Antivirals, Influenza
Therapeutic Class Review (TCR)

February 1, 2019

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FDA-APPROVED INDICATIONS

Drug	Manufacturer	FDA-Approved Indications
baloxavir marboxil (Xofluza™)[1]	Genentech	▪ Treatment of acute, uncomplicated influenza in patients ≥ 12 years of age who have been symptomatic for ≤ 48 hours
oseltamivir (Tamiflu®)[2]	Genentech, generic	▪ Treatment of acute, uncomplicated illness due to influenza infection in patients 2 weeks of age and older who have been symptomatic for no more than 2 days ▪ Prophylaxis of influenza in patients older than 1 year of age – There is no evidence for efficacy of oseltamivir in any illness caused by agents other than influenza virus A and B. – Efficacy of oseltamivir in patients who begin treatment after more than 48 hours of symptoms has not been established.
rimantadine (Flumadine®)[3]	Caraco, generic	▪ Prophylaxis and treatment of illness caused by influenza A virus in adults (≥ 17 years older) ▪ Prophylaxis of influenza A virus in patients older than 1 year of age (ages 1 to 16 years)
zanamivir (Relenza®)[4]	GlaxoSmithKline	▪ Treatment of uncomplicated acute illness due to influenza A or B virus in adults and pediatric patients 7 years and older who have been symptomatic for no more than 2 days ▪ Prophylaxis of influenza in patients older than 5 years of age – Not recommended for treatment or prophylaxis for influenza for patients with underlying airways diseases due to risk of bronchospasm – Not proven effective for treatment in patients with underlying airways diseases – Not proven effective for prophylaxis of influenza in nursing home residents

All antivirals for the treatment of influenza should be started as soon as possible and within 48 hours after illness onset to maximize the potential benefit of reducing duration of illness by 1 to 2 days.

Influenza viruses change over time. Emergence of drug resistance could decrease drug effectiveness. Prescribers should consider the most current available drug susceptibility information on influenza and treatment effects when deciding whether to use antiviral therapy.

Due to increased drug resistance and its additional indications for Parkinson's disease and drug-induced extrapyramidal reactions, amantadine is no longer Included in this class review. Rimantadine (Flumadine) is not recommended to be used for influenza prophylaxis due to resistance and is therefore, no longer reviewed here, but will remain listed as it is still available and FDA approved for this indication.

Peramivir (Rapivab™) is approved for the treatment of acute uncomplicated influenza in patients ≥ 2 years and older who have been symptomatic for no more than 2 days.[5] Notably, data for its use is stronger in patients with influenza A compared to influenza B due to fewer cases of influenza B enrolled in its clinical trials. In addition, efficacy is not established in patients with serious influenza requiring hospitalization. Since the focus of the review is on oral medications and the peramivir is administered by intravenous infusion, it is not included in this review.

Antiviral treatment for influenza is not a substitute for annual vaccination for influenza.

OVERVIEW

Influenza is a common illness affecting most people at least once in their lifetime. Influenza is most often self-limiting; however, very young, elderly, or immunocompromised patients are predisposed to secondary complications with potential fatalities. Symptoms include abrupt onset of fever, myalgia, headache, malaise, and respiratory signs and symptoms, including non-productive cough, sore throat, and rhinitis.[6,7] Children may also experience otitis media, nausea, and vomiting. Uncomplicated influenza illness typically resolves after 3 to 7 days for most patients; however, cough and malaise can persist for more than 2 weeks.

The influenza viruses that cause epidemic human disease are influenza A and B, which are separated into subtypes (for A viruses) and lineages (for B viruses). Influenza A viruses are categorized as hemagglutinin (HA) or neuraminidase (NA) based on 2 different surface antigens, while influenza B viruses are separated into 2 distinct genetic lineages; Yamagata and Victoria.[8]

While timing of the onset, peak, and end of influenza activity varies from season to season, annual epidemics of seasonal influenza typically occur in the United States (U.S.) between October and April.[9]

Vaccination

Influenza vaccination is the primary method for preventing influenza and the severe complications associated with influenza.[10,11] The Centers for Disease Control and Prevention' (CDC) Advisory Committee on Immunization Practices (ACIP) annual recommendation since 2010 has been an annual influenza vaccination for all people age 6 months and older, who do not have contraindications, at the beginning of flu season.[12]

For the 2018-2019 season, inactivated influenza vaccines, recombinant influenza vaccine, and live attenuated influenza vaccine (LAIV) are available. Inactivated influenza vaccines are available in quadrivalent and trivalent formulations, while recombinant influenza vaccine and LAIV4 are available in quadrivalent formulations. There is also a high-dose inactivated influenza vaccine and adjuvanted inactivated influenza vaccine available in trivalent formulations.[13] For the 2018–2019 season, the ACIP voted to recommend that providers may administer any licensed, age-appropriate influenza vaccine, including LAIV4 when appropriate; this was a change from the previous 2 seasons (2016–2017 and 2017–2018) during which time the ACIP recommended that LAIV4 not be used. Virus strains included in the 2018–2019 U.S. trivalent vaccines are an A/Michigan/45/2015 (H1N1)pdm09–like virus, an A/Singapore/INFIMH-16-0019/2016 (H3N2)-like virus, and a B/Colorado/06/2017–like virus (Victoria lineage). Quadrivalent vaccines contain an additional influenza B vaccine virus; a B/Phuket/3073/2013–like virus (Yamagata lineage).[14]

Treatment

There are 3 FDA-approved neuraminidase inhibitor antiviral drugs recommended by CDC for the 2018-2019 season: oseltamivir (Tamiflu), zanamivir (Relenza), and peramivir (Rapivab). The fourth recommended FDA-approved product is the cap-dependent endonuclease inhibitor baloxavir marboxil (Xofluza). Adamantanes (amantadine and rimantadine) are not recommended for use in the U.S. due to resistance to these drugs by many influenza A influenza B viruses.[15]

Studies indicate that early antiviral treatment can reduce the risk of complications from influenza, such as pneumonia, respiratory failure, and death.[16] Antiviral treatment is recommended as early as

possible for any patient with confirmed or suspected influenza who has severe, complicated, or progressive illness; is hospitalized; or is at high risk for influenza complications. According to the CDC, oseltamivir (oral or enterically-administered) is the recommended antiviral for patients with severe, complicated, or progressive illness or who are hospitalized. There are not sufficient data for zanamivir (Relenza), peramivir (Rapivab), or baloxavir marboxil (Xofluza) in patients with severe influenza.

