Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

44 Antiviral Drugs for Influenza and Other Respiratory Virus Infections

Fred Y. Aoki

SHORT VIEW SUMMARY

INFLUENZA A AND B: NEURAMINIDASE INHIBITORS

Oseltamivir
- Orally administered oseltamivir is effective in prevention and treatment of uncomplicated influenza in otherwise healthy adults.
- Observational studies suggest it is beneficial in serious illness.
- Toxicity is primarily gastrointestinal.

Zanamivir
- Administration is through oral inhalation as a powder.
- Effectiveness is similar to that of oseltamivir.
- It is active against some oseltamivir-resistant strains.
- Bronchospasm may occur in individuals with asthma or chronic obstructive pulmonary disease.

INFLUENZA A: ADAMANTANES

Amantadine and Rimantadine
- Widespread resistance to these agents is present in currently circulating influenza A viruses, and they should not be used unless sensitivity of isolates is demonstrated.
- Orally administered, they have shown efficacy against uncomplicated influenza A.
- Effectiveness in serious illness is not established.
- Toxicity with amantadine is primarily evident as central nervous system symptoms; with rimantadine it is gastrointestinal intolerance.

INVESTIGATIONAL AGENTS AGAINST INFLUENZA
- Peramivir: intravenously administrated neuraminidase inhibitor
- Laninamivir: orally inhaled neuraminidase inhibitor with prolonged presence in the respiratory tract

RESPIRATORY SYNCYTIAL VIRUS

Ribavirin
- A guanosine analogue, ribavirin has activity against a broad variety of viruses, including respiratory syncytial virus (RSV) and influenza.
- It is approved for aerosol administration to children hospitalized with RSV pneumonia or bronchiolitis and has been used to treat viral respiratory tract infections in immunosuppressed patients.
- It is teratogenic and should not be used near potentially pregnant staff.

RSV604
- An investigational agent, RSV604 inhibits RSV through interaction with the nucleocapsid protein.
- It is well absorbed orally, and phase II studies are underway.

PARAINFLUENZA VIRUSES

DAS181 (Fludase)
- DAS181 is an investigational compound with activity against parainfluenza and influenza viruses.
- An orally inhaled sialidase, it reduces virus binding to epithelial cells.
- It has been used to treat parainfluenza virus type 3 infections in immunosuppressed patients.

In this chapter, antiviral agents against influenza viruses and certain other respiratory viruses such as parainfluenza and respiratory syncytial virus are reviewed (Table 44-1). The antiviral agents are presented in alphabetical order and include licensed (approved) as well as investigational agents. Agents that have been investigated in rhinovirus infections but have been utilized primarily in non–respiratory tract infections, such as interferons and pleconaril, are discussed in Chapter 47.

AMANTADINE AND RIMANTADINE

Spectrum

Amantadine (1-adamantanamine hydrochloride; Symmetrel) and rimantadine (α-methyl-1-adamantane methylamine hydrochloride; Flumadine) are symmetrical tricyclic amines (Fig. 44-1A and B) that specifically inhibit the replication of influenza A viruses at low concentrations (<1 μg/mL). Influenza B and C viruses are resistant.[1] In the past, epidemic human and avian strains of influenza viruses have generally been susceptible to amantadine.[2] However, since 2008-2009, isolates of influenza A/H1N1 and H3N2, highly pathogenic avian H5N1, and A (H1N1)pdm09 are resistant to amantadine and rimantadine (see later discussion).[3] By plaque assay, inhibitory concentrations of the drugs range from 0.1 to 0.4 μg/mL or less for sensitive human influenza A viruses. Rimantadine is 4 to 10 times more active than amantadine in some assay systems. Both drugs are inhibitory for virus containing the M protein from the 1918 pandemic strain.[4]

Higher concentrations (10 to 50 μg/mL) inhibit other enveloped viruses in vitro, including parainfluenza, influenza B, rubella, dengue, several arenaviruses (Junin, Lassa, Pichinde), rabies, and African swine fever virus, but these concentrations are not achievable clinically and can be cytotoxic in vitro.[5] Rimantadine has pH-dependent trypanocidal activity at concentrations of approximately 1 μg/mL[6]; amantadine at the same concentration in combination with doxycycline inhibits *Coxiella burnetii*.[7] Amantadine may transiently inhibit hepatitis C virus (HCV) replication in humans.[8]

These agents have prophylactic and therapeutic activity in experimental influenza A virus infection of animals after oral or parenteral dosing. Combinations of M2 inhibitors and neuraminidase inhibitors and ribavirin show enhanced antiviral and therapeutic effects in vitro or in animal models of influenza.[9-12]

Mechanism of Action

Amantadine and rimantadine share two concentration-dependent mechanisms of anti-influenza action. Low concentrations inhibit the ion channel function of the M2 protein of influenza A viruses, which affects two different stages in virus replication.[13-15] The primary effect involves inhibition of viral uncoating or disassembly of the virion during endocytosis. For subtype H5 and H7 viruses, a late effect on hemagglutinin maturation and viral assembly is presumably mediated through altered pH regulation of the trans-Golgi network. Amantadine and rimantadine block proton permeation and prevent M2-mediated changes in pH. This action probably accounts for inhibition of the acid-mediated dissociation of the matrix protein from the ribonucleoprotein complex within endosomes early in replication and potentiation of acidic pH–induced alterations in the hemagglutinin during its transport late in infection.

Amantadine and rimantadine are also concentrated in the lysosomal fraction of mammalian cells. Drug-mediated increases in lysosomal pH may inhibit virus-induced membrane fusion events and account for the broader antiviral spectrum at higher concentrations. In contrast, the selective anti–influenza A virus effects are quickly lost after removal of the drug from the surrounding medium, which

KEYWORDS

amantadine; chemoprophylaxis; chemotherapy; DAS181 (Fludase); influenza; inhaled; laninamivir; oseltamivir; outbreak (control); peramivir; pharmacokinetics; postexposure; resistance; respiratory syncytial virus; ribavirin; rimantadine; RSV604; seasonal; zanamivir

TABLE 44-1 Antiviral Agents of Established Therapeutic Effectiveness for Respiratory Virus Infection

VIRAL INFECTION	DRUG	ROUTE	USUAL ADULT DOSAGE
Influenza A and B viruses	Oseltamivir	Oral	75 mg bid for 5 days[a]
	Peramivir	Intravenous	300 or 600 mg once
	Zanamivir	Inhalation	10 mg bid by inhaler for 5 days[b]
	Laninamivir octanoate	Inhalation	40 mg once[c]
Influenza A virus	Amantadine	Oral	100 mg bid for 5 days for treatment[d]
	Rimantadine	Oral	100 mg bid for 5 days for treatment[e]
Respiratory syncytial virus	Ribavirin	Aerosol	Aerosol treatment 18 hr/day for 3-7 days[f]

[a]Pediatric dosages: For infants 2 wk to <1 yr of age dose is 3 mg/kg twice daily. For children ≥1 yr of age, doses are weight adjusted: 30 mg bid for <15 kg, 45 mg bid for 16-23 kg, 60 mg bid for 24-40 kg, and 75 mg bid for >40 kg. Prophylactic dosage is given once daily (one half of total daily treatment dosage). Not FDA approved currently for prophylaxis in children <1 yr old or treatment in children <2 wk old.

[b]FDA approved at same dosage for treatment of children ≥7 yr of age. Prophylactic dosage is 10 mg inhaled once daily for adults and children ≥5 yr of age.

[c]Adult dose and for children ≥10 yr of age. Pediatric dose: 20 mg once for children <10 yr of age.

[d]Maximum recommended dosage for older adults (≥65 yr) is 100 mg/day. Recommended pediatric dosage is 5 mg/kg/day up to a maximum of 150 mg/day in divided doses. For prophylaxis, the same daily dosage should be given for period at risk.

[e]Pediatric dosage is 5 mg/kg up to a maximum of 150 mg/day in divided doses. Not approved by FDA for treatment in children <13 yr of age. For prophylaxis, same daily dosage should be given for period at risk.

[f]Reservoir concentration of 20 mg/mL. Special aerosol-generating device (available from manufacturer) and expert respiratory therapy monitoring for administration are required. Higher reservoir concentration (60 mg/mL) given for 2 hr tid is an alternative.

Note: Please consult text and manufacturer's product prescribing information for dosage adjustments in renal or hepatic insufficiency and in other circumstances.

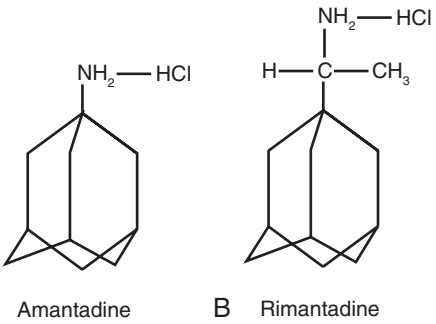

FIGURE 44-1 Chemical structures of amantadine hydrochloride (A) and rimantadine hydrochloride (B).

suggests that drug must be present in extracellular fluid early in the replicative cycle.

Amantadine inhibits the ion channel activity of expressed HCV p7 protein at low concentrations,[16] an effect that might account for its reported anti-HCV effects in vivo. Neither agent inhibits HCV enzyme functions or internal ribosome entry in biochemical assays.[17]

Resistance

Amantadine-resistant virus is readily selected by virus passage in the presence of drug. Resistance with more than 100-fold increases in inhibitory concentrations has been associated with single amino-acid substitutions at critical sites (positions 26, 27, 30, 31, 34) in the *trans*-membrane region of the M2 protein.[13] Amantadine and rimantadine share cross-resistance. In avian models, resistant viruses are virulent, genetically stable, and able to compete with wild-type virus so that transmission of drug-resistant virus may occur after cessation of drug use.

Before 2003, a small percentage of untreated patients (<1%) had infection with resistant influenza A virus.[18] Approximately 30% of drug-treated ambulatory children and adults and 80% of hospitalized children or immunocompromised patients shed resistant virus.[19-21] Immunocompetent individuals shedding resistant virus resolve their illness promptly,[22] whereas immunocompromised hosts may experience prolonged illness associated with persistent virus shedding.[20] Transmission of M2 inhibitor–resistant virus, associated with failure of drug prophylaxis, occurs in household contacts of treated index cases[23] and in nursing home residents.[24] Resistant variants can cause typical influenza illness. It is prudent to avoid contact between treated patients and susceptible high-risk contacts and to avoid use of treatment (specifically of young children) and postexposure prophylaxis in the same household.

Globally, up to 2003, epidemic influenza A H1N1 and H3N2 strains were M2 inhibitor sensitive. Since 2003, the prevalence of amantadine resistance has increased progressively, although rates vary by virus type and geography.[25,26] Among H3N2 isolates, amantadine resistance increased from 12% worldwide in 2003[25] to 91% by 2005 and greater than 95% in 2008-2009.[26] In the United States prior to March 2009, nearly all of the A/H1N1 isolates tested were sensitive to the adamantanes and, subsequently, virtually all A/H1N1 isolates have been resistant up to the present, including the A (H1N1)pdm09 virus.[27] Among nonpandemic H1N1 isolates, the prevalence of amantadine resistance was 4% in 2004-2005 worldwide and 16% in isolates from 2005-2006, with rates ranging from 2% in South Korea to 72% in China.[26,28,29] The reason for the emergence and global spread of amantadine-resistant strains is unclear. Widespread inappropriate use of amantadine[30] and acquisition of undefined advantageous mutations combined with lack of fitness impairment may have been contributing factors. Ribavirin and the neuraminidase inhibitors zanamivir and oseltamivir carboxylate are active in vitro against M2 inhibitor–resistant strains.

The triple combination of amantadine, oseltamivir, and ribavirin impedes the selection of drug-resistant influenza A virus in vitro at clinically achievable concentrations[31] compared with double combinations and the agents used singly in vitro.[32] The same combination of drugs was also synergistic in vitro in inhibiting the growth of both amantadine- and oseltamivir-resistant influenza A virus strains at concentrations that had no activity as single agents.[32]

Pharmacokinetics

The clinical pharmacokinetic characteristics of amantadine and rimantadine are shown in Table 44-2.

