PharmaNote®

Vol. 34, Issue 9 June 2019 Established 1985

Baloxavir marboxil (XOFLUZA®) and the Management of Uncomplicated Influenza

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Influenza (seasonal flu) is an acute respiratory illness that is caused by the influenza virus. Although influenza viruses can be detectable throughout the year, flu season is typically prevalent in the months of October through March. Centers of Disease Control (CDC) has monitored flu activity for a 36-year period ranging from 1982/1983 through 2017/2018 flu seasons. In the 36 year period, flu activity has peaked in February (15 seasons out of 36 seasons) followed by December (7 seasons), January (6 seasons), and March (6 seasons).[1] In the 2017/2018 flu season alone, the CDC estimates that 48.8 million people were infected with influenza, 959,000 hospitalizations, and 79,400 deaths from influenza. Influenza A is usually predominant from October through February, whereas influenza B viruses predominated from March onward.[2] Strains that cause influenza vary from year to year and even within months of each season. The burden of influenza has been elevated since the 2009 pandemic in terms of number of symptomatic illnesses, medical visits, hospitalizations and death. There are four types of influenza viruses A, B, C and D. Influenza type A and B are responsible for seasonal epidemics in the United States. Influenza virus is transmitted through droplets from people infected with influenza through coughing, sneezing, or talking and can spread to others up to 6 feet away. Symptoms from influenza begin 2 days after the virus is transmitted to the person, and that person can pass the influenza virus to others before signs and symptoms appear.[3] Common signs and symptoms of influenza include fever, cough, sore throat, rhinitis, fatigue, muscle pain or headaches.

Treatment for influenza consist of antivirals and non-pharmacological options. Common antivirals used for influenza include oseltamivir (TAMIFLU®), others less commonly used are zenamivir (RELENZA DISKINHALER®), and peramivir (RAPIVAB®). Adamantanes (Amantadine and Rimantadine) are not recommended for influenza due to increasing resistance from influenza type A strains. Treatment should be initiated with antivirals within 48 hours of the appearance of symptoms to prevent complications of influenza, which can include viral pneumonia, exacerbations of asthma or COPD, secondary bacterial pneumonia, or otitis media.[5] The purpose of this article is to discuss the newly FDA approved drug, baloxavir marboxil (XOFLUZA®), for the treatment of uncomplicated influenza and to briefly review the current treatment options of oseltamivir (TAMIFLU®), zenamivir (RELENZA DISKINHALER®), and Peramivir (RAPIVAB®) for influenza.

Flu Prevention with Vaccines

The CDC recommends obtaining a flu shot yearly for individuals who do not a contraindication to the flu.[6] The influenza vaccine should be administered during the start of the flu season in October and offered to everyone over 6 months of age, especially to those individuals who are at high risk of developing flu related complications. These high risk individuals are children younger than 5, adults who are 65 or older, pregnant women, and residents of long-term facilities. Other individuals with asthma, chronic obstructive pulmonary disease (COPD), heart disease, weakened immune system, blood disorders, kidney disorder, and liver disorder should all receive the flu vaccine.[6]

Due to the varying strains of influenza each year, the influenza vaccine effectiveness can vary from year to year. Recent studies show that flu vaccination can reduce the risk of flu illness by 40% to 60%, when the most prevalent circulating influenza viruses are well matched to the flu vaccine.[9] When the flu vaccine is not well matched with the circulating influenza virus, the flu vaccine may provide little (vaccine effectiveness of 10%) or no benefit. Virus effectiveness studies have shown that flu vaccines provide better protection against influenza B and influenza A (H1N1) viruses rather than influenza A (H3N2) virus. This is believed to be due to the fact that influenza A (H3N2) have more genetic changes yearly than other types of influenza strain, which makes matching for the virus difficult in terms of influenza vaccine production. Protection provided from the influenza vaccine is thought to persist for at least 6 months. Protection declines over time because of decreasing antibodies and because of changes in the circulating influenza virus from year to year.[10]