Patient groups at high risk for influenza complications include children younger than 5 years of age but especially children younger than 2 years of age; adults 65 years of age and older; women who are pregnant or post-partum (within 2 weeks after delivery); residents of nursing homes and other chronic-care facilities; American Indians; and Alaskan Natives. Additional people at high risk include those with asthma; neurological and neurodevelopmental conditions (brain, spinal cord, peripheral nerve, cerebral palsy, epilepsy, stroke, intellectual disability, moderate to severe developmental delay, muscular dystrophy, or spinal cord injury); chronic lung disease (chronic obstructive pulmonary disease [COPD], cystic fibrosis); heart disease; blood disorders (sickle cell disease); endocrine disorders (diabetes mellitus); kidney disorders; liver disorder; metabolic disorders (inherited metabolic disorders and mitochondrial disorders); weakened immune system due to disease or medication (HIV/AIDS, cancer, those on chronic steroids); younger than 19 years of age who are receiving long-term aspirin therapy; and who are morbidly obese (Body Mass Index ≥ 40).[17] Clinical judgment, based on the patient's disease severity and progression, age, underlying medical conditions, likelihood of influenza, and time since onset of symptoms, is important to consider when making antiviral treatment decisions for high-risk outpatients.[18]

Pregnant women are at a higher risk for severe complications and death from influenza. The CDC recommended treatment with oseltamivir or zanamivir for pregnant women or women who are up to 2 weeks postpartum (including following pregnancy loss) with suspected or confirmed influenza.[19] Treatment can be given during any trimester of pregnancy. The CDC gives preference to oseltamivir is to treat pregnant women. Some providers may prefer zanamivir due to its limited systemic absorption; however, the potential for respiratory complications with zanamivir because of its inhaled route of administration should be considered, especially in women at risk for respiratory problems. The CDC does not recommend baloxavir marboxil (Xofluza) for treatment of pregnant women or breastfeeding mothers as there are no available efficacy or safety data in this population.[20]

In the outpatient setting, antiviral treatment can also be considered for any previously healthy, symptomatic patient not at high risk for influenza complications, who is diagnosed with confirmed or suspected influenza, if treatment can be initiated within 48 hours of illness onset.[21] For acute uncomplicated influenza, oseltamivir (Tamiflu), zanamivir (Relenza), peramivir (Rapivab), or baloxavir marboxil (Xofluza) may be used for treatment. Studies show that treatment initiated early (e.g., within 48 hours of illness onset) is more likely to provide benefit. The decision to treat should be based patient clinical presentation consistent with influenza and on epidemiologic factors.[22] Treatment should not be delayed pending laboratory confirmation of influenza.

In 2018, the Infectious-Diseases Society of America (IDSA) published updated guidelines regarding the management of influenza. Recommendations are similar to those provided by the CDC; however, no recommendations are made regarding baloxavir marboxil, as it was approved after the finalization of the guidelines.[23]

Prophylaxis

According to the CDC, antiviral medications are about 70% to 90% effective in preventing influenza and are useful adjuncts to influenza vaccination, but annual influenza vaccination is the best way to prevent influenza. Because of the possibility of emergence of antiviral resistance viruses, widespread or routine use of antiviral medications for chemoprophylaxis is not recommended.[24]

Antiviral chemoprophylaxis generally should be reserved for people at higher risk for influenza-related complications who have had contact with someone likely to have been infected with influenza.[25] The infectious period for influenza is defined as 1 day before until 24 hours after fever ends. Children can shed influenza viruses for longer periods. Antivirals are not generally recommended if more than 48 hours have elapsed since the last contact with an infectious person. Antiviral chemoprophylaxis is not appropriate for healthy children or adults based on potential exposure in the community. An emphasis on early treatment and monitoring is an alternative to chemoprophylaxis after a suspected exposure for some people. Prophylaxis may be considered for the following patient groups: people at high risk of influenza complications during the first 2 weeks following vaccination after exposure to an infectious person; people with severe immune deficiencies or others who might not respond to influenza vaccination, such as people receiving immunosuppressive medications, after exposure to an infectious person; people at high risk for complications from influenza who cannot receive influenza vaccine due to a contraindication after exposure to an infectious person; and residents of institutions, such as long-term care facilities, during influenza outbreaks in the institution.[26]

In the community setting, the IDSA also recommends preexposure and postexposure prophylaxis, using oseltamivir or zanamivir, in select individuals at high risk for influenza complications.

PHARMACOLOGY[27,28,29]

Drug Mechanism of Action	Mechanism of Action
baloxavir marboxil (Xofluza)	▪ Baloxavir marboxil is a prodrug, which after oral administration, is converted to its active metabolite, baloxavir. It interferes with viral RNA transcription and blocks virus replication through inhibition of the polymerase acidic protein. Baloxavir is active against influenza A and B viruses. ▪ Baloxavir may be active against select oseltamivir-resistant strains and Avian strains (H7N9, H5N1), as suggested in non-clinical studies
oseltamivir (Tamiflu)	▪ Oseltamivir is a prodrug that is converted to the active form, oseltamivir carboxylate. It inhibits influenza virus neuraminidase with the possibility of alteration of virus particle aggregation and release. Oseltamivir is active against influenza A and B viruses.
zanamivir (Relenza)	▪ Zanamivir inhibits influenza virus neuraminidase with the possibility of alteration of virus particle aggregation and release. Zanamivir is active against influenza A and B viruses.