Amantadine

Amantadine is well absorbed after oral administration of capsule, tablet, or syrup forms.[5] Steady-state peak plasma concentrations average 0.5 to 0.8 μg/mL with a 100-mg twice-daily regimen in healthy young adults. Older adults require only one half of the weight-adjusted dosage needed for young adults to achieve equivalent trough plasma levels of 0.3 μg/mL. Plasma protein binding of amantadine is about 67%, and amantadine's volume of distribution (V_d) is large (4 to 5 L/kg). Nasal secretion and salivary levels of amantadine approximate those found in the serum. Cerebrospinal fluid levels are 52% to 96% of those in plasma, and amantadine is excreted in breast milk.

Amantadine is eliminated largely unchanged in the urine by glomerular filtration and probably by tubular secretion by a bicarbonate-dependent organic cation transporter.[33] The plasma elimination half-life ($t_{½elim}$) is 12 to 18 hours, ranges widely, and correlates with the creatinine clearance (CrCl). Because of age-related declines in renal function, $t_{½elim}$ increases twofold in older adults and even more in patients with impaired renal function. Dosage reductions are required in renal insufficiency (Table 44-3). Amantadine is inefficiently cleared in patients receiving hemodialysis or continuous ambulatory peritoneal dialysis, and additional doses are not required. Monitoring of plasma concentrations in such patients is desirable but impractical.

Amantadine pharmacokinetics remained unaffected by concurrent administration of oseltamivir and ribavirin in healthy adult volunteers or stable immunocompromised patients.[34]

TABLE 44-2 Clinical Pharmacokinetic Characteristics of Amantadine and Rimantadine in Healthy Adults

	AMANTADINE		RIMANTADINE	
CHARACTERISTIC	**Young**	**Elderly**	**Young**	**Elderly**
Relative oral bioavailability (%)	62-93	53-100	75-93	NA
V_d (L/kg) at 200 mg/day	6.1 ± 2.1	3.6 ± 1.1	18.4 ± 9.6	11.5 ± 2.9
Plasma protein binding (%)	67	NA	40	NA
Clearance (mL/min/kg)				
Plasma or total	5 ± 2.1	2 ± 0.9	6.1 ± 1.9	4.7 ± 2
Renal	6.4 ± 3.7	2 ± 1.1	1.2 ± 0.4	NA
Nonrenal	0	0	6.4 ± 1.4	NA
Urinary excretion of unchanged drug (%)	62-93	53-100	8.3-43	NA
Plasma half-life (hr)	14.8 ± 6.2	26.1 ± 9.7	29.1 ± 9.7	36.5 ± 14.5
Therapeutic range (ng/mL)				
C_{max}				
200 mg/day	475 ± 110	—	416 ± 108	447 ± 108
100 mg/day	—	362 ± 158	—	—
C_{trough}				
200 mg/day	302 ± 80	—	300 ± 75	310 ± 87
100 mg/day	—	301 ± 75	—	—

NA, not available.

Adapted from Hayden FG, Aoki FY. Amantadine, rimantadine, and related agents. In: Yu VL, Edwards D, McKinnon S, et al, eds. Antimicrobial Therapy and Vaccines. *2nd ed. Pittsburgh: E Sun Technologies; 2002:714.*

TABLE 44-3 Amantadine Dosage Regimens for Prophylaxis and Alterations in Renal Failure

CONDITION	SUGGESTED DOSAGE
No Renal Insufficiency	
Children 1-9 yr	5 mg/kg/day in two divided doses, ≤150 mg/day
Ages 10-64 yr	100 mg twice daily
Ages ≥65 yr	100 mg once daily*
Creatinine Clearance (mL/min/1.73 m²)†	
≥80	100 mg (1.4 mg/kg) twice daily
79-35	100 mg once daily
34-25	100 mg every 2 days
24-15	100 mg every 3 days
<15	100 mg every 7 days
Older Adults and Creatinine Clearance (mL/min/1.73 m²)‡	
≥80	100 mg daily
60-79	100 mg and 50 mg on alternate days
40-59	100 mg every 2 days
30-39	100 mg twice weekly
20-29	50 mg twice weekly
10-19	100 mg and 50 mg on alternate weeks

*Use weight-adjusted dosing for smaller patients (<50 kg). Dosages of 1.4 mg/kg/day have been suggested.[5]

†Based on adult dosage of 200 mg/day. Proportionate reductions should be made for older adults receiving lower dosages and for children.

‡This dosing schedule for older adults with renal insufficiency is taken from the Canadian guidelines and has been found to be reasonably well tolerated.[44]

Modified from Wu MJ, Ing TS, Soung LS, et al. Amantadine hydrochloride pharmacokinetics in patients with impaired renal function. Clin Nephrol. *1982;17:19-23.*

Rimantadine

Rimantadine is well but slowly absorbed, with the time to peak plasma concentration averaging 2 to 6 hours. Absorption does not seem to be decreased by food. With multiple doses of 100 mg twice daily, the steady-state peak and trough plasma concentrations in healthy adults are 0.4 to 0.5 µg/mL and 0.2 to 0.4 µg/mL. In infants receiving dosages of 3 mg/kg each day, peak serum levels range from 0.1 to 0.6 µg/mL. No important age-related changes in pharmacokinetics have been found in healthy older adults or in children. However, steady-state plasma concentrations in older nursing home residents receiving 100 mg twice daily average more than twofold higher (mean, 1.2 µg/mL) than concentrations observed in healthy adults, which indicates the need for lower dosages in these patients. Plasma protein binding is about 40%. Rimantadine has a very large V_d (~12 L/kg), and concentrations in nasal mucus average 50% higher than those in plasma.

In contrast to amantadine, rimantadine undergoes extensive metabolism by hydroxylation, conjugation, and glucuronidation before renal excretion.[5] The plasma $t_{½elim}$ of rimantadine averages 24 to 36 hours. No clinically important differences in pharmacokinetics are found in patients with chronic liver disease without significant hepatocellular dysfunction. In hemodialysis patients with severe renal failure, the clearance of rimantadine is decreased by 40% and the $t_{½elim}$ is about 55% longer. Reducing dosages by one half (e.g., to 100 mg/day) is recommended for marked hepatic or renal insufficiency (CrCl <10 mL/min). Hemodialysis removes only a small amount of rimantadine, so supplemental doses are not required.

Interactions

The risks for central nervous system (CNS) adverse effects with amantadine and possibly with rimantadine are increased by concomitant ingestion of antihistamines, antidepressants, anticholinergic drugs, and other drugs affecting CNS function. Concurrent use of trimethoprim-sulfamethoxazole or triamterene-hydrochlorothiazide has been associated with CNS toxicity resulting from decreased renal clearance of amantadine. Cimetidine is associated with 15% to 20% increases, and aspirin or acetaminophen is associated with 10% decreases in plasma rimantadine concentrations, but such changes are unlikely to be significant. Neither adverse clinical nor adverse pharmacokinetic effects are observed when amantadine and oseltamivir are co-administered.[35]

Concurrent administration of recommended doses of amantadine, oseltamivir, and ribavirin for 10 days was well tolerated.[34]

Toxicity

Amantadine or rimantadine given in treatment courses of 5 days is generally well tolerated in young healthy adults.[36] Longer periods of administration, such as 6 weeks for seasonal prophylaxis in young adults,[36] and administration to fragile, elderly nursing home residents, such as octogenarians, for 10 days for outbreak control are associated with a significant frequency of adverse reactions and drug withdrawals.[37]

A case-control study demonstrated that in children younger than 12 months of age, amantadine and rimantadine were well tolerated, as was oseltamivir.[38] No evidence of adverse maternal or neonatal outcomes were observed after antepartum influenza treatment with adamantane antiviral agents.[39]

The most common side effects related to amantadine ingestion are minor, dose-related gastrointestinal and CNS complaints, including nervousness, lightheadedness, difficulty concentrating, confusion, insomnia, and loss of appetite or nausea.[40] Complaints typically develop within the first week of administration, often resolve despite continued ingestion, and are reversible on drug discontinuation. CNS side effects occur in 5% to 33% of amantadine recipients at dosages of 200 mg/day but are significantly less frequent with rimantadine. When used for influenza prophylaxis in ambulatory adults, dosages of 200 mg/day are associated with excess withdrawals in 6% to 11% of recipients because of drug side effects. Dosages of 100 mg/day are better tolerated and may be protective against influenza illness. Amantadine dosage reductions are required in older adults (100 mg/day), but 20% to 40% of nursing home residents experience significant adverse effects on this lower dosage despite some adjustment for renal insufficiency.[41-43] Consequently, further dosage reductions based on CrCl are warranted in this population.[44]

In the setting of renal insufficiency or high dosages, serious neurotoxic reactions, including delirium, hostility, hallucinations, tremor, myoclonus, seizures, or coma; cardiac arrhythmias; and death can occur in association with elevated amantadine plasma concentrations

(1 to 5 μg/mL).[45] Neurotoxic reactions may be transiently reversed by physostigmine administration, and lidocaine has been used to treat ventricular arrhythmias. Long-term amantadine ingestion has been associated with livedo reticularis, peripheral edema, orthostatic hypotension, and, rarely, congestive heart failure, vision loss, or urinary retention. Peripheral edema and livedo reticularis may improve if treatment is switched from amantadine to rimantadine.[46] Patients with preexisting seizure disorders have an increased frequency of major motor seizures during amantadine use, and dosage reductions are advised. Psychiatric side effects in patients with Parkinson's disease and psychotic exacerbations in patients with schizophrenia may occur with addition of amantadine. Rash and leukopenia have been described rarely.

Rimantadine administration is associated with dose-related side effects similar to side effects observed with amantadine, although the risk for CNS side effects is lower with rimantadine at dosages of 200 mg/day or 300 mg/day in ambulatory adults.[5] During prophylaxis, excess withdrawal rates are usually less than 5%. In older nursing home residents, dosages of 200 mg/day are associated with higher side effect rates, whereas dosages of 100 mg/day seem to be better tolerated.[41,47] Rimantadine may uncommonly cause exacerbations of seizures in patients not receiving anticonvulsants and was associated with an unexplained excess mortality in one nursing home study.[47]

The clinical observations of dry mouth, pupillary dilation, toxic psychosis, and urinary retention in acute amantadine overdose suggest that anticholinergic activity is present in humans. Amantadine shows activity on the adrenergic nervous system by affecting accumulation, release, and reuptake of catecholamines in the CNS and in the peripheral nervous system. Malignant ventricular arrhythmia after amantadine overdose has been described in humans.

Amantadine and rimantadine lack mutagenicity in vitro; carcinogenicity studies have not been reported for either. Amantadine is teratogenic and embryotoxic in rats, and rimantadine may cause teratogenic effects in rabbits and maternal toxicity and embryotoxicity at high dosages in rodents. Both drugs are classified in pregnancy category C. Birth defects have been reported after amantadine exposure during pregnancy.[48] The safety of neither amantadine nor rimantadine has been established in pregnancy. Because of excretion in breast milk, use is not recommended in nursing mothers.

Clinical Studies

Influenza A

Amantadine and rimantadine have been efficacious for the prevention and treatment of influenza A virus infections in young healthy adults.[5,40,49] A systematic review of published studies in children and the elderly concluded that available data only demonstrate that amantadine has prophylactic efficacy and a modest therapeutic effect in children.[50] In the elderly, no data were available to support a conclusion of prophylactic or therapeutic efficacy of either adamantane. The emergence of widespread and nearly complete amantadine resistance among influenza A/H3N2 isolates,[26] as well as the amantadine resistance of the pandemic A (H1N1)pdm09 strains, precludes the empirical use of adamantanes for management of an untyped influenza A outbreak. Amantadine and rimantadine, both at a dosage of 200 mg/day in adults, are about 70% to 90% protective against clinical illness caused by various susceptible influenza A subtypes, including susceptible pandemic strains.[51] Prophylaxis is effective in preventing nosocomial influenza and possibly in curtailing nosocomial outbreaks caused by such strains. Protection seems to be additive to that provided by vaccine.[52]

Rimantadine was less effective than zanamivir in reducing cases of influenza A illness in adults in a long-term care facility.[53] The difference in protective efficacy was largely due to the emergence of rimantadine-resistant viruses that caused rimantadine prophylactic failure; no zanamivir-resistant viruses were isolated. Rimantadine administration to school-aged children (5 mg/kg/day) decreased the risk for influenza A illness in recipients and possibly in their family contacts. Postexposure prophylaxis with these drugs provided inconsistent protection to family contacts, however, in part, depending on whether ill index children were treated.[19] Dosages of 100 mg/day seem to be protective against influenza A illness and are well tolerated in adults.[54]

Amantadine and rimantadine are also effective therapies for uncomplicated adamantane-susceptible influenza A illness in healthy adults,[5,22] but it is uncertain whether treatment reduces the risk for complications in high-risk patients or is useful in patients with established pulmonary complications. Early treatment in ambulatory adults (200 mg/day for 5 days) reduces the duration of fever and systemic complaints by 1 to 2 days, decreases virus shedding, and shortens time to resumption of usual activities.[22] In illness caused by H3N2-subtype influenza viruses, certain abnormalities of peripheral airways function, but not of airway hyperreactivity, resolve more quickly in amantadine-treated patients. Amantadine or rimantadine treatment in adults with leukemia or stem cell transplantation may reduce the risk for pneumonia,[55] but more recent data suggest that in stem cell transplant recipients, early neuraminidase inhibitor therapy may be preferred to adamantanes, because it may prevent progression to pneumonia and decrease viral shedding, thereby possibly preventing both influenza-related death in index patients and nosocomial transmission to others.[56] In children, rimantadine treatment is associated with lower symptom burden, fever, and viral titers during the first 2 days of treatment compared with acetaminophen administration, but rimantadine-treated children have more prolonged shedding of virus. Treatment generally does not seem to affect humoral immune responses to infection, but may blunt secretory antibody levels.[57]

Intermittent aerosol administration of amantadine or rimantadine seems to be therapeutically useful in uncomplicated influenza. No injectable formulation of either drug is available in the United States.