There are three types of influenza vaccines available: inactivated influenza vaccine (IIV), recombinant influenza vaccine (RIV), or live attenuated influenza vaccine (LAIV). No preference is given for any influenza vaccine over another. A trivalent and

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quadrivalent flu vaccine are both available. For children receiving their first flu shot, CDC recommends a two-dose flu shot that are four weeks apart.[10]

Flu vaccine can keep the general population from getting sick and it can reduce the risk of flu associated hospitalization by 37% and can reduce the risk of ICU admission by 82%. Obtaining the flu vaccine can also help protect the people around those vaccinated, especially those people who cannot obtain a flu shot due to an absolute contraindication. Common side effects of the flu shot include soreness, redness, swelling, fever and aches. Common side effects of the nasal flu vaccine include runny nose, wheezing, headache, vomiting, fever, sore throat, and cough.[11]

Baloxavir Marboxil Overview

Pharmacology

Baloxavir marboxil is a prodrug that is converted to the active metabolite baloxavir by hydrolysis, which has anti-influenza activity. Baloxavir inhibits the endonuclease activity of polymerase acid (PA) protein, which is an enzyme in the RNA polymerase complex required for viral gene transcription and subsequently viral replication. The 50% inhibitory concentration (IC_{50}) of baloxavir was 1.4 to 3.1 nM (n=4) for influenza A viruses and 4.5 to 8.9 nM (n=3) for influenza B viruses in a PA endonuclease assay. The median IC_{50} values of baloxavir were 0.73 nM (n=19; range: 0.20-1.85 nM) for subtype A/H1N1 strains, 0.68 nM (n=19; range: 0.35-1.87 nM) for subtype A/H3N2 strains, and 5.28 nM (n=21; range: 3.33-13.00 nM) for type B strains. Amino acid substitutions in the PA protein will result in reduced susceptibility to baloxavir. The relationship between antiviral activity in cell culture response to treatment in humans has not been established.[12]

Pharmacokinetic of baloxavir marboxil are listed in **Table 1**.[12] In a phase 3 trail, a 40 mg dose in patients infected with influenza and weighing less than 80 kg resulted in a baloxavir C_{max} and $AUC_{0\text{-}inf}$ of 96.4 ng/mL and 6160 ng·hr/mL, respectively. In patient weighing 80 kg and more, a 80 mg dose was given and the baloxavir C_{max} and $AUC_{0\text{-}inf}$ were 107 ng/mL and 8009 ng·hr/mL, respectively. Individuals with a creatinine clearance (CrCl) of ≥50 mL/min do not require a dosing adjustment. Dosing for patients with a CrCl ≤50 mL/min has not been evaluated and needs to be assessed. Individuals with moderate hepatic impairment (Child-Pugh Class B) and normal hepatic function did not have any clinically meaningful differences in pharmacokinetics of baloxavir. Use of baloxavir has not been assessed in individuals with severe hepatic impairment.[12]

Table 1 | Baloxavir Marboxil Pharmacokinetics[12]

Parameters	Value
Absorption	
T_{max}	4 hours
Effect of Food (Compared to fasting)	C_{max}: ↓48% AUC: ↓36%
Distribution	
% Protein Bound	92.9—93.9
V_d	1180 L
Metabolism	
Metabolic pathway	UGT1A3 (main) CYP3A4
Elimination	
Half-life	79.1 hours
Urine	18.0%
Feces	80.1%

AUC = area under the curve; **C_{max}** = maximum concentration; **L** = liters; **T_{max}** = median time to maximum concentrations; **V_d** = volume of distribution

Baloxavir Clinical Trials

Baloxavir marboxil is indicated for acute uncomplicated influenza type A and B in patients who are 12 years of age or older who have been symptomatic for ≤48 hour. The indication for baloxavir marboxil comes from a phase 2 and phase 3, multicenter, randomized, double-blinded study (CAPSTONE 1) which compares baloxavir marboxil with placebo or oseltamivir in individuals with uncomplicated influenza infection.[13] The following section will review this trial.