Viral Resistance

The CDC monitors viral resistance and responds to changes in resistance by publishing recommendations based on the incidence of viral resistance.[30] Because there were no significant changes in antiviral resistance patterns during 2017-2018 flu season, the 2018-2019 guidance on the use of influenza antiviral drugs has not changed; the majority of circulating influenza viruses are susceptible to oseltamivir (Tamiflu), zanamivir (Relenza), and peramivir (Rapivab) and the newer agent,

baloxavir marboxil (Xofluza). Due to high levels of resistance, amantadine and rimantadine are not recommended.

According to the World Health Organization (WHO), the risk of viral resistance is considered higher in patients with severely compromised or suppressed immune systems who have prolonged illness, have received oseltamivir treatment (especially for an extended duration), but still have evidence of persistent viral replication.[31] The risk of resistance is also considered higher in people who receive oseltamivir for post-exposure prophylaxis and who then develop illness despite taking oseltamivir. No evidence exists that oseltamivir-resistant viruses are causing different or more severe forms of illness. According to the CDC, since October 1, 2018, greater than 99% of influenza samples tested were determined to be susceptible to oseltamivir, peramivir, and zanamivir.[32] Due to consistent high levels of resistance, rimantadine is no longer tested by the CDC for resistance levels. To date, testing results for susceptibility to baloxavir were not reported by the CDC.

Susceptibilities as of October 1, 2018 according to CDC[33]

Influenza type	baloxavir	oseltamivir	zanamivir
Influenza A (H3N2)	nr	Susceptible	Susceptible
Influenza A(H1N1)pdm09	nr	Susceptible	Susceptible
Influenza B (Victoria)	nr	Susceptible	Susceptible
Influenza B (Yamagata)	nr	Susceptible	Susceptible

nr=not reported

PHARMACOKINETICS[34,35,36]

Drug	Bioavailability (%)	Half-Life (hr)	Metabolism	Excretion
baloxavir marboxil (Xofluza)	nr	79.1	1 active metabolite – baloxavir	Predominantly feces
oseltamivir (Tamiflu)	75	1–3 (parent); 6-10 (metabolite)	1 active metabolite – oseltamivir carboxylate	Predominantly renal
zanamivir (Relenza)	4–17	2.5–5.1	No metabolites	Renally excreted

nr=not reported

CONTRAINDICATIONS/WARNINGS[37,38,39]

Baloxavir marboxil (Xofluza), oseltamivir (Tamiflu), and zanamivir (Relenza) are contraindicated in patients who have hypersensitivity to any component of the product. Zanamivir should also not be used in patients with a history of allergic reaction to milk proteins.

A risk of serious bacterial infections, may coexist with, or occur as a complication of influenza. Baloxavir marboxil and oseltamivir have not been shown to prevent these complications, including bacterial infection. There is no evidence of efficacy of baloxavir marboxil, oseltamivir, zanamivir in any illness due to pathogens other than influenza viruses.

Severe allergic reactions have included anaphylaxis and serious skin reactions, including toxic epidermal necrolysis, Stevens-Johnson syndrome, and erythema multiforme. Efficacy of oseltamivir for

the treatment of influenza has not been established in patients with chronic cardiac disease and/or respiratory disease. No difference in the incidence of complications was observed between the treatment and placebo groups in this population. No information is available regarding treatment of influenza in patients with any medical condition sufficiently severe or unstable to be considered at imminent risk of requiring hospitalization. Efficacy of oseltamivir for treatment or prophylaxis of influenza has not been established in immunocompromised patients.

Zanamivir is not recommended for treatment or prophylaxis of influenza in individuals with underlying airway diseases, such as asthma or COPD, due to risk of serious bronchospasm. Zanamivir should be discontinued in any patient who develops bronchospasm or respiratory difficulty; immediate treatment, including hospitalization, may be necessary. Effectiveness of prophylaxis of influenza in the nursing home setting has not been established. Allergic-like reactions, including oropharyngeal edema, serious skin rashes, and anaphylaxis have been reported in postmarketing experience with zanamivir. Zanamivir must not be made into an extemporaneous solution for administration by nebulization or mechanical ventilation. Zanamivir inhalation powder must only be administered using the device provided.

Neuropsychiatric Reactions

Hallucinations, delirium, and abnormal behavior have been reported with influenza infection. Neuropsychiatric reactions have been noted in postmarketing surveillance of oseltamivir and zanamivir. Reports including those with fatal outcomes have described self-injury and delirium in mostly pediatric patients on oseltamivir or zanamivir with influenza. Event reports in pediatric patients have noted abrupt onset and rapid resolution of neuropsychiatric events. Unusual behavior should be reported to a healthcare professional promptly. If neuropsychiatric events occur, the risks and benefits of continuing treatment should be evaluated.

DRUG INTERACTIONS[40,41,42,43]

Concurrent administration of agents in this class with intranasal live attenuated influenza virus vaccine (FluMist®) has not been evaluated. Because of the potential interference between the antivirals and FluMist, it is advisable that FluMist not be administered until 48 hours after cessation of anti-influenza antiviral therapy. Anti-influenza antivirals should not be administered until 2 weeks after the FluMist vaccine administration unless medically necessary. Trivalent inactivated influenza vaccine can be administered at any time relative to use of drugs in this category.