Other Viruses

Amantadine has been used in multiple trials for treatment of chronic hepatitis C with inconsistent evidence for increases in sustained viral response (SVR). In treatment-naïve patients, the addition of amantadine (200 mg daily in single or divided doses) to interferon[58,59] or to interferon plus ribavirin[60] may modestly increase biochemical responses and the likelihood of SVR. In re-treatment of interferon nonresponders, the combination of interferon plus amantadine is ineffective[61] but the addition of amantadine to the combination of interferon plus ribavirin may be associated with SVR in 10% to 25%.[62] Amantadine plus combined pegylated interferon and ribavirin may increase SVR modestly in treatment-experienced patients compared with pegylated interferon plus ribavirin.[63] Reports of possible activity in bornavirus infections and associated neuropsychiatric symptoms require confirmation.

DAS181 (FLUDASE)

DAS181 is an investigational antiviral agent with activity against influenza A and B viruses and parainfluenza viruses types 1-3.[64-69] It has a novel mechanism of action in that it is a sialidase from *Actinomyces viscosus* (Fig. 44-2) linked to a respiratory epithelium-anchoring domain.[70] It cleaves the terminal sialic acid residues on the surface of human respiratory cells, thus reducing the binding of respiratory viruses, which use those as receptors. Desialylation is rapid and results in an antiviral effect, which lasts for at least 2 days.[64] The effective concentration (EC) for 50% of all isolates (EC_{50}) against influenza A and B viruses ranges from 0.04 to 0.9 μM.[65] DAS181 is active against influenza viruses that are resistant to neuraminidase inhibitors.[71] Low-level resistance to DAS181 can be induced, but resistant variants appear to be reduced in fitness.[72]

DAS181 is administered by oral inhalation and appears to be generally well tolerated. A phase II placebo-controlled study was recently conducted in 177 subjects with influenza A and B virus infections.[73] DAS181 was administered either as a single 10-mg dose or as a daily 10-mg dose for 3 days. Compared with placebo recipients, DAS181 recipients had a statistically significant decrease in virus load determined by polymerase chain reaction (PCR) assay between days 1 and 3 and days 1 and 5. However, there were no differences in resolution of clinical illness among the groups. Administration of DAS181 appeared to be generally well tolerated, although transient elevations in alkaline phosphatase level were reported.[73]

DAS181 has also been utilized to treat parainfluenza virus type 3 infections in lung transplant and stem cell transplant patients.[74,75] These case reports described clinical improvement, increased pulmonary

function, and decreased virus loads. Additional clinical studies of DAS181 are being planned.

LANINAMIVIR OCTANOATE

Laninamivir octanoate (Inavir) is an investigational drug except for its approval in Japan. It is the prodrug of laninamivir, an inhibitor of influenza A and B neuraminidases.[76] Laninamivir is (2R,3R,4S)-3-acetamido-2-[CIR,2R-2,3-dihydroxy-1-methoxypropyl]-4-quanidino-3,4-dihydro-2-H-pyram-6-carboxylic acid (Fig. 44-3D). Laninamivir octanoate consists of an octanoic acid ester side chain attached at the C_3 position of laninamivir. Laninamivir octanoate, like polymeric zanamivir conjugates, shares the pharmacokinetic characteristic of persisting for a prolonged period in the respiratory tract after administration intranasally or intratracheally in animals or by oral inhalation in humans. These observations have presaged therapeutic effects of a single dose in animals with experimentally induced influenza in patients as well.

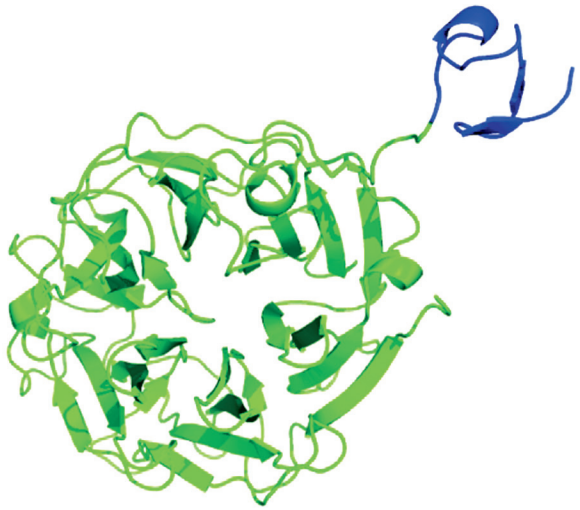

FIGURE 44-2 Molecular model of DAS181. The catalytic domain of the sialidase (AvCD) is shown in *green* and the protruding anchoring domain (AR) on the carboxyl terminus in *blue*. *(From Malakhov M, Aschenbrenner L, Smee D, et al. Sialidase fusion protein as a novel broad-spectrum inhibitor of influenza virus infection.* Antimicrob Agents Chemother. *2006;50:1470.)*

Spectrum

Laninamivir octanoate exhibits little or no influenza virus neuraminidase inhibitory activity in vitro.[77] However, its hydrolysis product is a potent inhibitor of neuraminidases of N1 to N9 influenza A viruses plus influenza B and their replication in cell culture at nanomolar concentrations.[78] These include seasonal and pandemic influenza A/H1N1, highly pathogenic avian influenza (HPAI) H5N1 viruses, and clinical isolates of oseltamivir-resistant H1N1, H3N2, H5N1, and A (H1N1)pdm09. Median inhibitory concentrations in cell culture vary over a wide range and in general appear to be intermediate between those of oseltamivir carboxylate (lower) and zanamivir (higher), but the clinical importance of these differences is not yet known.

In preclinical studies, laninamivir octanoate reduced fever in ferrets, mortality in mice, and virus concentrations in lung in ferrets and mice and brain in mice after induced influenza with a variety of viruses: A/PR/8/34, HPAI H5N1, A (H1N1)pdm09, B/Malaysia/2506/2004, as well as oseltamivir-resistant A H1N1 and HPAI H5N1 clinical isolates possessing the H274Y mutation, as reviewed by Yamashita and associates.[78] In these studies, laninamivir octanoate was administered as a single intranasal dose after intranasal inoculation of virus and was either as or more efficacious than multiple doses of oral oseltamivir or intranasal zanamivir. The results of these studies in animals with experimental influenza have been replicated in part in therapeutic trials of a single laninamivir octanoate dose in the clinic (see later).

Single doses of laninamivir octanoate are also efficacious prophylactically in mice. One dose prevents mortality and reduces virus concentration in lungs and brain when administered as much as 7 days before virus challenge.[79]

Mechanism of Action

See subsequent discussion of mechanism of action under "Oseltamivir."

The basis for the prolonged persistence of laninamivir in the respiratory tract after intranasal or intratracheal administration of laninamivir octanoate in animals or oral inhalation in humans is not completely understood. In human volunteers, bronchoalveolar lavage samples obtained serially over 24 hours after oral inhalation of a single 40-mg dose of laninamivir octanoate reveal concentrations that exceed influenza virus neuraminidase inhibitory concentrations at all test times.[80] In mice, intranasal administration of carbon-14 (^{14}C)–labeled laninamivir octanoate demonstrates prolonged retention of laninamivir in lung tissues. Microautoradiography indicates that laninamivir octanoate is taken into airway epithelial cells, seemingly hydrolyzed to the antiviral molecule laninamivir by intracellular esterases, and then released slowly extracellularly, perhaps as a result of its hydrophobic

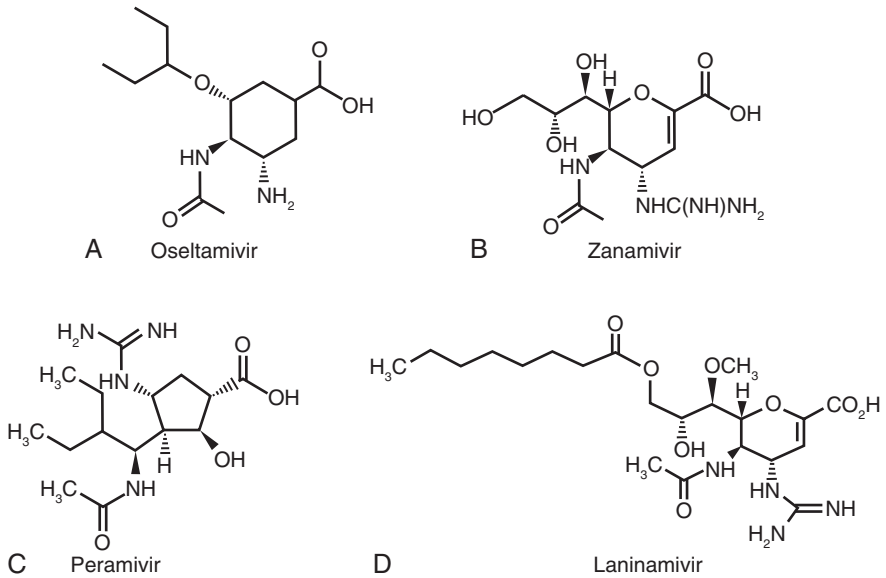

FIGURE 44-3 Chemical structures of oseltamivir carboxylate (A), zanamivir (B), peramivir (C) and laninamivir (D).

poor membrane permeability.[81] The cellular and molecular processes underlying these observations are not yet determined.

Resistance

No extensive studies have been reported on the emergence of laninamivir-resistant strains after laninamivir exposure in vitro or laninamivir octanoate treatment in animals or patients. However, in one study in mice infected with an A H1N1 virus, no viruses with reduced susceptibility to laninamivir were recovered.[82]

Pharmacokinetics

Epithelial lining fluid concentrations of laninamivir octanoate and laninamivir calculated from analysis of bronchoalveolar lavage washings after a single oral inhalation of 40 mg laninamivir octanoate were 102.4 and 8.6 μg/mL, respectively, at 4 hours in healthy adult volunteers.[76] The disappearance half-times in bronchoalveolar lavage fluid were 41 and 141 to 241 hours, respectively. The plasma $t_{½elim}$ values were 2.6 and 45.7 hours, respectively. Laninamivir concentrations in epithelial lining fluid exceeded the median inhibitory concentrations for influenza neuraminidases at all time points for 240 hours after dose inhalation. In other healthy adult volunteers, evaluation of the pharmacokinetics of laninamivir octanoate and laninamivir was done after oral inhalation of single doses from 5 to 120 mg.[83] Laninamivir octanoate appeared rapidly in plasma with a C_{max} at 0.5 to 1.0 hour compared with 4.0 hours for laninamivir. Plasma $t_{½elim}$ values were 1.8 and 71.6 to 80.8 hours, respectively. The plasma area under the concentration-time curve (AUC) of laninamivir octanoate was linearly related to dose, while that of laninamivir increased disproproportionately. The mean cumulative excretion in urine over 144 hours was 2.3% to 3.6% and 10.7% to 14.6%, respectively.