Hayden et al. conducted a single-center, double-blinded (n=400), placebo-controlled, dose-ranging, randomized trial (randomized ratio, 1:1:1:1) of singles doses of baloxavir 10, 20, 40 mg and placebo. The trail enrolled Japanese adults 20 to 64 years of age with acute influenza from December 2015 through March 2016. The majority of the patients (61-71%) were infected with influenza A (H1N1) pdm09 virus. Inclusion criteria in phase 2 study were the following: age greater than or equal to 20 to 65 years, ≤48 hours since onset of flu symptoms (defined as time to first increase in body temperature or time when the patient experiences at least one general or respiratory symptom), positive rapid antigen test (RAT) for influenza with nasal or throat swabs and diagnosis of influenza virus infection, which included a fever (greater than equal to 38 degrees Celsius), one general systemic symptoms (headache, muscle, or fatigue), and at least one of the following respiratory symptoms associated with influenza (cough, sore throat, nasal congestion). Exclusion criteria were severe influenza virus requiring inpatient treatment, an allergy to oseltamivir, weight less than 40 kg, women who are pregnant, breastfeeding, or have a positive pregnancy test at enrollment, subjects with concurrent infections requiring antimicrobial therapy, concurrent infections requiring antimicrobial treatment, or specific comorbid conditions (chronic respiratory diseases, neurological and neurodevelopmental disorders, heart disease, liver disorders or kidney disorders).[13]

Patients were assessed four times daily for day 1 of treatment to day 3 and patients were assessed twice daily from day 4 to day 14. Baseline characteristic were comparable in both groups with no statically significant differences. The primary endpoint of this study was time to alleviation of influenza symptoms (duration of influenza). The median time to alleviation of symptoms in each of the baloxavir dose groups was reported as 54.2 hours in the 10-mg group, 51.0 hours in the 20-mg group, and 49.5 hours in the 40-mg group which were all significantly shorter than in the placebo group (77.7 hours) (P=0.009, P=0.02, and P=0.005, respectively). All three baloxavir dose groups had greater reductions in influenza virus titers compared to placebo. The median reduction of baloxavir after one day of administration of baloxavir was 4.5 $\log_{10}$ 50% tissue-culture infective dose ($TCID_{50}$) per milliliter in the baloxavir 40-mg group, as compared with 1.6 $\log_{10}$ $TCID_{50}$ per milliliter in the placebo group. There was no exposure-response (time to alleviation of symptoms) relationship that was observed. There were no differences in rates of adverse events when comparing baloxavir to placebo or between the different doses administered.[13] Common adverse events seen in this trial include headache (4%), diarrhea (2%), vertigo (2%), and naso-

pharyngitis (1%). Baloxavir Marboxil 40 mg was the approved dose due to decreased median time to alleviation of symptoms compared to baloxavir 10 and 20 mg and also due to similar adverse events when compared to baloxavir 10 and 20 mg.[13]

The phase 3 trial (CAPSTONE-1) was multicenter, duble blinded, placebo and oseltamivir-controlled, randomized trial that enrolled ambulatory patients 12 to 64 years of age with uncomplicated influenza infection (defined as influenza not requiring inpatient treatment or influenza without any accompanying exacerbation of underlying chronic illness) and took place in United States and Japan from December 2016 to March 2017. Patients (n=1436) were randomly assigned in a 2:2:1 ratio to receive a single dose (dosing of baloxavir marboxil is weight based, 40 mg for weights between 40 kg to 80 kg and 80 mg for weights >80 kg.) of baloxavir marboxil and 4 days of placebo, oseltamivir (75 mg twice daily for 5 days), or placebo for five days. The primary objective of this study is to evaluate the efficacy of a single, oral dose of Baloxavir Marboxil compared with placebo by measuring the time to alleviation of symptoms in patients with uncomplicated influenza virus infection. Inclusion criteria in the phase 3 study were identical to those included in the phase trial.[13]

