figure 1 shows the Canadian data for flu outbreaks by month.

The diagnosis of influenza A, the most significant of the influenza viruses, is based primarily on clinical grounds. Common clinical findings include the presence of fever > 38.5°C, significant myalgias, dry cough, profound fatigue and headache. Less common symptoms include rhinorrhea, sore throat and gastrointestinal complaints. (Figure 2). When influenza is circulating in the community, a susceptible patient with a cough and fever of higher than 37.8°C has a 79% positive-predictive value of a diagnosis of influenza. The positive-predictive value also increases with a rise in the patient’s temperature. If influenza is circulating in the community, a patient presenting with a 48-hour (or less) history of high fever, cough and influenza-like symptoms is very likely to have influenza, based on this clinical presentation alone.

Case Discussion

You advise Mrs. Jones her son likely has influenza. She has heard that this is contagious and wonders if her 14-year-old daughter, Janessa, might be coming down with the flu. Janessa has just developed a fever and feels achy. Mrs. Jones wonders if she will get the flu. She is less concerned about her husband, who was immunized at work the previous September.

Is it likely the rest of the family will come down with influenza?

Summary

New Treatments for Influenza

• Influenza circulates predictably once a year during the winter months. The flu usually circulates extensively in a community over a six-week period, and then remains sporadic throughout the year.

• Vaccination is 70% to 90% effective in preventing influenza in “healthy” individuals during the years that there is a good match between the vaccine and the circulating virus. Although the efficacy of immunization decreases in the elderly, there is a significant decrease in morbidity in immunized patients who do get the disease.

• The only drug that is currently licensed in Canada for preventing influenza is amantadine. It must be noted that amantadine is only effective for the prophylaxis and treatment of influenza A. It is not an effective treatment for influenza B. Although not approved for prophylaxis in Canada at the time of printing this article, clinical trials have demonstrated the efficacy of both oseltamivir and zanamivir in preventing influenza.

• Aggressive immunization of high-risk individuals and health-care workers for influenza A and B remains the most important public health measure in the war against the “flu bug.”
Influenza circulates throughout the community with an attack rate of approximately 20%. Some studies have demonstrated higher attack rates with certain strains. Children and teenagers suffer the highest attack rate, with studies reporting this as high as 40%. Influenza often first appears in elementary school settings, where a high absenteeism rate often signals the start of “flu season.” The virus quickly spreads to susceptible adults in the family and then into the workplace. The attack rate in families has been reported to vary between 20% and 30%.

Vaccination is 70% to 90% effective in preventing influenza in “healthy” individuals during the years in which there is a good match between the vaccine and the circulating virus. Although the efficacy of immunization decreases in the elderly, there is a significant decrease in morbidity in immunized patients who do get the disease. Therefore, even though there are more vaccine failures in the elderly, they become less ill and have decreased mortality, as compared with non-immunized elderly patients who contract influenza. This significant clinical efficacy is what is important in reducing complications of influenza in the elderly.

The “younger, healthy” population will be protected for as long as six months following vaccination. This has significance when considering when to immunize in the community. Early immunization and a late flu season will increase the number of susceptible individuals in the population. There are no current recommendations regarding a second immunization for high-risk patients if a late-season flu were to occur.

Unique strains of influenza A are defined by their characteristic surface glycoproteins that confer antigenic differences. (Figure 3). The hemagglutinin and neuraminidase surface glycoproteins also play a major role in the virus’ rate of infection. They have been identified and uniquely characterized numeri-
Cally. The Asian/57 virus (H2N2) and the Hong Kong virus (H3N2), therefore, share structurally similar neuraminidase glycoproteins, but have dissimilar hemagglutinin surface glycoproteins.