After intravenous administration of ^{14}C-laninamivir in rats, almost 90% of the radioactivity was recovered in urine.[84] In human volunteers, the clearance of both laninamivir octanoate and laninamivir is linearly related to CrCl.[85] In subjects with none, mild, moderate, or severe renal impairment given a single orally inhaled dose of 20 mg laninamivir octanoate, the renal clearance of laninamivir octanoate and laninamivir is directly related to CrCl, whereas $t_{½elim}$ values are not. Geometric mean laninamivir octanoate clearance values declined from 26.0 mL/min in normal control subjects to 6.5 mL/min in patients with severe renal impairment. However, $t_{½elim}$ values were 2.3 to 3.5 hours and not different among the four groups. Laninamivir renal clearance declined from 65.0 to 12.7 mL/min across the four groups, whereas $t_{½elim}$ was not different among the groups, ranging from 53.2 to 57.0 hours. The likely explanation is that the elimination of both laninamivir octanoate and laninamivir reflect slow release of these compounds from tissues into plasma, rather than renal elimination, a pharmacokinetic concept called "flip-flop."[86] These pharmacokinetic data indicate that reduction of laninamivir octanoate doses may be appropriate for patients with renal impairment for pharmacokinetic reasons, but the lack of clear dose-related toxicity (see later) and the minimal absorption of orally inhaled drugs suggest that no dose adjustment will be needed.

Toxicity

Like orally inhaled zanamivir, orally inhaled laninamivir octanoate powder is well tolerated. In a double-blind study in healthy adult volunteers, single doses from 5 to 120 mg or multiple doses of 20 or 40 mg twice daily for 5 days were as well tolerated as placebo.[85]

In clinical trials, patients with influenza were randomized to single laninamivir octanoate doses of 20 or 40 mg in adults or children 10 years old or older, 20 mg in children younger than 10 years old, or inhaled zanamivir as the control neuraminidase inhibitor treatments. Laninamivir octanoate inhaled once was as well tolerated as inhaled zanamivir 20 mg twice daily for 5 days.[87] In a double-blind trial in children 9 years of age or younger with influenza, a single dose of inhaled laninamivir octanoate of 20 or 40 mg was as well tolerated as oseltamivir at 2 mg/kg body weight twice daily for 5 days.[88] In a phase III double-blind trial in adults 20 years of age or older with influenza, a single dose of inhaled laninamivir octanoate of 20 or 40 mg was as well tolerated as oral oseltamivir at 75 mg twice daily for 5 days.[89] Notwithstanding the lack of data from large, randomized, placebo-controlled, double-blind trials to establish the tolerability of laninamivir octanoate across the range of persons in healthy and high-risk groups, these published data on laninamivir octanoate tolerance plus those from studies of orally inhaled zanamivir collectively suggest that orally inhaled laninamivir octanoate will likely prove to be well tolerated and safe in the clinic.

Postmarketing studies of laninamivir octanoate in Japan concluded that the safety profile of laninamivir octanoate for abnormal behavior/delirium and syncope is similar to that of other neuraminidase inhibitors.[90] In Japan, it is recommended in the product labeling that teenage patients inhaling laninamivir octanoate should remain under constant parental supervision for at least 2 days to monitor for behavioral changes to prevent associated self-injury. To avoid syncope, patients should inhale laninamivir octanoate in a relaxed sitting position. In another postmarketing survey for laninamivir octanoate tolerance, 50 patients of 3542 (1.4%) reported an adverse event.[91] Commonly reported adverse events included psychiatric disorders (abnormal behavior), gastrointestinal symptoms, and nervous system disorders such as dizziness, with frequencies of 0.48%, 0.45%, and 0.17%, respectively. These usually appeared on the day of laninamivir octanoate treatment and resolved in 3 days. These adverse reactions and their frequency were considered comparable to those previously observed during clinical trials, and thus were believed to confirm no noticeable problem with safety.

Clinical Studies

Limited data from controlled trials are available on the efficacy of orally inhaled laninamivir octanoate for influenza treatment, although three randomized, controlled trials on the efficacy and tolerance of laninamivir octanoate and one observational study comparing it with other neuraminidase inhibitors have been reported. In these trials, laninamivir octanoate has been administered as an orally inhaled powder with a proprietary device that has two containers of 10-mg dry laninamivir octanoate powder. The manufacturer's instructions recommend two inhalations from each 10-mg changer. For children, four inhalations are necessary, whereas eight inhalations from two devices are required for adults. Occasionally, young children do not inhale the medication completely owing to technical difficulty with the device.[87]

Of 87 pediatric patients with influenza of less than 48 hours in duration, 44 were randomized to treatment with a single inhaled dose of laninamivir octanoate ($N = 55$), 20 or 40 mg, according to age, or inhaled zanamivir, 10 mg twice daily for 5 days ($N = 41$).[87] Median times to fever resolution were 36 hours in the laninamivir octanoate groups and 37 hours in the zanamivir-treated group. This relatively small study suggested that a single dose of inhaled laninamivir octanoate was as efficacious as the recommended 5-day treatment with zanamivir. In another study, 180 children 9 years or younger with influenza of less than 36 hours in duration were randomized to a single oral inhalation of 40 ($N = 61$) or 20 mg ($N = 61$) laninamivir octanoate or oseltamivir 2 mg/kg ($N = 62$) ingested twice daily for 5 days.[88] Of the 180 children, 62% (112) were infected with influenza A H1N1 virus, of which all but 4 possessed the H274Y mutation, mediating oseltamivir resistance. Oseltamivir therapy was likely not to have been different from placebo. The median times to alleviation of influenza illness in children were significantly less (49.6 and 44.3 hours) in the 40- and 20-mg laninamivir groups, respectively, than in the oseltamivir-treated group (110.5 hours). Treatment effects on virus concentration and persistence in upper airway secretions were inconsistent, although on day 3, 10%, none, and 25% of subjects in the three groups, respectively, were still excreting virus. There were no clinical therapeutic or virologic differences among children infected with influenza A H3N2 or B viruses, but the numbers of cases were small.

In a double-blind, randomized noninferiority trial, 1003 young healthy adults with febrile influenza for no more than 36 hours were randomized to receive either 40 mg or 20 mg of laninamivir octanoate by oral inhalation once or oseltamivir, 75 mg twice daily orally, for 5 days.[89] The primary end point was time to influenza illness alleviation. Unfortunately, as in the pediatric study of Sugaya and Ohashi,[88] 66% of the subjects were infected with oseltamivir-resistant influenza A H1N1 virus. The median times to resolution of illness in patients infected with this virus were 74.0, 85.8, and 77.8 hours, respectively, which were not different. Virus was detected by culture significantly

less often at day 3 in the laninamivir octanoate 40-mg (28%) and 20-mg (32%) groups than in the oseltamivir group, which might be considered analogous to a placebo-treated cohort. Among individuals infected with influenza A H3N2 virus, median times to illness alleviation were not different between those treated with laninamivir octanoate 40 mg (73.5 hours) and oseltamivir (67.5 hours) but significantly longer in the group treated with laninamivir octanoate 20 mg (91.2 hours). There were no differences among the groups in H3N2 virus concentration in upper airway secretions or persistence. The 95% confidence intervals of the pooled analysis of all data were less than the prescribed noninferiority margin. It was concluded that a single inhalation of laninamivir octanoate is effective for treatment of seasonal influenza including that caused by oseltamivir-resistant virus in adults.

In an observational study, 211 children with febrile influenza of less than 48 hours due to influenza A H3N2 infection and 45 with A (H1N1)pdm09 infection were treated according to the recommendations of clinicians and the preference of patients or their guardians.[92] Of the 256 children, 119 were treated with oseltamivir in weight-appropriate doses, zanamivir (124 cases), one dose of intravenous peramivir (4 children),[79] or a single dose of orally inhaled laninamivir octanoate of 40 mg for children 10 years or older or 20 mg for those younger than 10 years (9 children). The primary end point was duration of fever from the first dose of neuraminidase inhibitor. There were no differences in the duration of fever among the oseltamivir, zanamivir, or laninamivir octanoate groups. The median time to resolution of fever in the peramivir group (17.0 hours) was significantly less than in the other three groups.

Available data suggest that a single inhaled dose of laninamivir octanoate is efficacious in children with influenza of less than 48 hours, but efficacy in other populations, especially those with high-risk conditions, remains to be evaluated, as does the impact on complications of influenza.

OSELTAMIVIR

Spectrum

Oseltamivir phosphate (Tamiflu) is the ethyl ester prodrug of oseltamivir carboxylate, a sialic acid analogue (see Fig. 44-3A) that is a potent, specific inhibitor of the neuraminidases of influenza A and B viruses.[93,94] The metabolite, oseltamivir carboxylate, is approximately 50-fold more potent than the phosphate prodrug.[95] Oseltamivir carboxylate competitively and reversibly interacts with the active enzyme site to inhibit neuraminidase activity at low nanomolar concentrations.[96] Inhibitory concentrations for neuraminidase inhibitors in cell culture have a broad range (≥1000-fold), depending on the assay method, and may not correlate with in vivo activity.[97,98] Oseltamivir carboxylate is active against viruses containing all nine influenza A neuraminidase subtypes recognized in nature, including more recent pathogenic avian viruses (H5N1, H7N7, H9N2), reassortant virus containing neuraminidase from the 1918 pandemic strain, M2 inhibitor–resistant strains,[4,99] and the recently circulating (2009) pandemic A/H1N1 viruses (S-OIV).[27] Resistance to oseltamivir has been recently reported in an H7N9 isolate.[100]

Influenza B viruses are 10-fold to 20-fold less susceptible to oseltamivir carboxylate than influenza A viruses, and influenza B virus illness responds less well clinically and virologically to oseltamivir than influenza A illness.[101,102,103] The carboxylate is not cytotoxic and inhibits neuraminidases from mammalian sources or other pathogens only at 10^6-fold higher concentrations. Oral oseltamivir is active in murine and ferret models of influenza.[94,97] A prophylactic regimen given orally twice daily for 10 days completely protected ferrets against morbidity and mortality caused by H5N1 infection and did not interfere with development of a protective immunity against subsequent H5N1 infection.[104] Neuraminidase inhibitors combined with M2 inhibitors or ribavirin show enhanced antiviral activity in vitro and in animal models of influenza A virus infection,[105] including H5N1 virus.[106,107] Amantadine combined with oseltamivir prevented the emergence of amantadine resistance in cell culture.[108]

Mechanism of Action

The neuraminidase inhibitor drugs oseltamivir, zanamivir, peramivir, and laninamivir share a common mechanism of action. Influenza neuraminidase cleaves terminal sialic acid residues on glycoconjugates and destroys the receptors recognized by viral hemagglutinin on cells, on newly released virions, and on respiratory tract mucins. This action is essential for release of virus from infected cells and for spread within the respiratory tract.[109] Inhibition of neuraminidase action causes newly formed virions to adhere to the cell surface and to form viral aggregates. Inhibitors limit spread of virus within the respiratory tract and may prevent virus penetration of respiratory secretions to initiate replication.