The primary efficacy end point was the time to alleviation of symptoms, which was defined as the time from the start of therapy to the time when all seven influenza-related symptoms. These were rated by the patients as absent or mild for at least 21.5 hours. The seven influenza-associated symptoms assessed by the patients were cough, sore throat, headache, nasal congestion, feverishness or chills, muscle or joint pain, and fatigue. They were rated on a 4 -point scale, with 0 indicating no symptoms, 1 mild symptoms, 2 moderate symptoms, and 3 severe symptoms. The secondary outcomes included time to resolution of fever, the time to a return to baseline health, and newly acquired complications leading to antibiotic use.[12] The secondary efficacy analysis also compared the time to alleviation of symptoms between baloxavir marboxil and oseltamivir.[13]

Patients (n=1436) were randomized into either baloxavir (n=612), oseltamivir (n=310), or placebo group (n=514), 1366 patient completed the trial. After confirming an influenza infection by RT-PCR assay, patients taking baloxavir (n=456), oseltamivir (n=231), or placebo group (n=377) were included in the intention to treat analysis. There was no relevant differences seen in basline characteristics among the treatment groups. Influenza A (H3N2) virus accounted for 84.8 to 88.1% of infections in the three groups, while Influenza H1N1 accounted for 0.5% to 3% of infections in the three groups. Influenza B accounted for 1.3 to 1.8% of infections in the three groups. The majority of patient included in this trial were enrolled in Japan (77.2%).[13]

Baloxavir marboxil was superior to placebo in alleviating influenza symptoms quicker in patients with uncomplicated influenza (53.7 hours vs 80.2 hours, p<0.001). A shorter time to alleviation of symptoms with baloxavir was observed when compared to placebo in both adolescents who are 12-19 years of age (median difference, 38.6 hours; p=0.006) and adults who are 20-64 years of age (median difference, 25.6 hours). The difference in the time to alleviations of symptoms between baloxavir group and the placebo group was greater in patients who initiated the trail regimen within 24 hours after symptom onset (median difference, 32.8 hours; p<0.001) compared to the patients who initiated baloxavir after 24 hours of symptom onset (median difference, 13.2 hours). The median time to alleviation of symptoms was similar in the baloxavir group (53.5 hours) and the oseltamivir group (53.8 hours). The median time to the resolution of fever was shorter with baloxavir than with placebo (24.5 hours vs 42.0 hours, p<0.001). There were no deaths that occurred during this trail. Baloxavir was associated with significantly more rapid decline in infectious viral load than placebo or oseltamivir. The first day after initiation of the treatment regimen, the median reductions from baseline were 4.8, 2.8, and 1.3 $\log_{10}$ $TCID_{50}$ per milliliter in the baloxavir, oseltamivir, and placebo groups, respectively. These reductions were significantly greater (p<.001) in baloxavir compared to placebo and oseltamivir. Results of the primary and secondary efficacy outcomes are summarized in **Table 2**.[13]

Safety

In terms of adverse events, the most commonly reported for baloxavir marboxil, were diarrhea (3%), bronchitis (2%), nausea (1%), nasopharyngitis (1%) and headaches (1%).[13] The previously approved neuraminidase inhibitors have shown neurological and

Table 2 | Summary of Primary and Secondary Endpoint of the CAPSTONE-1 Clinical Trial[13]