Co-administration of baloxavir marboxil (Xofluza) with polyvalent cation-containing laxatives, antacids, or oral supplements (e.g., calcium, iron, magnesium, selenium, or zinc) should be avoided.

ADVERSE EFFECTS[44,45,46]

Drug	Headache	Nausea	Dizziness	Vomiting	Diarrhea
baloxavir marboxil (Xofluza) n=710; placebo n=409	1 (2)	1 (1)	nr	nr	3 (5)
oseltamivir (Tamiflu) 75 mg twice daily Treatment n=2,464 placebo n=1,977 Prophylaxis n=1,943 Placebo n=1,586	2 (2) 17 (16	10 (6) 8 (4)	nr nr	8 (3) 2 (1)	nr nr
zanamivir (Relenza) 10 mg twice daily n=1,132 adults; placebo n=1,520	2 (3)	3 (3)	2 (< 1)	1 (2)	3 (4)

Adverse effects are reported as a percentage. Adverse effects data are obtained from prescribing information and are not meant to be comparative or all inclusive. Incidences for the placebo group are indicated in parentheses. nr = not reported.

The adverse reactions reported in adolescents for baloxavir are similar to those reported in adults.

In the treatment of influenza, vomiting was the most common adverse effect in children receiving oseltamivir (15% versus 9% in the placebo group). Vomiting is also the most common adverse event in children undergoing prophylaxis for influenza with oseltamivir. Oseltamivir may be administered with or without food; however, drug tolerability may be increased for certain patients if taken with food.

The most common adverse effect in children receiving zanamivir was ear, nose, and throat infections. These occurred at a rate of 5% for both zanamivir-treated and placebo-treated patients.

SPECIAL POPULATIONS[47,48,49]

Pediatrics

Baloxavir marboxil (Xofluza) is approved for the treatment of influenza in children 12 years of age and older weighing at least 40 kg. Oseltamivir (Tamiflu) is approved for treatment of influenza in children 2 weeks of age and older and for prevention of influenza in children 1 year of age and older, and remains the drug of choice for pediatric patients. Zanamivir (Relenza) is approved for prevention of influenza in children as young as 5 years and is approved for the treatment of influenza for children ages 7 years and older. The limitation of zanamivir is the dose administration technique of the inhaler.[50]

Pregnancy

Previously Pregnancy Category C, the label for oseltamivir and zanamivir have been updated to comply with the Pregnancy and Lactation Labeling Rule (PLLR) and advise that while data are lacking to inform of any drug-related risk of adverse developmental outcomes, the limited available data suggest that oseltamivir and zanamivir not associated with an increased risk of maternal and/or fetal adverse outcomes. Baloxavir marboxil labeling instructs that there no pregnancy data is available to inform of a drug-associated risk to the fetus.

Geriatrics

Clinical trials for baloxavir marboxil (Xofluza) did not include patients 65 years of age or older. No dosage adjustment is required for oseltamivir or zanamivir in the geriatric population.

Renal Impairment

Oseltamivir dose and/or interval should be reduced in patients with an estimated creatinine clearance (CrCl) of 10 to 60 mL/minute or in patients with end stage renal disease (ESRD).

DOSAGES[51,52,53]

Drug/ Dosage Forms	Treatment of influenza		Prophylaxis of influenza	
	Adults	Pediatrics	Adults	Pediatrics
baloxavir marboxil (Xofluza) 20 mg, 40 mg tablets	In patients weighing 40 kg to < 80 kg, a single dose of 40 mg is recommended Patients weighing ≥ 80 kg should take a single dose of 80 mg	Ages ≥ 12 years In patients weighing 40 kg to < 80 kg, a single dose of 40 mg is recommended Patients weighing ≥ 80 kg should take a single dose of 80 mg	--	--
oseltamivir (Tamiflu) 30 mg, 45 mg, 75 mg capsules; 6 mg/mL oral suspension	75 mg twice daily for 5 days (≥ 13 years) Initiate therapy within 2 days of onset of symptoms.	2 weeks to 1 year: 3mg/kg twice daily >1 to <13 years: < 15 kg: 30 mg twice daily; 15-23 kg: 45 mg twice daily; 23-40 kg: 60 mg twice daily; > 40 kg: 75 mg twice daily	75 mg daily for 10 days (≥ 13 years) Initiate therapy within 2 days of exposure.	>1 to < 13 years: < 15 kg: 30 mg daily for 10 days; 15-23 kg: 45 mg daily for 10 days; 23-40 kg: 60 mg daily for 10 days; > 40 kg: 75 mg daily for 10 days May give for up to 6 weeks for community outbreak.
zanamivir (Relenza) 5 mg diskhaler*	Two inhalations (10 mg) twice daily for 5 days Initiate therapy within 2 days of onset of symptoms.	≥7 years: Two inhalations (10 mg) twice daily for 5 days	2 inhalations (10 mg) once daily for 10 days (household setting) or 28 days (community outbreaks)	≥5 years: 2 inhalations (10 mg) once daily for 10 days (household setting) or 28 days (community outbreaks)

*Patients scheduled to use an inhaled bronchodilator at the same time as zanamivir (Relenza) should use their bronchodilator before taking zanamivir.