Resistance

Resistant variants selected by in vitro passage with oseltamivir carboxylate or zanamivir have point mutations in the viral hemagglutinin or neuraminidase genes.[98,110] Hemagglutinin variants generally have mutations in or near the receptor binding site that make them less dependent on neuraminidase action for release from cells in vitro and that confer cross-resistance among neuraminidase inhibitors. Most of these variants retain full susceptibility in vivo.[98] Neuraminidase variants contain single amino-acid substitutions in the framework or catalytic residues of the active enzyme site that alter drug binding and cause approximately 30-fold to more than 1000-fold reduced susceptibility in enzyme inhibition assays.[96] Influenza A variants selected by oseltamivir carboxylate are subtype specific, most commonly Arg292Lys in N2 and H275Y in N1, without cross-resistance to zanamivir. The altered neuraminidases have reduced activity or stability in vitro, and early studies of these variants usually demonstrated decreased infectivity and transmissibility in animals.[111]

Oseltamivir therapy has been associated with recovery of viruses with reduced susceptibility in about 1% of immunocompetent adult and 18% of pediatric recipients.[112,113] Generally, emergence of resistant variants has not been associated with clinical worsening, although prolonged recovery of resistant variants, sometimes in combination with M2 inhibitor resistance, has been observed in highly immunocompromised hosts.[114] Transmission of oseltamivir-resistant virus has been documented.[115,116]

Although isolation of oseltamivir-resistant strains from treated immunocompetent patients was uncommon, in 2007-2008, oseltamivir-resistant seasonal H1N1 virus appeared widely in immunocompetent individuals in Norway in the absence of antiviral pressure.[117] This mutant virus became the transmissible, pathogenic prevalent global H1N1 virus strain. Similarly, during the 2009 A (H1N1)pdm09 pandemic, there was no linkage between prevalent use of oseltamivir in immunocompetent patients and the appearance of oseltamivir-resistant A (H1N1)pdm09 strains, which was uncommon. The prevalence of oseltamivir-resistance ranged from 0.6% (5/804 strains) tested in Ontario, Canada,[118] to 1.0% in the United States[119] and 1.1% (16/1488 isolates) in Southeast Asia.[120] The prevalence was 8.11% in children whose immunocompetence was not specified.[121]

On the other hand, oseltamivir-resistant isolates are not uncommonly recovered from immunocompromised patients being treated with the drug. Reports indicated that some of the A (H1N1)pdm09 oseltamivir-resistant strains retained replicative fitness,[116] transmissibility,[122] and pathogenicity comparable with wild-type oseltamivir strains in murine and ferret models of influenza infection.[123] Clinical illness caused by oseltamivir-resistant H1N1 strains in immunocompetent children responded less well to oseltamivir,[124] as evidenced by higher fever at day 4 or 5 of treatment, although some found no evidence of prolonged illness in children infected with drug-resistant virus.[125] Others reported a significantly longer time to achieve nondetectable virus load in patients with oseltamivir-resistant H1N1 compared with oseltamivir-sensitive strains.[126]

Pharmacokinetics

Oral oseltamivir is rapidly absorbed and metabolized by esterases in the gastrointestinal tract, liver, and blood to the active carboxylate. The estimated bioavailability of the carboxylate is approximately 80%,[127] and its time to maximal plasma concentrations averages 2 to 4 hours. Dose proportionality of oseltamivir has been reported over the dose range from 75 to 675 mg. Only low blood levels of the prodrug are detectable. Rarely, possession of a constitutive variant of carboxylesterase 1, the enzyme that normally catalyzes the conversion of

oseltamivir phosphate to carboxylate, can markedly impair the hydrolysis of the parent compound, resulting in the potential for a compromised antiviral effect after oseltamivir administration.[128,129] Ingestion with food delays absorption slightly but does not decrease overall bioavailability. Oseltamivir administered via a nasogastric tube to patients with respiratory failure requiring mechanical ventilation was well absorbed and converted to oseltamivir carboxylate.[130,131] In healthy adults, peak and trough plasma concentrations average 0.35 μg/mL and 0.14 μg/mL after 75-mg doses.[132] In infants up to 1 year of age, systemic exposure ($AUC_{0\text{-}12\ hr}$) to the carboxylate exhibits decreasing variability while clearance increases.[121] Recommended doses of oseltamivir are 3.0 mg/kg twice daily for infants from birth to 8 months of age and 3.5 mg/kg twice daily for those 9 to 11 months of age. In children older than 1 year, carboxylate exposure increases gradually with increasing age[132] so that weight-based dosing is recommended.[133] In healthy elderly adults, overall drug exposure is about 25% greater than in younger adults, most likely owing to differences in renal elimination. Morbid obesity (body mass index ≥40 kg/m^2) does not alter oseltamivir pharmacokinetics.[134] The effects of pregnancy on the pharmacokinetics of oseltamivir are unclear. One study reported no differences among women in the third trimester of pregnancy and historical controls,[135] whereas another reported a 25% to 30% reduction in systemic ($AUC_{0\text{-}12\ hr}$) oseltamivir-carboxylate exposure in pregnant women compared with concurrent nonpregnant controls, perhaps suggesting a need for 75 mg three times a day of oseltamivir for treatment.[136]

Plasma protein binding of the prodrug (42%) and the carboxylate (<3%) is low.[127] The V_d is moderate (23 to 26 L). In animals, lower respiratory tract levels are similar to or exceed the levels in blood[137]; and in humans, the carboxylate is detectable in middle ear and maxillary sinus fluid at concentrations similar to those in plasma.[138]

Oseltamivir concentrations occur in breast milk.[139] In the ex vivo human placenta model, oseltamivir was extensively metabolized to the carboxylate moiety, but transplacental passage of oseltamivir carboxylate occurred at a low rate, inferring that fetal exposure during maternal treatment with oseltamivir may be minimal.[140] No carboxylate was detected in cerebrospinal fluid in one child,[141] whereas C_{max} values in cerebrospinal fluid were 2.1% and 3.5% for corresponding plasma concentrations for oseltamivir and oseltamivir carboxylate in eight healthy adults after ingestion of 150 mg of oseltamivir.[142] After oral oseltamivir, the plasma $t_{½elim}$ of the carboxylate averages 6 to 10 hours in healthy adults. The prodrug and carboxylate are excreted primarily unchanged through the kidney; the carboxylate is eliminated by glomerular filtration and tubular secretion via a probenecid-sensitive anionic transporter. Clearance varies linearly with CrCl, such that $t_{½elim}$ increases to 22 hours in patients with CrCl less than 30 mL/min, and dosage reductions are needed.[127] Oseltamivir carboxylate is removed with different degrees of efficiency by different renal replacement therapies (peritoneal, hemodialysis, and continuous renal replacement therapies). Doses of oseltamivir for patients with renal impairment receiving renal replacement therapy have been published.[143]

Uncomplicated influenza illness does not seem to alter the pharmacokinetics of oseltamivir.[127] Cystic fibrosis patients appear to clear oseltamivir carboxylate more rapidly than patients who do not have the disease.[144]

Interactions

Probenecid reduces renal clearance of oseltamivir by about 50%.[145] Few other clinically important drug interactions have been recognized. Sotalol appeared to induce a torsades de pointes cardiac arrhythmia during oseltamivir therapy for influenza.[146] Specific studies have found no interactions with antacids, acetaminophen, or aspirin or known inhibitors of selected renal tubular secretion pathways, amoxicillin, cimetidine, cyclosporine, mycophenolate, tacrolimus,[127,147] warfarin,[148] or rimantadine.[149]

Toxicity

Preclinical studies have found no evidence of mutagenic, teratogenic, or oncogenic effects. High-dose oseltamivir causes renal tubular mineralization in mice and maternal toxicity in rabbits. It is classified as pregnancy category C.

Oseltamivir is generally well tolerated in patients of all ages, including pregnant women and fetuses,[150,151] and no serious end-organ toxicity has been recognized.[97,152-154] Oral administration is associated with nausea, epigastric distress, or emesis in 10% to 15% of adults receiving 75 to 150 mg twice daily. These gastrointestinal complaints are usually mild to moderate in intensity, resolve despite continued dosing, and are ameliorated by administration with food. Nausea and vomiting (and possibly, dizziness) are dose related in adults.[155] Discontinuation rates of 1% to 2% were observed in controlled treatment studies. The mechanism of nausea and vomiting is uncertain, but the risk seems to be lower in older adults. Long-term prophylaxis has not been associated with an increased risk for adverse events,[97,156] although headache may occur in older recipients. Self-injury, delirium, and psychiatric illness have been reported in patients, primarily pediatric or adolescent, with influenza treated with oseltamivir, mostly in Japan.[157] Analyses of neuropsychiatric reactions among patients with influenza treated with oseltamivir in three large U.S. administrative databases did not demonstrate such an association.[158-160] The decline in cases in Japan after a regulatory recommendation to restrict oseltamivir use in children 10 to 19 years of age has been associated with a decline in oseltamivir-related cases but a corresponding rise in cases associated with zanamivir, the inhaled, minimally systemically bioavailable neuraminidase inhibitor. The latter fact raises further doubts about a causal association between oseltamivir therapy and neuropsychiatric and behavioral adverse reactions in patients with influenza.[161] Erythematous rashes and rare instances of severe eruptions or Stevens-Johnson syndrome, hepatic inflammation, hemorrhagic colitis, anaphylaxis, and thrombocytopenia have been reported, but their relationship to oseltamivir is uncertain.

Clinical Studies

Oseltamivir is efficacious for the prevention and treatment of influenza A and B virus infection. In the United States, it is approved for the prevention of influenza in patients 1 year and older and the treatment of acute uncomplicated influenza in patients 2 weeks of age and older who have been symptomatic for no more than 2 days.[133]

In early clinical experiments in volunteers with induced influenza it was demonstrated that oral oseltamivir is highly protective against experimental human influenza, and early treatment is associated with reductions in viral titers, symptoms, nasal cytokines, and middle ear pressure abnormalities.[97] Subsequent controlled trials in patients—mostly healthy adults and children with naturally acquired seasonal influenza A infection—demonstrated that early oseltamivir treatment of acute influenza reduces the time to illness alleviation by 1 to 1½ days, fever duration, and viral titers in the upper respiratory tract.[112,162-164] Earlier treatment maximizes the speed of resolution of illness.[165] Treatment of children reduces the risk for otitis media and decreases overall antibiotic use.[112] In healthy and high-risk adults, early treatment has been reported to decrease the risk for lower respiratory tract complications leading to antibiotic administration and to hospitalization,[166] but this has been questioned.[167] A meta-analysis of observational studies of high-risk patients with seasonal influenza concluded that oseltamivir treatment may reduce hospitalization, whereas treatment of hospitalized patients reduces respiratory failure, intensive care unit admission, and mortality.[168,169] A recent meta-analysis based on a large number of observational data from individual cases suggested that oseltamivir treatment may be associated with a reduction in mortality risk.[169a] However, a Cochrane analysis did not conclude that the evidence indicated that oseltamivir treatment reduced complications or hospitalizations.[169b] In hospitalized patients with infection with influenza A (H1N1)pdm09, oseltamivir provides similar benefits even if treatment is started more than 48 hours after clinical illness has begun.[170-172]

It is uncertain to what extent oseltamivir treatment may reduce transmission, although a review of four trials of prophylaxis suggests that oseltamivir may have reduced transmission.[173,174]

Oseltamivir is less efficacious for the treatment of influenza B than for influenza A virus infection in children[175,176] and adults.[176] An analysis of 284 cumulated cases of influenza A (H5N1) infections in a global registry demonstrated that crude mortality was significantly less in those treated with oseltamivir (40%) than in those not treated (76%) when started up to 6 to 8 days after symptoms onset.[177]

Oseltamivir treatment of hematopoietic stem cell transplant recipients with influenza may prevent the development of pneumonia and virus shedding, thereby both preventing influenza-related death in index patients and nosocomial transmission to others.[178] Of 21 patients with leukemia who developed influenza and were treated with oseltamivir, none died, compared with 3 of 8 who were not treated.[179]

Prophylactic administration of once-daily oral oseltamivir (75 mg) is highly effective in reducing the risk for developing febrile illness during influenza season in unimmunized adults (efficacy 84%),[180] immunized nursing home residents (efficacy 92%),[181] and transplant recipients (efficacy 80%).[156] Prevention of influenza may reduce secondary complications in institutionalized older adults.[181] Once-daily oseltamivir for 7 to 10 days is also effective for postexposure prophylaxis in household contacts, including children, and when ill index cases receive concurrent treatment.[182,183] Oseltamivir chemoprophylaxis has been used to control institutional outbreaks of influenza A continuing despite M2 inhibitor use and of influenza B.[184]

PERAMIVIR

Spectrum

Peramivir ([1S,2S,3S,4R]-3-[(1S)-1-(acetylamino)-2-ethylbutyl]-4-[(aminoiminomethyl)amino]-2-hydroxy-cyclopentanecarboxylic acid; Rapiacta) (see Fig. 44-3C) is an investigational agent in the United States but is approved in Japan, China, and South Korea. It is a potent, selective inhibitor of influenza A and B virus neuraminidases, including that of all nine avian NA subtypes[185] and influenza A (H1N1) pdm09.[186] It is a sialic acid analogue designed to be structurally distinct from oseltamivir and zanamivir such that cross-resistance to it among oseltamivir-resistant and zanamivir-resistant strains is not consistently observed.[187,188] Like oseltamivir and zanamivir, peramivir inhibits influenza neuraminidase in enzyme assays at nanomolar concentrations[189] and requires micromolar concentrations to inhibit influenza replication in cell culture.[190] It is a more potent inhibitor of influenza A than B viruses in vitro than is oseltamivir or zanamivir.[190] The clinical relevance of this difference has not yet been evaluated. Combination treatment of influenza A virus infection in cell culture and in mice with peramivir and ribavirin yields additive or synergistic interactions with no increase in toxicity.[191] The antiviral effect of combinations of peramivir plus rimantadine in vitro is variable, ranging from additive to synergistic.[192] In mice with experimental influenza infections, the combination of peramivir and rimantadine is synergistic.[193] In murine and ferret models of influenza infection, peramivir is effective when administered intranasally,[194] orally,[195] and intramuscularly.[196]

Mechanism of Action

See previous discussion of mechanism of action under "Oseltamivir."