Phase 3 Trial Outcomes	Intervention	Outcomes	Comparison Results
Time to alleviation of symptoms[a]	Baloxavir (n=507)[b] 40 or 80 mg x1 dose Oseltamivir (n=514) 75 mg twice daily x 5 days Placebo (n=231)	Baloxavir: 53.5 hours[c] (95% CI, 48.0 to 58.5) Oseltamivir: 53.8 hours (95% CI, 50.2 to 56.4) Placebo: 80.2 hours (95% CI, 72.6 to 87.1)	Baloxavir difference from placebo: 26.5 hours (95% CI, 17.8 to 35.8) No comparison statistics between baloxavir and oseltamivir reported
Time to Cessation of Infection Virus Detection	Baloxavir (n=351)[b] Oseltamivir (n=357) Baloxavir (n=426)[d] Placebo (n=209)	Baloxavir: 24.0 hours Oseltamivir: 72.0 hours Placebo: 96.0 hours	Baloxavir compared to both oseltamivir and placebo: p<0.001

a: The time to alleviation of symptoms was defined as the time from the start of the trial regimen to the time when all seven influenza-related symptoms were rated by the patients as absent or mild for at least 21.5 hours. The seven symptoms were the following: cough, sore throat, headache, nasal congestion, feverishness or chills, muscle or joint pain, and fatigue. **b**: Intention-to-treat infected population and adults 20-64 years. **c**: Values represent median time. **d**: Randomized patient population

behavioral adverse reactions (hallucinations, delirium and abnormal behavior), however, currently there are no reports of these in the baloxavir mardboxil trials.[13]

Warnings and Precautions

Baloxavir marboxil has only been shown to be efficacious for influenza. Serious bacterial infections may begin with influenza-like symptoms, may coexist with, or occur as a complication of influenza. Baloxavir marboxil has not been shown to prevent bacterial infections. In phase 3 clinical trials, the frequency of complications in antibiotic treatment was low (3.5% with baloxavir, 4.3% with placebo, and 2.4% with oseltamivir).[13]

Dosing and administration

Baloxavir marboxil is taken orally as a single dose and may be taken with or without food. The dosing of baloxavir marboxil weight based, 40 mg for weights between 40 kg to 80 kg and 80 mg for weights >80 kg.[11] Baloxavir marboxil comes in both a 20 mg (2 tablets of 20 mg tablets per blister card or 4 tablets of 20 mg tablets per blister card) and 40 mg tablet (1 tablet of 40 mg per blister card or 2 tablets of 40 mg per blister card). Co-administration with dairy products, calcium-fortified beverages, polyvalent cation medication such as laxatives, antacids, or oral supplements that contain calcium, iron, magnesium or zinc should be avoided as cation-containing products may decrease plasma concentration of baloxavir marboxil resulting in a decrease in baloxavir marboxil efficacy. Avoid coadmSafety and efficacy in patients less than 12 years of age or weighing less than 40 kg has not been established for baloxavir marboxil.[13]

Oseltamivir

Oseltamivir (TAMIFLU®) is one of the most prescribed medication for an influenza infection. Oseltamivir is indicated, like baloxavir marboxil, for the treatment of acute uncomplicated influenza infection in patients 2 weeks or older and who have been symptomatic for no more than two days. Oseltamivir is a prodrug and is converted to the active drug oseltamivir carboxylate, which inhibits the influenza virus enzyme called neuraminidase and prevents the release of the virus. This prevents further viral replication and infections of the host cell.[14]

Oseltamivir, like baloxavir marboxil, should be initiated within 48 hours of symptoms of influenza virus. The recommended dose of oseltamivir for adults and children over 13 years of age is 75 mg twice daily for 5 days. In patients who are 2 weeks to 1 year of age, the dose is 3 mg/kg twice daily for 5 days. In patients who are 1 to 12 years of age, dosing is weight dependent. Patients who weigh less than 15 kg, the dose is 30 mg twice daily. For patient who weight 15.1 kg thru 23 kg, the dosing is 45 mg twice a daily. The dose for patients who weight 23.1 kg thru 40 kg, the dose is 60 mg twice daily. Lastly, the dose for patients who weigh 40.1 kg or more, the dose is 75 mg twice daily. In patient who have renal impairment (creatinine clearance between 10 and 30 ml/min), oseltamivir should be dosed as 75 mg once daily.[14]

Oseltamivir was approved by FDA in 1999 based on results from two randomized, double-blinded, placebo-controlled trails. In patients that were randomized to the oseltamivir 75 mg twice daily for 5 days group, there was 1.3-day reduction in time to symptom improvement compared to placebo.[15] A recent double blinded, placebo-controlled trail shows that there may be benefits of using oseltamivir after 48 hours of symptom onset. Oseltamivir did show a reduction in viral load after 48 hours of symptom onset by 12% to 50% regardless of whether treatment was started before or after 2 days of symptom onset when compared with placebo.16 Still its use after 48 hrs of symptoms is not recommended.