Dosage Adjustments

Drug/ Dosage Forms	Treatment of influenza		Prophylaxis of influenza	
	Disease state/concurrent condition	Recommended dosage adjustment	Disease state/concurrent condition	Recommended dosage adjustment
oseltamivir (Tamiflu)	Renal impairment *Moderate:* CrCl > 30-60 mL/min	30 mg twice daily for 5 days	Renal impairment *Moderate:* CrCl > 30-60 mL/min	30 mg once daily
	Severe: CrCl > 10-30 mL/min	30 mg once daily for 5 days	*Severe:* CrCl > 10-30 mL/min	30 mg every other day
	ESRD (hemodialysis): CrCl ≤ 10 mL/min	30 mg after hemodialysis cycles not to exceed 5 days	*ESRD (hemodialysis):* CrCl ≤ 10 mL/min	30 mg after alternate hemodialysis cycles
	ESRD (CAPD): CrCl ≤ 10 mL/min	30 mg immediately after a dialysis exchange	*ESRD (CAPD):* CrCl ≤ 10 mL/min	30 mg once weekly after dialysis exchange
zanamivir (Relenza)	Not recommended for patients with airway diseases such as COPD and asthma			

CrCl = creatinine clearance; ESRD = end stage renal disease; CAPD = continuous ambulatory peritoneal dialysis

CLINICAL TRIALS

Studies were identified through searches performed on PubMed and review of information sent by manufacturers. Search strategy included the FDA-approved use of all drugs in this class. Randomized, controlled trials performed in the U.S. comparing oral and inhaled agents within this class in an outpatient setting for the approved indications are considered the most relevant in this category. Due to changes in resistance and practice patterns over time, studies conducted more than 15 years ago were excluded, but due to the paucity of active controlled trials, studies that were placebo-controlled, randomized trials in humans using antiviral agents for the treatment or prevention of influenza were included. Key approval studies for products remain in the review regardless of date published. Studies included for analysis in the review were published in English, performed with human participants, and randomly allocated participants to comparison groups. In addition, studies must contain clearly stated, predetermined outcome measure(s) of known or probable clinical importance, use data analysis techniques consistent with the study question, and include follow-up (endpoint assessment) of at least 80% of participants entering the investigation. Despite some inherent bias found in all studies, including those sponsored and/or funded by pharmaceutical manufacturers, the studies in this therapeutic class review were determined to have results or conclusions that do not suggest systematic error in their experimental study design. While the potential influence of manufacturer sponsorship and/or funding must be considered, the studies in this review have also been evaluated for validity and importance.

Influenza – Treatment

Children

baloxavir marboxil (Xofluza) versus placebo

The use of baloxavir marboxil in pediatric patients 12 years of age and older weighing at least 40 kg, is supported by the randomized, double-blind CAPSTONE-1 trial in which 118 adolescents 12 to 19 years of age with acute uncomplicated influenza were randomized to receive either baloxavir (n=80) or placebo (n=38).[54,55] The study included patients from both the United States and Japan from December 2016 through March 2017. A single dose of baloxivir marboxil or placebo was administered within 48 hours of influenza symptom onset. The primary endpoint of median time to alleviation of symptoms in adolescents was 54 hours for baloxavir marboxil and 93 hours for placebo. The secondary endpoint of difference in the time to alleviation of symptoms (for baloxavir marboxil and placebo) was greater in patients who initiated therapy within 24 hours of symptom onset ($p<0.001$). Baloxavir marboxil resulted with significantly greater declines in infectious viral load than placebo. Reductions in susceptibility were observed in 9.7% of baloxavir marboxil patients in those with influenza A(H3N2).

oseltamivir (Tamiflu) versus placebo

Oseltamivir was studied in a randomized, double-blind, placebo-controlled trial with 695 children ages 1 to 12 years with fever and history of cough or coryza of less than 48 hours of duration.[56] Patients were randomized to oseltamivir 2 mg/kg twice daily or placebo for 5 days. Sixty-five percent of children (n=465) were found to have influenza. Oseltamivir reduced the median duration of illness by 36 hours (26%) in the influenza-infected children compared to placebo (101 hours versus 137 hours, $p<0.0001$). Oseltamivir reduced cough, coryza, and duration of fever. New diagnoses of acute otitis media were also reduced in the oseltamivir group (12% versus 21%, respectively). Use of antibiotics was significantly lower in the influenza-infected oseltamivir group compared to the influenza-infected placebo group (31% versus 41%, respectively, $p=0.03$). Oseltamivir group experienced more emesis than placebo group.

zanamivir (Relenza) versus placebo

A double-blind, randomized, placebo-controlled, parallel-group, multicenter study enrolled children, 5 to 12 years of age, with influenza-like symptoms for no more than 36 hours.[57] Patients were randomized to zanamivir 10 mg twice daily or placebo for 5 days. Symptoms were recorded on diary cards twice daily during treatment, 9 days after treatment, and potentially an additional 14 days, if symptoms persisted. Of the 471 children enrolled in the study, 346 (73%) patients were influenza-positive by culture, serology, or polymerase chain reaction. Of those with confirmed infection, 65% had influenza A and 35% had influenza B. Zanamivir reduced the median time to symptom alleviation by 1.25 days compared with placebo among patients with confirmed influenza infection ($p<0.001$). Zanamivir-treated patients returned to normal activities significantly faster and took significantly fewer relief medications than placebo-treated patients. Zanamivir was well-tolerated.