Resistance

Peramivir-resistant influenza virus has been selected in vitro,[187,188,197,198] but not from peramivir-treated mice with experimental influenza infection,[199] healthy volunteers given peramivir for prevention or treatment of experimentally induced influenza A or B infection, or healthy treated patients.[200] A peramivir-resistant virus possessing the H275Y mutation emerged during intravenous therapy for pandemic 2009 influenza A/H1N1 in an immunocompromised patient.[201] Peramivir-resistant mutants generated in vitro may possess unaltered or diminished virulence and replicative capacity in mice and ferrets.[202] Peramivir resistance associated solely with an alteration in the hemagglutinin gene conferred cross-resistance to oseltamivir and zanamivir and could cause lethal disease in mice. Infection with the resistant virus in mice was still amenable to peramivir therapy, however.[198]

Naturally occurring oseltamivir-resistant influenza viruses possessing the H275Y mutation have a 100-[186] to 661-fold[202] reduced susceptibility to peramivir, less than that of oseltamivir (982-fold). Studies suggest that infection due to viruses possessing the H275Y mutation may be successfully treated with higher dose regimens of injected peramivir in mice[203] and high-risk patients.[204] However, intravenous peramivir was not more effective than oseltamivir in a case report[201] and in an observational study of influenza caused by H275Y mutant strains.[204] In 2009, the World Health Organization recommended that for treatment of infection due to influenza A (H1N1)pdm-09 strains possessing the H275Y mutation, intravenous peramivir is likely to be suboptimal and intravenous zanamivir is preferred.[205]

Pharmacokinetics

The absolute oral bioavailability of peramivir is 2%.[206] As a result, clinical development has focused on its efficacy and safety after intramuscular and intravenous injection. Fortunately, its long elimination half-life supports single-dose intravenous treatment regimens. At doses up to 2 mg/kg in adults, plasma $t_{1/2}$ and $AUC_{0\text{-}\alpha}$ increase in proportion to dose. At higher doses of greater than 2 mg/kg being used in clinical trials in adults, the plasma $t_{1/2}$ in healthy adults is approximately 20 hours, which supports single-dose treatment; apparent V_d is approximately 2 L/kg, and systemic clearance is 85 mL/hr/kg. The corresponding values for children with mean age of 9 years are 7.7 hours, 0.3 L/kg, and 173 mL/hr/kg.[207] The physiologic counterpart of this large V_d is unknown, because no locus of drug sequestration has been identified. Plasma protein binding is less than 30%. Peramivir concentrations in plasma are 10-fold to 50-fold higher than concurrent levels in nasal wash or pharyngeal gargle solutions.[206] Peramivir is detectable at these sites 24 hours after dosing, at concentrations greater than levels that inhibit neuraminidases of most strains of influenza virus. The clinical relevance of these data is unknown.

A 300-mg dose injected intravenously once in young healthy adults with influenza illness of less than 48 hours' duration is efficacious and well tolerated.[208] Infusion of this dose over a median of 38 minutes produced median plasma concentrations of 18,100 ng/mL at the end of the infusion and 14.8 ng/mL 18 to 24 hours later. The 600-mg dose yielded corresponding values of 36,300 and 32.8 ng/mL. The median inhibitory concentration for 50% of isolates (IC_{50}) for the neuraminidase of the patient viruses ranged from 1.15 nmol/L for influenza A/H1N1, 1.36 nmol/L for influenza A/H3N2, and 2.81 nmol/L for influenza B isolates.[204] In pediatric patients 1 month to 15 years of age infected with influenza A (H1N1)pdm09, an intravenous infusion of 10 mg/kg once daily produced comparable plasma concentrations to those seen in young healthy adults (see earlier): median peramivir plasma concentrations were 33,150 ng/mL at the end of the infusion and 20.7 ng/mL 18 to 24 hours later.[207] The relationship of these plasma concentration data to efficacy is unclear. In mice, plasma AUC of peramivir is the pharmacokinetic characteristic related to efficacy.[209]

Data on peramivir distribution into breast milk in humans are unavailable.[206] Less than 5% of ^{14}C-labeled peramivir administered to rats is recovered in breast milk. Peramivir is eliminated unchanged into urine by glomerular filtration, and probenecid does not affect its excretion. In patients with renal insufficiency, mean $t_{1/2}$ ranges from 24 to 30 hours in subjects with mean CrCl of 21 to 68 mL/min. In individuals with dialysis-dependent renal failure, $t_{1/2}$ averages 79 hours.

In October 2009, the U.S. Food and Drug Administration issued an Emergency Use Authorization (EUA) for the administration of intravenous peramivir for the treatment of hospitalized patients with suspected or confirmed cases of influenza A (H1N1)pdm09 infection, because no other intravenous neuraminidase inhibitor drug was available. In adults with normal renal function, the recommended intravenous dose was 600 mg/day; and in children 6 to 17 years of age it was 10 mg/kg intravenously once daily. Doses for other age groups and patients with renal impairment including end-stage renal disease requiring different renal-replacement therapies have been suggested.[210] The EUA was terminated in 2010, and peramivir was to be available only through clinical trials (see "Clinical Studies," later).

Interactions

Adverse drug-drug interactions have not been reported in subjects given peramivir, but the number of individuals exposed is still modest. No pharmacokinetic interaction of intravenous peramivir and oral oseltamivir or rimantadine was observed in healthy volunteers.[211] Drug-drug interactions in individuals receiving peramivir are unlikely because it neither induces nor inhibits important drug-metabolizing cytochrome P-450 enzymes.

Toxicity

Peramivir is generally nontoxic and well tolerated. Preclinical studies revealed no genotoxicity, reproductive toxicity, or developmental

toxicity.[206] In multiple species of animals, the only apparent adverse effect is reversible nephrotoxicity, which is species (rabbit only) and gender (female) specific. The nephrotoxic dose is greater than 200 mg/kg/day intravenously for 9 days.

The largest doses administered to humans, 800 mg orally[200] and 600 mg intravenously,[208] have not been associated with consistent adverse symptoms or laboratory abnormalities compared with placebo.[208] In placebo-controlled clinical trials of peramivir orally up to 800 mg/day for 4 to 5 days,[200] 300 mg/day intramuscularly once,[212] and 600 mg intravenously once,[208] adverse symptoms were not reported more frequently in peramivir recipients than in placebo recipients.

In controlled, blinded trials as well as uncontrolled studies of intravenous peramivir, it has been generally well tolerated and safe. In a randomized, double-blind study comparing a single dose of peramivir of 300 or 600 mg and a matching placebo given intravenously to 300 young healthy adults in an outpatient setting,[208] nausea may have been reported more frequently in drug recipients (3.0%, 6.1%, and 1.0%, respectively, in the three groups). Extensive blood and urine laboratory tests revealed no differences among groups. In a randomized, double-blind, double-dummy trial in young healthy adults with influenza treated with peramivir, 300 mg and 600 mg intravenously once, or oseltamivir, 75 mg orally twice daily for 5 days, the overall incidence of adverse effects was lowest in the 300-mg group: 14.0% compared with 18.1% and 20.0% in the other groups, respectively. Diarrhea (3.8%, 5.5%, and 5.2%), nausea (0.5%, 1.9%, and 4.4%), and a decreased neutrophil count (2.5%, 3.8%, and 3.6%) all tended to be lowest in the 300-mg peramivir group.[213] In a randomized, unblinded study in hospitalized patients treated for influenza with intravenous peramivir at 200 or 400 mg once daily, or oseltamivir at 75 mg orally twice daily, all for 5 days, the "incidence of adverse events was low and generally similar among treatment groups."[214]

Assessment of side effects of intravenous peramivir in uncontrolled studies in hospitalized adults with high-risk comorbid conditions[204] also suggested that the drug was generally well tolerated. A single case of dilated cardiomyopathy or myocarditis in a volunteer infected with an influenza B challenge virus and treated with peramivir has been reported.[200] The relationship of the cardiac disorder to the drug is unknown.

Clinical Studies

In a study in serosusceptible volunteers, peramivir prophylaxis with 50 to 800 mg orally daily or placebo, initiated 24 hours before influenza A or B virus challenge and continued for 5 days, tended to prevent illness at doses of 200 mg or greater and to reduce viral shedding and titer in nasal washings in subjects inoculated with influenza A virus. No effect on preventing illness caused by influenza B virus was observed, although the duration of virus shedding tended to be less in individuals receiving 400 mg and 800 mg of peramivir.[200]

In early studies in patients with influenza, oral peramivir therapy with doses of 400 to 800 mg daily for 5 days[200] and single intramuscular doses of 150 or 300 mg[206] reduced median times to relief of symptoms, but the differences were not statistically significant from controls. Subsequently, controlled trials with an intravenous formulation demonstrated peramivir therapeutic efficacy and tolerance in patients with influenza due to susceptible virus strains. Peramivir treatment of naturally acquired influenza in young adults with illness of 48 hours' duration or less with 300 or 600 mg injected once intravenously versus placebo, reduced median time to relief of symptoms significantly from 82 hours in the placebo group to 59 hours and 60 hours in the peramivir 300-mg and 600-mg groups in the outpatient setting.[208] Peramivir treatments also significantly reduced the proportion of subjects still excreting virus in nasal and throat secretions at day 3 from 51% in placebo recipients to 26% to 37% in those treated with peramivir, 600 or 300 mg, respectively.[208]

In 137 hospitalized patients randomized to 5 days' treatment with intravenous peramivir, 200 or 400 g/day, compared with historical reports with oral oseltamivir at 75 mg twice daily, the reduction in virus concentration in nasopharyngeal secretion was similar across the three treatments.[211] An additional study utilizing a higher dose of peramivir (300 mg twice daily or 600 mg four times a day) in 234 hospitalized patients also showed no differences in virologic or clinical end points among the peramivir-treated regimens or compared with reported patients treated with oseltamivir.[215] A randomized controlled study of intravenously administered peramivir plus standard of care versus standard of care alone in patients hospitalized with influenza was recently terminated because of futility to show a difference between the peramivir and control groups.[215,216]

As noted earlier, intravenous peramivir is probably not effective for treatment of patients with oseltamivir resistance due to possession of the H275Y mutation; intravenous zanamivir has been recommended.

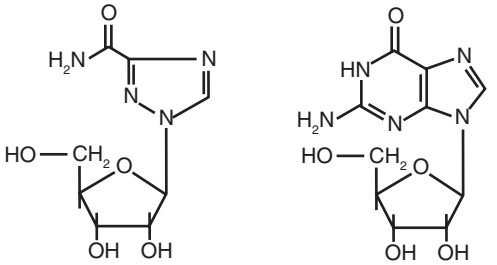

FIGURE 44-4 Chemical structure of ribavirin (A) and the nucleoside guanosine (B).

RIBAVIRIN

Spectrum

Ribavirin (1-β-D-ribofuranosyl-1,2,4-thiazole-3-carboxamide; Virazole, Rebetol, Copegus) is a guanosine analogue (Fig. 44-4A) in which the base and the D-ribose sugar are necessary for antiviral activity. Ribavirin inhibits the in vitro replication of a wide range of RNA and DNA viruses, including myxoviruses, paramyxoviruses, arenaviruses, flaviviruses, bunyaviruses, coronaviruses, togaviruses, reoviruses, herpesviruses, adenoviruses, poxviruses, and retroviruses. By plaque assay, inhibitory concentrations range from 3 to 10 μg/mL for influenza, parainfluenza, and respiratory syncytial virus (RSV). High concentrations inhibit group C adenoviruses[214] and pathogenic flaviviruses,[217] including West Nile virus in neural cells. Ribavirin does not inhibit severe acute respiratory virus (SARS) coronavirus in vitro.[218]

Low concentrations of ribavirin (1 to 10 μg/mL) reversibly inhibit macromolecular synthesis and the proliferation of rapidly dividing cells.[219] Ribavirin decreases nucleic acid and protein synthesis, inhibits interferon-γ release, and increases apoptosis in human peripheral blood mononuclear cells in vitro,[218,220] but it does not adversely affect polymorphonuclear leukocyte functions.[221] Ribavirin has been postulated to enhance cell-mediated immune responses by increasing type 1 and suppressing type 2 cytokine responses in T cells[221] and to decrease proinflammatory cytokine elaboration and inflammatory cell numbers. Inhibition of mast cell secretory responses occurs in vitro.