Common adverse events of oseltamivir are presented in **Table 3**. In post marketing experience, cases of anaphylaxis and serious skin reactions including toxic epidermal necrolysis, Stevens-Johnson Syndrome, and erythema multiforme. Post marketing reports have also shown neurologic and behavioral system adverse events that includes hallucinations, delirium and abnormal behavior have been reported mostly from Japan in pediatric population. These neurologic and behavioral system adverse events had an abrupt onset and rapid resolution.[14]

Zanamivir

Zanamivir (RELENZA DISKINHALER®) is approved by FDA in 1999 for uncomplicated acute illness due to influenza type A and B in persons who are 7 years or older and have been symptomatic for no more than 2 days. Zanamivir works by inhibiting the influenza virus enzyme called neuraminidase, which releases the viral particles from the host cell. Zanamivir is not recommended for treatment of influenza for individuals with underlying airway disease such as asthma and COPD due to risk of bronchospasm.[17]

Zanamivir is given as 10 mg twice daily (provided by 2 inhalations of one 5 mg blister per inhalation) for 5 days. Marty et al. composed a phase 3 trail that compared zanamivir with oseltamivir. A median time to clinical response of 5.14 days was found in the 600 mg zanamivir group and 5.63 days (difference of −0.48 days, 95% CI −2.11 to 0.97; p=0.39) in the oseltamivir group. Zanamivir was shown to be non-inferior to oseltamivir. Common adverse effects of zanamivir are presented in **Table 3**. Post marketing reports have also shown neurologic and behavioral system adverse events that includes hallucinations, delirium and abnormal behavior have been reported mostly from Japan.[18]

Peramivir

Peramivir was approved in 2014 as an intravenous formulation, indicated for the treatment of acute uncomplicated influenza in patients who are 18 years of age or older within 48 hours of symptom onset. Peramivir works by inhibiting the influenza virus enzyme called neuraminidase, which releases the viral particles from the host cell. Peramivir is given as single 600 mg dose, and it is administered via intravenous infusion for 15 to 30 minutes. Dosing adjustment is required in patients with renal impairments. Patients with a creatinine clearance of 30-49 ml/min should receive a dose of 200 mg, whereas patients with a creatinine clearance of 10-29 ml/min should receive a dose of 100 mg.[19]

Efficacy of peramivir is based on a phase III multicenter, randomized, double blinded controlled trial. The trial compared peramivir (single dose of 600 mg) with oseltamivir and found that when the patients were treated within 48 hours, peramivir was noninferior to oseltamivir. The median times to alleviation of symptoms were 81.0 (95% CI, 72.7, 91.5) and 81.8 (95% CI, 73.2, 91.1) h in the 600-mg-peramivir and oseltamivir groups, respectively. Peramivir groups demonstrated noninferiority to oseltamivir.[20] Although peramivir covers both influenza type A and B, the efficacy trial predominately treated patients with influenza A and there were limited number of subjects infected with influenza B. Post marketing reports have also shown neurologic and behavior-