Adults

baloxavir marboxil (Xofluza) versus oseltamivir (Tamiflu)

In the active- and placebo-controlled CAPSTONE-1 trial, baloxavir was studied in 1,436 patients 12 to 64 years of age weighing at least 40 kg in the U.S. and Japan. At enrollment, patients had influenza symptoms for no longer than 48 hours. Adults ages 20 to 64 years received baloxavir marboxil or placebo as a single oral dose on day 1 (plus oseltamivir-matched placebo) or oseltamivir twice a day for 5 days. Subjects weighing < 80 kg received baloxavir marboxil at a dose of 40 mg and subjects weighing ≥ 80 kg received an 80 mg dose. In the intention-to-treat infected population, the median time to alleviation of symptoms (primary endpoint) was 53.7 hours and 80.2 hours, for baloxavir marboxil and placebo, respectively (p<0.001). The difference in the time to alleviation of symptoms between the baloxavir marboxil group and the placebo group was greater in patients who initiated the trial regimen within 24 hours after symptom onset (median difference, 32.8 hours; p<0.001) than in those who initiated it later (median difference, 13.2 hours; p=0.008). There was no difference in the median time to alleviation of symptoms between baloxavir marboxil and oseltamivir (approximately 54 hours for both). Baloxavir marboxil resulted in significantly greater declines in infectious viral load than placebo and oseltamivir. Reductions in susceptibility were observed in 9.7% of baloxavir marboxil patients in those with influenza A(H3N2), which was the predominant virus identified among patients. Incidence of diarrhea of any grade was 3% with baloxavir marboxil, 2.1% with oseltamivir, and 4.5% with placebo; bronchitis was reported in 2.6%, 3.5%, and 5.5% among the 3 groups, respectively.

oseltamivir (Tamiflu) versus placebo

A randomized, double-blind study was performed in 629 healthy nonimmunized adults in the U.S. with febrile illness of less than 36 hours duration.[58] Patients were randomized to receive oseltamivir 75 mg or 150 mg or matching placebo twice daily. In the 374 patients infected with influenza, median duration of illness was shorter in the oseltamivir 75 mg (71.5 hours; p<0.001 versus placebo) and 150 mg groups (69.9 hours; p=0.006 versus placebo) compared to placebo (103.3 hours). There was no difference observed between the 2 active treatment regimens. Secondary complications, such as bronchitis and sinusitis, occurred more frequently in the placebo group (15%) than the oseltamivir groups (7%; p=0.03). Additionally, oseltamivir-treated patients returned to usual activities 2 to 3 days earlier than placebo-treated patients (p≤0.05). Nausea and vomiting occurred more frequently in the oseltamivir groups (combined incidence of 18 and 14.1%, respectively; p=0.002) compared to placebo (7.4 and 3.4%; p<0.001).

A randomized, double-blind, controlled trial was conducted in 726 previously healthy nonimmunized adults with febrile influenza-like illness of up to 36 hours duration.[59] Patients were assigned to oseltamivir 75 mg, oseltamivir 150 mg, or placebo twice daily for 5 days. Infection was confirmed in 66% of patients. Compared to placebo (median duration 116.5 hours), the duration of illness, the primary endpoint, was 29 hours shorter in the oseltamivir 75 mg group (median duration 87.4 hours; p=0.02) and 35 hours shorter in the oseltamivir 150 mg group (median duration 81.8 hours; p=0.01). The effect of oseltamivir was apparent within 24 hours of the start of treatment. In patients treated within 24 hours of symptom onset, symptoms were alleviated in 74.5 hours in the oseltamivir 75 mg group, in 70.7 hours in the oseltamivir 150 mg group and in 117.5 hours in the placebo group (p≤0.02 for both active treatments compared to placebo). Oseltamivir was associated with lower symptom

scores, less viral shedding, and improved health, activity, and sleep quality. Oseltamivir was well tolerated.

zanamivir (Relenza) versus placebo

In a double-blind trial, 27 otherwise healthy adult patients were randomized to zanamivir 10 mg twice daily for 5 days or matching placebo.[60] Treatment was started within the first or second day of a flu-like illness. After 12 hours of treatment (e.g., 1 dose), median virus titers changed by -1.0 log10 TCID50/mL in the zanamivir group compared with +0.42-log10 change in the placebo group (p=0.08). This was associated with a 4.5 day (47.4%) reduction in the median time to alleviation of all significant flu symptoms in the zanamivir recipients (p=0.03 after adjusting for the initial virus titer and the time between onset of symptoms and treatment). Resistance to zanamivir was not detected in virus isolates.

In a randomized, double-blind trial, 356 patients aged 12 years and older were recruited within 2 days of onset of typical influenza symptoms.[61] Patients were randomized to receive inhaled zanamivir 10 mg twice daily for 5 days or matching placebo. Influenza was laboratory-confirmed in 277 (78%) of the patients; 32 (9%) patients were considered high-risk (elderly or with underlying medical conditions). The primary endpoint, time to alleviation of clinically significant symptoms of influenza, was significantly reduced by zanamivir compared to placebo (5 and 7.5 days, respectively; p<0.001). Zanamivir was well tolerated.

oseltamivir (Tamiflu) and zanamivir (Relenza)

Although the study was conducted in an open-label manner, it has been included due to a lack of other direct comparative data. In a Japanese study, the effectiveness of zanamivir with oseltamivir for influenza A and B were compared in 1,113 patients during the 2006-2007 influenza season.[62] The duration of fever (≥ 37.5° C) after the first dose was less with zanamivir (31.8 hours) compared to oseltamivir (35.5 hours; p<0.05) in patients with influenza A. For patients with influenza B, fever duration after starting zanamivir therapy (35.8 hours) was significantly shorter than that of oseltamivir (52.7 hours; p<0.001). By multiple regression analysis, therapy (zanamivir or oseltamivir) was the major determinant affecting the duration of fever for influenza B.

Influenza – Prophylaxis

oseltamivir (Tamiflu) versus placebo

A study compared the efficacy of oseltamivir in prevention of household contacts acquiring influenza from the index case. A total of 955 household contacts of people with influenza were enrolled in a preventative, double-blind study and randomized to oseltamivir 75 mg once daily or placebo for 7 days.[63] Randomization occurred by household within 48 hours of symptom onset of the index case of influenza. The index case patients did not receive therapy in the study. The overall protective efficacy of oseltamivir against clinical influenza was 89% for individuals (95% confidence interval [CI], 67-97%; p<0.001) and 84% for households (95% CI, 49-95%; p<0.001). Gastrointestinal adverse events were similar in both groups (oseltamivir, 9.3%; placebo, 7.2%).