Aerosol administration is more effective than parenteral dosing in animal models of influenza and RSV infection. Parenteral ribavirin has antiviral and therapeutic activity in animal models of infection with Lassa virus, other arenaviruses, and bunyavirus (see Chapters 47, 168, and 169). Combinations of ribavirin with immunoglobulin in RSV infection and with M2 or neuraminidase inhibitors in influenza A infection or with neuraminidase inhibitors in influenza B infection show enhanced antiviral activity.[12] The use of ribavirin in treatment of hepatitis B and C is discussed in Chapter 46.

Mechanism of Action

The antiviral mechanisms of action of ribavirin are complex and most likely vary for different viruses. Ribavirin causes alterations of cellular nucleotide pools, inhibits viral RNA synthesis, and may cause lethal mutagenesis of certain RNA virus genomes.[221-223] Intracellular phosphorylation to the monophosphate, diphosphate, and triphosphate derivatives is mediated by host cell enzymes. In uninfected and RSV-infected cells, the predominant derivative (>80%) is the triphosphate, which is rapidly lost, with an intracellular $t_{½elim}$ of less than 2 hours.

Ribavirin monophosphate competitively inhibits inosine monophosphate dehydrogenase and interferes with the synthesis of

guanosine triphosphate (GTP) and with nucleic acid synthesis. Decreased concentrations of competing GTP likely potentiate ribavirin's other antiviral effects. Ribavirin triphosphate inhibits influenza virus RNA polymerase activity and the GTP-dependent 5′-capping of viral mRNA. The monophosphate is incorporated inefficiently into viral RNA genomes, and this may lead to lethal mutagenesis and contribute to antiviral activity.[222] HCV RNA polymerase incorporates ribavirin monophosphate into viral RNA, which causes mutations and inhibits viral RNA synthesis.[224] Ribavirin diphosphates and triphosphates also inhibit human immunodeficiency virus (HIV) reverse transcriptase activity.[225]

Ribavirin has immunosuppressive effects in experimental animals and shows therapeutic activity against transplantable virus-induced tumors and certain autoimmune diseases. Ribavirin increases type 1 cytokine–mediated immune responses in vivo, an effect that may contribute to its therapeutic activities,[221] and seems to augment type-1 cytokine responses ex vivo in peripheral blood mononuclear cells from patients with chronic hepatitis C.[223]

Resistance

Antiviral resistance to ribavirin has been documented only in Sindbis virus and HCV to date. One HCV RNA polymerase variant (F415Y) selected in genotype 1a–infected, ribavirin-treated patients has been associated with ribavirin resistance in vitro.[226] No ribavirin-resistant RSVs have been detected during aerosol therapy of children.

Pharmacokinetics

Oral ribavirin is well absorbed, but bioavailability averages 45% to 65% in adults because of first-pass metabolism.[227-230] Administration with food increases absorption and peak plasma concentrations by 70%.[227] After single oral doses of 600 mg, 1200 mg, or 2400 mg, peak plasma concentrations occur at 1 to 2 hours and average 1.3 μg/mL, 2.5 μg/mL, and 3.2 μg/mL. Plasma concentrations average approximately 24 μg/mL and 17 μg/mL after intravenous doses of 1000 mg and 500 mg in patients with Lassa fever. During long-term administration, overall exposure and $t_{½elim}$ increase substantially.[227] Steady-state plasma levels of about 1 to 4 μg/mL occur by about 4 weeks with weight-adjusted dosing in chronic hepatitis C, and higher concentrations at 4 weeks correlate with decline in hemoglobin and likelihood of sustained viral responses.[231] Plasma protein binding is negligible, and ribavirin has a large V_d (>2000 L). At steady state, cerebrospinal fluid levels are about 70% of those in plasma.[229]

The disposition of ribavirin is complex, involving renal elimination and metabolism. After rapid initial distribution, there is a prolonged terminal $t_{½elim}$ of 37 to 79 hours.[227-229] Ribavirin triphosphate concentrates in erythrocytes with an erythrocyte-to-plasma ratio of 40:1 or greater, and erythrocyte levels gradually decrease, with an apparent $t_{½}$ of 40 days. Renal excretion accounts for 30% to 60% of ribavirin's overall clearance, but hepatic metabolism is contributory. About 5% to 10% is recovered unchanged in the urine, and a much greater fraction is excreted as triazole carboxamide and carboxylic acid metabolites.[227] Plasma clearance is reduced threefold in patients with advanced renal impairment (CrCl ≤30 mL/min). Dosage adjustments are needed for renal insufficiency, and ribavirin should be used with caution in patients with CrCl less than 50 mL/min. Hemodialysis and hemofiltration remove small amounts of drug. Higher initial blood levels occur in severe hepatic dysfunction.[230]

With aerosol administration, systemic absorption is low (<1% of deposited dose). Peak plasma levels range from 0.5 to 2.2 μg/mL after 8 hours' exposure and from 0.8 to 3.3 μg/mL after 20 hours in pediatric patients. Respiratory secretion levels often exceed 1000 μg/mL and persist with a $t_{½}$ of 1.4 to 2.5 hours. A special aerosol generator (SPAG-2, ICN Pharmaceuticals) is needed to produce particles of proper aerodynamic size to reach the lower respiratory tract. The delivered dose is twice as high in infants (1.8 mg/kg/hr) than in adults.

Toxicity

Systemic ribavirin causes dose-related anemia because of extravascular hemolysis and, at higher dosages, suppression of bone marrow release of erythroid elements.[232] Reversible increases of serum bilirubin (in one fourth of recipients), serum iron, and uric acid concentrations occur during short-term oral administration. Long-term use of oral ribavirin at dosages greater than 800 mg daily causes hemoglobin decreases of 2 to 4 g/dL in most recipients, usually within 4 weeks. When used in combination with interferon, hemoglobin levels less than 11 g/dL develop in 25% to 30% of patients.[233] Renal impairment increases the risk for hemolysis. Severe anemia requires dosage reduction or cessation, although erythropoietin has been used effectively.[233] Other reported side effects include pruritus, myalgia, rash, nausea, depression, nervousness, and cough or respiratory symptoms.[234] High-dose intravenous ribavirin is associated with headache, hypomagnesemia, and hypocalcemia.[235] Bolus intravenous dosing may cause rigors, and infusion over 10 to 15 minutes is advised.

Aerosolized ribavirin may cause conjunctival irritation, rash, bronchospasm, reversible deterioration in pulmonary function, and, rarely, acute water intoxication. No adverse hematologic effects have been associated with aerosolized ribavirin. The drug may precipitate on contact lenses, so they should not be worn during aerosol exposure. Ribavirin exposure may occur in health care workers working in the environment of aerosol-treated infants.[235,236] Health care worker exposure is higher during delivery by oxygen hood than by ventilator or vacuum-exhausted hood systems.[235] Use of aerosol containment and scavenging systems, turning off the aerosol generator before providing routine care, and use of personal protective equipment have been recommended.[236]

When ribavirin is used in conjunction with mechanical ventilation, in-line filters, modified circuitry, and frequent monitoring are required to prevent plugging of ventilator valves and tubing with precipitates of ribavirin. The possible effects of such modifications on drug delivery to the lower respiratory tract are undefined.

In preclinical studies, ribavirin is mutagenic, gonadotoxic, and teratogenic.[232] Low oral dosages have been teratogenic or embryotoxic in multiple species. Use of ribavirin is relatively contraindicated during pregnancy, and pregnant women should not directly care for patients receiving ribavirin aerosol. Ribavirin is categorized as pregnancy category X, and effective means of contraception for men and women are recommended for at least 6 months after discontinuation of treatment or exposure.

Interactions

Antacids slightly decrease the oral bioavailability of ribavirin. During co-administration clinically, ribavirin, amantadine, and oseltamivir do not interact pharmacokinetically.[34] Ribavirin antagonizes the anti-HIV-1 effects of zidovudine but enhances the activity of purine dideoxynucleosides. Ribavirin use in patients who are coinfected with HIV and HCV and on antiretroviral drugs, particularly combined with didanosine, seems to increase the risk for mitochondrial toxicity and lactic acidosis. Ribavirin may inhibit the effect of warfarin.

Clinical Studies

Ribavirin aerosol is approved in the United States for treatment of RSV bronchiolitis and pneumonia in hospitalized children. Oral ribavirin in combination with various interferons is approved for treatment of chronic hepatitis C. The following describes only clinical studies on the prevention and treatment of respiratory virus infection with ribavirin. Treatment for infection with HCV is discussed elsewhere (see Chapters 46, 119, and 156).

Respiratory Syncytial Virus

Aerosolized ribavirin (18-hour exposure daily for 3 to 6 days) variably shortens the duration of virus shedding and may improve certain clinical measures in infants hospitalized with RSV illness.[238] No consistent reductions in need for ventilatory support or duration of hospitalization have been documented, however. In infants receiving mechanical ventilation for RSV-related respiratory failure, no significant reductions in duration of ventilatory support, hospitalization, or mortality have been found.[238,239] Intermittent, high-dose therapy (2-hour exposures three times daily for 5 days) is well tolerated and may be as effective as prolonged exposure.[240]

Use of aerosolized ribavirin is limited by concerns regarding its efficacy, ease of administration, risk of occupational exposure, and cost. The American Academy of Pediatrics states that aerosol treatment

for RSV infection "is not recommended for routine use but may be considered for use in selected patients with documented, potentially life-threatening RSV infection."[241] Decreased RSV-specific serum neutralizing antibody titers and diminished nasopharyngeal secretion RSV-specific IgE and IgA responses may occur in ribavirin-treated children. No long-term adverse or beneficial effects of ribavirin therapy have been documented in children.[242]

Combinations of aerosolized ribavirin and intravenous immunoglobulin or palivizumab may be beneficial in treating RSV pneumonia in hematopoietic stem cell transplant recipients,[243-246] whereas intravenous ribavirin alone is ineffective.[247] Therapy with either aerosolized[248-250] or oral[251,252] ribavirin appears to prevent progression from upper to lower respiratory tract illness in such patients. A similar benefit of preemptive treatment of RSV upper respiratory tract infection in lung transplant recipients with oral and inhaled ribavirin has been reported.[253,254]

Other Respiratory Viruses

Intravenous and aerosolized forms of ribavirin have been used to treat severe influenza virus infections.[255,256] Aerosolized ribavirin inconsistently reduces viral titers and illness measures in adults with uncomplicated influenza A or B and has modest efficacy in children hospitalized with influenza.[257] However, oral ribavirin 300 mg three times per day combined with amantadine and oseltamivir may possibly be effective for treatment of influenza A (H1N1)pdm09 disease and more so than oseltamivir alone.[258] Oral, intravenous, and aerosolized ribavirin have been used in immunosuppressed patients with severe parainfluenza virus and adenovirus infections with inconsistent clinical benefits.[255,259,260] Intravenous ribavirin has been used to treat adenovirus-associated hemorrhagic cystitis, pneumonia, and invasive infections in immunocompromised patients, and it may be effective even in severe disease.[261,262] Treatment with intravenous[263,264] and oral[265] ribavirin of human metapneumovirus pneumonia in immunocompromised patients has been associated with resolution. Aerosolized ribavirin has been used in treating parainfluenza virus infections in solid-organ transplant recipients, but seems ineffective in parainfluenza virus pneumonia in hematopoietic stem cell transplant recipients.[259] Oral ribavirin was effective in accelerating functional graft recovery and reducing late bronchiolitis obliterans in 38 lung transplant recipients[266] and in a bone marrow transplant recipient[267] with paramyxovirus respiratory infection. Intravenous ribavirin therapy was associated with successful treatment of paramyxovirus type 3 respiratory infection in cardiac transplant recipients.[268,269] Ribavirin has been used extensively in treating SARS coronavirus infections without proven antiviral effects in vitro[218] or in patients[270] and has been associated with frequent adverse effects.[235] Intravenous ribavirin seems to be ineffective in treatment of hantavirus cardiopulmonary syndrome.[271] However, it inhibits Andes virus in vitro, an important cause of this syndrome, and is effective in a hamster model of hantavirus cardiopulmonary syndrome caused by this virus (see Chapter 168).[272]

RSV604

RSV604 is an oral benzodiazepine compound ($C_{22}H_{17}FN_4O_2$) under development for treatment of RSV infections (Fig. 44-5).[273,274] It inhibits both RSV A and B subtypes at submicromolar concentrations. Its antiviral activity is expressed through interaction with the RSV nucleocapsid (N) protein, which is highly conserved.[275] The drug is well absorbed orally, and a single dose per day is sufficient to achieve antiviral EC_{90} levels. In vitro resistance can be elicited, at an apparent low rate, and resistant virus appears similarly fit to wild-type RSV in terms of replication.[275] Phase II studies of RSV604 are underway in transplant patients with RSV infections.