Table 3 | Comparisons of Antivirals for the Treatment of Acute Influenza

	Oseltamivir	Baloxavir Marboxil	Zanamivir	Peramivir
Mechanism	Neuraminidase Inhibitor	Endonuclease Inhibitor	Neuraminidase Inhibitor	Neuraminidase Inhibitor
Formulations	Oral Capsule Oral Suspension	Oral Tablet	Inhalation Powder	Intravenous
Common Adverse Events	nausea (10%) vomiting (9%) diarrhea (7%) bronchitis (2%) abdominal pain (2%) dizziness (2%) headache (2%) cough (1%) insomnia (1%) fatigue (1%)	diarrhea (3%) nausea (3%) bronchitis (2%) cough (2%) sinusitis (3%) dizziness (2%)	diarrhea (3%) nausea (3%) Sinusitis bronchitis (2%) cough (2%) headache (2%) urti (1%)	diarrhea (8%) neutropenia (8%) constipation (4%) elevated hepatic enzymes (3%) hyperglycemia (5%) insomnia (3%) fever (2%)
Cost[a]	$13.66 - $15.46 per capsule	$150 per treatment	$63.95 per treatment	$19.00 per treatment
Coverage	Influenza A and B	Influenza A and B	Influenza A and B	Influenza A and B
Dosing	Adults: 75 mg BID x 5 days	40-80 kg: 40 mg single dose >80 kg: 80 mg single dose	10 mg BID x 5 days (2 inhalations of one 5 mg blister per inhalation)	600 mg dose intravenous infusion over 15-30 minutes

a: Price listed is estimated retail cash prices from Gainesville, Florida as of May 2019

al system adverse events that includes hallucinations, delirium and abnormal behavior have been reported mostly from Japan.[19]

Antiviral Susceptibility of Influenza Viruses

To assess antiviral susceptibility of influenza viruses with different antivirals, the CDC randomly tested 2,569 influenza virus specimen (304 influenza A, 1303 influenza A, and 962 influenza B viruses) that were collected in the United States during October 2016 to May 2017. All 2569 influenza viruses tested were 100% susceptible to oseltamivir, zanamivir, and peramivir. Due to the presence of no resistance, CDC recommends using anyone of these antivirals for treatment of influenza. Other antivirals like adamantanes (amantadine and rimantadine) are not recommended in influenza treatment due to high resistance (>99%) from circulating influenza A viruses (H3N2 and H1N1).[21]

Discussion

There are a few options of antiviral treatment for an influenza infection (**Table 3**). Baloxavir marboxil is the newest antiviral which appears to be both efficacious and safe to use however use may be limited at this time due to its high cost. Baloxavir marboxil should be used in those patients that cannot tolerate oseltamivir. Baloxavir marboxil should also be used in patients that have an influenza virus strain resistant to neuraminidase inhibitors (Hemagglutinin substitutions associated with influenza A H3N2 and H1N9), as the neuraminidase inhibitors would be ineffective in eradicating the influenza virus.

Oseltamivir remains the most prescribed treatment option for uncomplicated influenza because of its generic pricing and oral availability. Lastly, based on the limited data, it appears that baloxavir marboxil is equally efficacious when compared with other antivirals in terms of time to symptom alleviation. One limitation in the phase 3 trail that led to the approval of baloxavir marboxil, is that the majority of patients included in this trial were enrolled in Japan (77.2%), which limits the generalizability to patients in the US. All antivirals are indicated for influenza virus, as long as they are used within 48 hours of symptom onset.

Conclusion

Individuals who are greater than 6 months of age and who do not have a contraindication to the flu vaccine, should receive the flu vaccine as may prevent or reduce symptoms from the influenza virus. Obtaining yearly flu vaccines will also promote community immunity, where those individuals who are able to obtain the flu shot will be able to protect those individuals who are not able to get the flu shot. Yearly flu vaccine prevents complications from influenza and minimizes healthcare cost by preventing hospitalizations. When an individual is infected with influenza, appropriate treatment with an antiviral may help reduce the time symptoms are present. Baloxavir marboxil is the newest antiviral that is ap-

proved for use in acute uncomplicated influenza and appears to be both safe and efficacious in treating this infection. This new antiviral should remain a viable option when selecting an appropriate antiviral therapy.

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Published by the UF Family Practice Residency Program and the Departments of Community Health & Family Medicine and Pharmacotherapy & Translational Research

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