In a double-blind, placebo-controlled, parallel-group, multicenter study, 548 frail, elderly nursing home occupants (mean age 81 years, >80% vaccinated for influenza) were randomized to prophylaxis with oseltamivir 75 mg or placebo once daily for 6 weeks, beginning when influenza was detected locally.[64]

The administration of oseltamivir resulted in a 92% reduction in the incidence of laboratory-confirmed clinical influenza compared with placebo (0.4 and 4.4%, respectively; p=0.002). In vaccinated subjects, influenza was confirmed in 0.5% of oseltamivir patients and 5% of patients randomized to placebo (p=0.003). Oseltamivir use was also associated with a significant reduction in the incidence of secondary complications (0.4% versus 2.6% for placebo; p=0.037). Oseltamivir was well tolerated with a similar incidence of adverse events, including gastrointestinal effects, occurring in both groups.

zanamivir (Relenza) versus placebo

In a multicenter, randomized, double-blind, placebo-controlled, parallel-group study, the efficacy and safety of zanamivir for the prevention of influenza in community-dwelling patients who were at high risk for developing complications of influenza were evaluated.[65] The study was conducted in the 2000-2001 influenza season. To be enrolled, patients were able to use the Diskhaler device and were able to take the first dose of study medication within 5 days of laboratory-confirmed local influenza activity. Patients (n=3,363) were randomized to receive inhaled zanamivir 10 mg or placebo once daily for 28 days. The proportion of randomized subjects who developed symptomatic influenza during prophylaxis was significantly lower in those patients receiving zanamivir (4/1,678 versus 23/1,685; relative risk 0.17; [95% CI, 0.07 to 0.44, p<0.001]). Zanamivir provided a protective efficacy of 83%. Significantly fewer complications were observed in the zanamivir-treated patients (1/1,678 versus 8/1,685; relative risk 0.12 [95% CI, 0.002 to 0.73; p=0.042]). Influenza-like illness was reported in 9% in the zanamivir-treated patients and 10% in the placebo-treated patients. Adverse effects were similar between the groups with the most common reports being headache, cough, and throat and tonsil discomfort/pain. The incidences of viral respiratory infections or ear, nose, and throat infections were similar between the 2 groups. No resistance to zanamivir was identified in the study.

META-ANALYSES

Adults and Children

A 2014 systematic review of 107 clinical studies analyzed the effects of zanamivir and oseltamivir on time to first alleviation of influenza symptoms, influenza outcomes, complications, hospitalizations and adverse events in adults and children. Oseltamivir reduced the time to first alleviation of symptoms by 16.8 hours in adults (95% CI 8.4 to 25.1 hours, p<0.0001) and by 29 hours in otherwise healthy children (95% CI 12 to 47 hours, p=0.001); no effect was seen in asthmatic children. Zanamivir reduced the time to first alleviation of symptoms in adults by 0.6 days (95% CI 0.39 to 0.81 days, p<0.00001); the effect in children was not significant. Zanamivir significantly reduced the risk of bronchitis in adult treatment trials (RD 1.80%, 95% CI 0.65 to 2.80), but not oseltamivir. Neither zanamivir nor oseltamivir significantly reduced the risk of otitis media and sinusitis in both adults and children.

In prophylaxis trials, oseltamivir and zanamivir reduced the risk of symptomatic influenza in individuals (oseltamivir: risk difference [RD] 3.05% [95% CI 1.83 to 3.88]; zanamivir: RD 1.98% [95% CI 0.98 to 2.54]) and in households (oseltamivir: RD 13.6% [95% CI 9.52 to 15.47]; zanamivir: RD 14.84% [95% CI 12.18 to 16.55]). There was no significant effect on asymptomatic influenza (oseltamivir: RR 1.14 [95% CI 0.39 to 3.33]; zanamivir: RR 0.97 [95% CI 0.76 to 1.24]).

Oseltamivir in the treatment of adults increased the risk of nausea (RD 3.66%, 95% CI 0.9 to 7.39) and vomiting (RD 4.56%, 95% CI 2.39 to 7.58). The proportion of participants with 4-fold increases in antibody titer was significantly lower in the treated group compared to the control group (RR 0.92,

95% CI 0.86 to 0.97, I^2 statistic = 0%) (5% absolute difference between arms). Oseltamivir significantly decreased the risk of diarrhea (RD 2.33%, 95% CI 0.14 to 3.81) and cardiac events (RD 0.68%, 95% CI 0.04 to 1.0) compared to placebo during the on-treatment period. There was a dose-response effect on psychiatric events in the 2 oseltamivir "pivotal" treatment trials, WV15670 and WV15671, at 150 mg (standard dose) and 300 mg daily (high dose) (p=0.038). In the treatment of children, oseltamivir induced vomiting (RD 5.34%, 95% CI 1.75 to 10.29). There was a significantly lower proportion of children on oseltamivir with a 4-fold increase in antibodies (RR 0.9, 95% CI 0.8 to 1, I^2 = 0%).

In oseltamivir prophylaxis studies, psychiatric adverse events were increased in the combined on- and off-treatment periods (RD 1.06%, 95% CI 0.07 to 2.76). Oseltamivir increased the risk of headaches (RD 3.15%, 95% CI 0.88 to 5.78), renal events while on treatment (RD 0.67%, 95% CI -2.93 to 0.01), and nausea (RD 4.15%, 95% CI 0.86 to 9.51).