The effectiveness of immunization is based on the accuracy of the prediction of the circulating strains of influenza. The vaccine is comprised of several strains of influenza A and B that are likely to be circulating within the community. If a strain circulates that is not in the vaccine, attack rates will be higher. If a novel strain of influenza A appears and infects the human population, the illness will be severe and widespread, since there will be no native immunity to the new virus. This could lead to a pandemic. The last pandemic in 1968/1969 resulted from the new presence of H3N2 — the Hong Kong flu. The mortality from an influenza pandemic is significant. In the 1918/1919 pandemic, 20 million to 40 million people died worldwide. Infectious disease experts predict another influenza pandemic is due to occur.

**Treatment**

Mrs. Jones looks down at a very ill Jamie and says: “Our family has been planning this vacation for a long time. Isn’t there something that you can give us?”

How do you respond?
There are three antiviral drugs that are currently licensed for the treatment of influenza A — amantadine, oseltamivir and zanamivir. Two of these drugs, oseltamivir and zanamivir, are also approved for the treatment of influenza B. Amantadine has been shown to be effective in the treatment of influenza A, as compared to placebo, by shortening the duration of fever by one day. The effectiveness of amantadine is contingent upon initiation of therapy within 48 hours from the onset of symptoms. Tolerance of amantadine is limited by side effects, including neurological and gastrointestinal problems. The development of transmissible, amantadine-resistant strains has been reported in closed settings, where the index case was treated with amantadine.

Oseltamivir and zanamivir are two novel drugs currently licensed in Canada for the treatment of influenza A and B. Like amantadine, these drugs must be started within 48 hours of the onset of symptoms in order to be effective. These drugs belong to a new class of antiviral drugs that inhibit viral neuraminidase. Neuraminidase has two important features. It confers antigenicity and plays a crucial role in the spread of the virus in the host.

Functionally, the neuraminidase surface glycoprotein allows viral particles to release from infected human cells. The surface protein binds with infected host cells, allowing viral particles to escape. Neuraminidase inhibitors combine with these surface proteins, preventing release and, therefore, limiting the spread of the virus within the host. This decreases the rate of infection and the morbidity associated with the infection. The effectiveness of the neuraminidase inhibitors is maintained, regardless of the strain of the influenza virus. (Figure 4). They are effective in both influenza A and B viruses.

Studies of oseltamivir and zanamivir have demonstrated a decrease in the severity and duration of symptoms of influenza A and B when infected individuals are treated within the first 48 hours of the onset of symptoms. Resistance does not appear to be a clinical concern with either medication.4,7

In two large placebo-controlled trials, oseltamivir was shown to reduce the duration of symptoms of laboratory-confirmed influenza A and B from a medium duration of 103 hours in placebo groups to 70 hours in treatment groups.3,4 There was also a reduction in physician-diagnosed complications, a decrease in the need for antibiotics for complications and a more rapid return to normal activities in the treatment group, as compared with the control group.

Further analysis showed early treatment with oseltamivir resulted in a greater reduction in symptoms. Initiation of oseltamivir within the first 12 hours of the onset of symptoms resulted in a median duration of illness of 4.5 days, as compared to those subjects who started treatment later in the illness. Those who initiated
Influenza therapy at 48 hours took 7.6 days to recover. The earlier the treatment, therefore, the more effective the results in achieving rapid symptom resolution.

Oseltamivir is generally well-tolerated, although nausea and vomiting were more common in treatment groups, as compared to controls. Nausea was as high as 12% in the treatment group receiving 75 mg twice daily (bid) versus 7.4% in the control, and vomiting 10% versus 3% in the placebo group. Nevertheless, the withdrawal rate was the same in the treatment and placebo groups.

The recommended dosage of oseltamivir in Canada is 75 mg bid. Studies performed in children (dosage of 2 mg/kg bid), however, suggested that this drug is safe, well-tolerated and effective in children. A liquid form is available in the United States, where it is licensed for treatment in children.

Zanamivir is an inhaled neuraminidase inhibitor with minimal systemic absorption. It is delivered through an inhaler device, with its activity directly on the site of viral replication in the respiratory epithelium.