Trials with oseltamivir or zanamivir could not demonstrate a reduction in complications of influenza (such as pneumonia) due to lack of diagnostic definitions. Treatment of adults and children with oseltamivir had no significant effect on hospitalizations. Zanamivir hospitalization data were not reported.[66]

Adults

A 2009 systematic review included randomized placebo-controlled studies of neuraminidase inhibitors in otherwise healthy adults exposed to naturally occurring influenza.[67,68] A total of 20 trials were included. In the 4 trials evaluating prophylaxis, the neuraminidase inhibitors had no effect against influenza-like illness or asymptomatic influenza. The efficacy of oseltamivir 75 mg daily against symptomatic laboratory confirmed influenza was 61% (risk ratio 0.39; 95% CI, 0.18 to 0.85). Inhaled zanamivir 10 mg daily was 62% efficacious (risk ratio 0.38; 95% CI, 0.17 to 0.85). In post-exposure prophylaxis trials, oseltamivir had an efficacy of 58% (95% CI, 15 to 79) and 84% in 2 trials of households. Zanamivir performed similarly. For treatment, the hazard ratios for time to alleviation of influenza-like illness symptoms were in favor of treatment: 1.20 (95% CI, 1.06 to 1.35) for oseltamivir and 1.24 (95% CI, 1.13 to 1.36) for zanamivir. Regarding lower respiratory tract complications, evidence suggests oseltamivir did not reduce influenza related complications (risk ratio 0.55; 95% CI, 0.22 to 1.35).

A 2015 meta-analysis evaluated the efficacy of oseltamivir treatment for influenza in adults.[69] Data from 9 trials including 4,328 patients was used in the analysis. The analysis showed that oseltamivir in adults with influenza accelerates time to clinical symptom alleviation, reduces risk of lower respiratory tract complications, and admittance to hospital, but increases the occurrence of nausea and vomiting. In the analysis, time to alleviation of all symptoms was 21% shorter for oseltamivir versus placebo in the intention to treat infected population (time ratio 0.79, 95% CI 0.74-0.85; p<0.0001). The analysis also showed fewer lower respiratory tract complications requiring antibiotics more than 48 hours after randomization (risk ratio [RR] 0.56, 95% CI 0.42-0.75; p=0.0001) and also fewer admittances to hospital for any cause (RR 0.37, 95% CI 0.17-0.81; p=0.013) in the intention to treat infected population. Regarding safety, oseltamivir increased the risk of nausea (RR 1.60, 95% CI 1.29-1.99; p<0.0001) and vomiting (RR 2.43, 95% CI 1.83-3.23; p<0.0001).

Children

A 2009 systematic review evaluated the effects of the neuraminidase inhibitors in treatment of children (≤ 12 years old) with seasonal influenza and prevention of transmission to children in households.[70] Published and unpublished data were considered. A total of 4 randomized controlled trials with 1,766 children evaluated treatment with oseltamivir or zanamivir in the community setting with confirmed or clinically suspected influenza. Three randomized trials with 863 children evaluated post-exposure prophylaxis (1 trial for oseltamivir, 2 trials for zanamivir). The median time to resolution of symptoms or return to normal activities or both was reduced by 0.5 to 1.5 days, which was a significant finding in only 2 trials. A 10-day duration of post-exposure prophylaxis with zanamivir or oseltamivir resulted in an 8% (95% CI, 5 to 12) decrease in the incidence of symptomatic influenza. Based on only 1 trial, oseltamivir did not reduce asthma exacerbations and oseltamivir was not associated with a reduction in overall use of antibiotics (risk difference -0.3, 95% CI, -0.13 to 0.01). Zanamivir was well tolerated, but oseltamivir was associated with an increased risk of vomiting (0.05, 95% CI, 0.02 to 0.09, number needed to harm=20).

SUMMARY

Vaccination is the primary method of preventing influenza infection. Because of the possibility of emergence of antiviral resistance viruses, widespread or routine use of antiviral medications for chemoprophylaxis is not recommended, and use of these agents should be reserved for appropriate high risk populations.

Agents approved for influenza prevention and treatment include amantadine, rimantadine (Flumadine), oseltamivir (Tamiflu), zanamivir (Relenza), and peramivir (Rapivab). The CDC currently does not recommend the use of amantadine or rimantadine for the treatment or prophylaxis of influenza A due to viral resistance. Recently approved baloxavir marboxil (Xofluza) offers a new treatment option with a novel mechanism of action and with a convenient single dose for influenza treatment; it is not FDA-approved for influenza chemoprophylaxis. In clinical trials it has shown comparable efficacy to oseltamivir. Greater reduction in viral load was seen 1 day after drug administration with baloxavir marboxil compared to oseltamivir and placebo. Baloxavir marboxil may also have activity against select oseltamivir-resistant strains and Avian strains (H7N9, H5N1).

The Centers for Disease Control and Prevention (CDC) recommends antiviral treatment of influenza in hospitalized patients, patients with severe, complicated, or progressive illness, or patients at high risk for influenza complications. The CDC prefers use with oseltamivir in these patient populations over zanamivir, peramivir, or baloxavir marboxil. Antiviral treatment should be initiated as early as possible because studies show that treatment initiated early (e.g., within 48 hours of illness onset) is more likely to provide benefit. In the outpatient setting, antiviral treatment can also be considered for any previously healthy, patient with confirmed or suspected influenza who are not at high risk for influenza complications; no preference for use of baloxavir marboxil, oseltamivir, or zanamivir is given by the CDC. The Infectious Diseases Society of America (IDSA) does not include a recommendation for baloxavir marboxil use to treat influenza since the product was FDA approved after the guidelines were finalized.

Zanamivir uses a complex administration device for inhalation and should not be used in patients with pre-existing respiratory disorders. For the treatment of influenza B, either oseltamivir, zanamivir, or peramivir are recommended.

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