In six studies that looked at the effectiveness of zanamivir 10 mg bid for five days, pooled results indicated a reduction in the mean time to alleviation of symptoms from six days in placebo subjects to five days in treated volunteers (i.e., a reduction of 16%; p < 0.001). Zanamivir was extremely well-tolerated. Reported side effects did not differ from placebo.

While zanamivir is not licensed for use in the pediatric population in Canada, the safety and efficacy in healthy children aged five to 12 has been studied. Results in the children were similar to those adults, with a decrease in the time-to-symptom resolution. Furthermore, there was a reduction in both the complication rate and antibiotic use in children who were treated with zanamivir, as compared with those who received placebo.

In summary, neuraminidase inhibitors seem to be equally effective in reducing the duration of influenza symptoms when treatment is initiated within 48 hours of the onset of symptoms.

The physical examination is negative. You explain that antibiotics will not help Jamie, as you feel that he has had influenza A for more than 48 hours. You offer to treat Janessa for suspected influenza A. Mrs. Jones wonders if she or her husband can take something to prevent them from getting sick?

What would you do?
Study Results

The only drug that is currently licensed in Canada for preventing influenza is amantadine. It must be noted that amantadine is only effective for the prophylaxis and treatment of influenza A. It is not an effective treatment for influenza B.

The Cochrane consensus concluded that oral amantadine, compared to placebo was 61% efficacious in preventing influenza cases, defined clinically and with laboratory testing, and 23% efficacious in preventing clinically defined influenza.1

Although not approved for prophylaxis in Canada at press time, clinical trials have demonstrated the efficacy of both oseltamivir and zanamivir in preventing influenza.6,7 Zanamivir reduced the incidence of family members developing influenza after one household member came down with the flu. Zanamivir was given at a dose of 10 mg inhaled daily for 10 days. It reduced influenza in these household contacts by 79%. Contacts, who were treated with zanamivir prophylactically, but still came down with the disease, had a shorter and less severe illness, as compared with placebo groups.8 This study supports the prophylactic use of zanamivir in families where a member has influenza A or B.

In reviewing available studies, the Cochrane group concluded that the neuraminidase inhibitors were 74% effective, as compared to placebo, in preventing clinically defined influenza.8 Neither is licensed for this use in Canada, however. Both drugs have been studied in children over five years of age. The medications appear to be effective and safe in these age groups, although neither has been approved for this age group.

The Waiting Game

You decide to offer prophylactic treatment to Mr. and Mrs. Jones. Upon leaving your office, Mrs. Jones remarks: “It’s a good thing we were going away on holidays and came in today. Normally, we would have waited it out for a few days to see if things got better.”

Given the importance of timing in the treatment of influenza with the new neuraminidase inhibitors, how might your practice change?

The advice most physicians give patients who develop viral respiratory illness is to wait a few days from the onset of symptoms to see if the illness improves. Clearly, this approach does not lend itself to the optimal use of the new antiviral treatments for influenza. Should primary-care physicians change their office triage system and educate patients to present early when respiratory symptoms develop during flu season? Will the optimum role for neuraminidase inhibitors be for prophylactic treatment of family members and other patients who have been in contact with influenza sufferers?

Conclusion

The neuraminidase inhibitors offer a safe, well-tolerated and reasonably effective tool in the treatment of adult patients with influenza A and B, providing they present within 48 hours of the onset of symptoms. There is probably also a role for the prophylaxis of patients who are exposed to influenza A and B and also for the treatment
of children, although neither drug is approved for these indications in Canada.

Since there are no head-to-head trials comparing the efficacy of the two neuraminidase inhibitors with each other or with amantadine, physicians will have to weigh the features of ease of administration, cost and tolerability to decide on appropriate management for patients with influenza.

Aggressive immunization of high-risk individuals and health-care workers for influenza A and B remains the most important public health measure in the war against the “flu bug.”

References