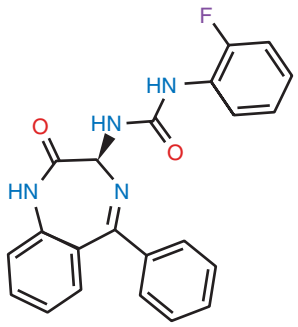

FIGURE 44-5 Chemical structure of RSV604.

ZANAMIVIR

Spectrum

Zanamivir (4-guanidino-2,4-dideoxy-*N*-acetylneuraminic acid; Relenza) is a sialic acid analogue (see Fig. 44-3B) that is a potent and specific inhibitor of the neuraminidases of influenza A and B viruses.[276] It inhibits influenza neuraminidase activity at nanomolar concentrations but has a higher and broader range of inhibitory concentrations in cell culture.[277,278] Compared with oseltamivir carboxylate, zanamivir is more active against influenza B, and data from a comparative trial in children indicate that this difference is clinically important.[279] Zanamivir is less active against neuraminidases of influenza A/N2 clinical isolates,[280] but the clinical importance of this difference is uncertain. Zanamivir inhibits certain influenza A neuraminidase variants that are resistant to oseltamivir carboxylate.[96] Combinations of zanamivir plus rimantadine inhibit strains of influenza A/H1N1 and H3N2 viruses synergistically, but some concentrations seem antagonistic when assessed by reductions in cell-associated virus yield.[281] Zanamivir is not cytotoxic and is highly selective for influenza neuraminidase, inhibiting neuraminidases from human[282] and other mammalian sources or other pathogens only at 10^6-fold higher concentrations. Millimolar concentrations inhibit parainfluenza virus type 3 in cell culture, most likely by blocking attachment.[283] Topical zanamivir in the respiratory tract is active in murine and ferret models of influenza.[277]

Resistance

Resistance to neuraminidase inhibitor drugs has developed less frequently than to the adamantane compounds and less frequently to zanamivir than to oseltamivir.

A recent systematic review of the prevalence of neuraminidase inhibitor resistance among influenza viruses cultured from immunocompetent ambulatory adults enrolled in prophylactic and therapeutic trials of zanamivir found no reports of zanamivir resistance.[284] In surveys of other collections of influenza isolates, a similar absence or dearth of zanamivir resistance was reported: influenza A H1N1 viruses circulating in the 2008-2009 influenza season in the United States prior to emergence of the 2009 pandemic were resistant to oseltamivir but susceptible to zanamivir.[285] Among 391 nonpandemic A/H1N1 isolates from Australia and Southeast Asia patients from 2006 to 2008, 2.3% were resistant to zanamivir[286] but susceptible to oseltamivir. Zanamivir resistance was not demonstrated among 3359 influenza A (H1N1)-pdm09 global isolates[287] nor among 304 oseltamivir-resistant isolates reported by the World Health Organization to August 2010.[288] Avian influenza A/H5N1 isolates from 2003 to 2005 were susceptible to zanamivir.[289] Of 680 influenza B viruses isolated in China from 2010 and 2011, one with D197N amino-acid substitution was resistant to zanamivir.[290]

Several neuraminidase mutations mediate diminished susceptibility to zanamivir: Q136K in an A (H1N1) seasonal virus (300-fold reduction in zanamivir susceptibility)[286] and S274N[291] in nonpandemic A/H1N1 virus and I223R (5-fold reduction)[292] in an A (H1N1)pdm09 isolate. The relationship of these virus resistance mutations and prior zanamivir therapy and immune competence was not consistently apparent. An influenza B virus with an Arg152Lys mutation resistant to both zanamivir and oseltamivir was recovered from an immunocompromised child with prolonged virus excretion despite receipt of nebulized zanamivir.[293] The effect of these neuraminidase mutations on infectivity and transmissibility compared with the wild-type parental strains is variable, but only some mutants have been characterized in this regard.[293-295]

An observational study in pediatric patients with influenza treated with oseltamivir or zanamivir suggested that the lower prevalence of zanamivir than oseltamivir resistance is more related to the intrinsic properties of the drugs than to differences in the prevalence of use of the drugs.[296]

Pharmacokinetics

The oral bioavailability of zanamivir is low (<5%). The approved formulation is a dry powder containing a lactose carrier delivered by oral inhalation with a proprietary Diskhaler device. The proprietary inhaler device for delivering zanamivir is breath activated and requires a cooperative, trained patient. The use of the Diskhaler device is unreliable in young children, very infirm or elderly patients, or cognitively impaired patients. Although the inhaler has been used effectively in many older adults,[297] more than half of hospitalized older adults could not correctly use the device after instruction.[298]

After inhalation of the dry powder using the Diskhaler, approximately 15% is deposited in the lower respiratory tract while the remainder is deposited in the oropharynx.[277] Zanamivir concentrations in epithelial lining fluid obtained by bronchoalveolar lavage may approximate concentrations in alveoli. Median epithelial lining fluid concentrations of zanamivir 12 hours after oral inhalation of the recommended 10-mg dose by Diskhaler in healthy volunteers ranged from 0.3 to 0.9 μg/mL.[299] In other uninfected individuals, median zanamivir levels in induced sputum were 1.34 μg/mL, 0.30 μg/mL, and 0.05 μg/mL at 6 hours, 12 hours, and 24 hours after dosing, with the pulmonary $t_{½elim}$ estimated to be 2.8 hours.[300] Approximately 4% to 17% of an inhaled dose is absorbed systemically, and peak plasma levels are low, averaging 0.04 to 0.05 μg/mL.[277] Because of the low bioavailability of zanamivir inhaled orally, dosage adjustments are not indicated in renal insufficiency.

After intravenous dosing, the plasma $t_{½elim}$ of zanamivir ranges from 1.6 to 2.9 hours,[277,299] with about 90% eliminated unchanged in the urine.[277] After intravenous administration of 600 mg zanamivir to healthy adults, the median serum C_{max} is 39.4 μg/mL, $AUC_{0\text{-}12\ hr}$ is 86.6 μg/mL, and C_{trough} is 0.6 μg/mL. The median epithelial lining fluid concentration 12 hours after dosing is 0.4 μg/mL, very similar to the value after inhalation of 10 mg (see earlier). This is 552 to 1653 times the in vitro IC_{50} for influenza A and B neuraminidases, respectively.[280]

The pharmacokinetics of zanamivir in 103 adults with influenza receiving 600 mg intravenously twice daily with dose adjustments for renal impairment were similar to those in previously described studies.[301] Zanamivir renal clearance declines linearly with increasing renal impairment.[302] The suggested dose for adults with normal renal function is 600 mg intravenously given twice daily. Doses for children and for patients with renal impairment who are or are not receiving replacement therapy have been published.[303]

Interactions

No clinically significant drug interactions have been recognized for inhaled zanamivir. No clinically relevant pharmacokinetic interaction was demonstrated between oseltamivir, 150 mg taken orally twice daily, and zanamivir, 600 mg administered intravenously every 12 hours, in healthy volunteers.[304] Zanamivir does not affect the immune response to injected inactivated influenza vaccine, but, similar to all antiviral medications, it has the potential to impair the immunogenicity of attenuated live influenza vaccine administered concurrently. Zanamivir should not be administered from 48 hours before to 2 weeks after intranasal administration of an attenuated influenza vaccine.[305]

Toxicity

Preclinical studies of zanamivir found no evidence of mutagenic, teratogenic, or oncogenic effects. In cell culture, the inhibitory effect of zanamivir on influenza virus replication was not impaired by analgesics, antihistamines, decongestants, or antibacterial drugs.[306] Zanamivir is classified as a pregnancy category C agent.

Orally inhaled zanamivir is generally well tolerated, and the frequencies of complaints are not significantly different from those in placebo recipients among adults and children 5 years old or older.[277,306,307] This includes once-daily oral inhalation for prophylaxis by adults for 16 weeks.[308] Most reported symptoms in treatment studies are likely the result of the underlying illness. Similarly, in high-risk patients receiving zanamivir or placebo, no differences in adverse reactions have been seen in controlled trials.[309] In patients with mild to moderate asthma or chronic obstructive pulmonary disease, orally inhaled zanamivir is associated with fewer bronchitis episodes, similar measurements of forced expired volume in 1 second, and more rapid improvement in peak expiratory flow rate than with inhaled placebo.[310] However, postmarketing reports indicate a potential risk for acute bronchospasm, respiratory arrest, or worsening of chronic obstructive pulmonary disease accompanied by pulmonary edema after zanamivir inhalation, particularly in patients with underlying airway disease.[311] Apparent declines in respiratory function have also been rarely reported in patients without recognized airway disease. Consequently, use in patients with underlying airway disease is not generally recommended in the United States, although treatment in at-risk patients is used in other countries.[312] If used in patients with obstructive airway disease, zanamivir should be administered cautiously under close observation and with availability of fast-acting bronchodilators.

Zanamivir inhaled as an experimental nebulized solution containing 16 mg/mL for 10 minutes four times a day for 5 days for treatment of serious influenza with lower respiratory tract signs in hospitalized patients 10 years or older was well tolerated.[313] However, when the oral formulation containing lactose has been reformulated as a solution and administered into the airway during mechanical ventilation, lactose precipitation in the airway filters has caused obstruction,[314] precluding the reformulation of the powder in the orally inhaled formulation into a solution for nebulization and inhalation.

Zanamivir injected intravenously to healthy volunteers in doses from 50 to 600 mg twice daily for 5 days was also well tolerated.[315] In 130 hospitalized adults with influenza treated with zanamivir, 600 mg intravenously twice daily for 5 days, or reduced doses in those with renal impairment, no safety signals or clinically significant trends in laboratory values, vital signs, or electrocardiograms were identified that were considered attributable to the drug.[316]

Clinical Studies

Zanamivir has been administered to patients intranasally as a spray, by oral inhalation as a dry powder, by nasal inhalation as an aerosol from a nebulized solution, and by intravenous injections.

Intranasal and intravenous zanamivir are highly protective against experimental human influenza, and early treatment is associated with reductions in viral titers, symptoms, and middle ear pressure abnormalities.[163,277,317] Orally inhaled zanamivir powder is approved in the United States for prevention of influenza in individuals 5 years old and older, and for treatment of influenza in individuals 7 years old and older. Zanamivir (10 mg twice daily for 5 days) inhaled early in the course of illness for treatment of uncomplicated influenza in previously healthy adults and children 5 to 12 years old shortens the times to illness resolution and return to usual activities by 1 to 3 days.[307,318,319] Treatment benefits seem to be greater in patients with severe symptoms at entry, in patients older than 50 years, and in higher-risk patients.[320] Inhaled zanamivir treatment in adults is associated with a 40% reduction in lower respiratory tract events leading to antibiotic use and a 28% overall reduction in antibiotic prescriptions.[321]

Zanamivir inhaled orally is equally efficacious for treatment of influenza A and B infection.[319,322] In individuals with influenza B illness, zanamivir reduces the median duration of fever by 32%, from 53 hours to 36 hours, compared with oseltamivir.[279] In high-risk patients with primarily mild to moderate asthma or other chronic cardiopulmonary conditions, orally inhaled zanamivir treatment reduces illness duration and the incidence of complications leading to antibiotic use.[310,323] It has been used to treat immunocompromised hosts with influenza A and B infections,[324] including a child to whom an aqueous zanamivir solution (16 mg/mL) was administered by aerosol and nebulizer via an endotracheal tube.[325] More recently, in an observational study, orally inhaled zanamivir was more efficacious for treatment of oseltamivir-resistant influenza A/H1N1 than oseltamivir.[326]

Prophylactic administration of once-daily inhaled zanamivir (10 mg) prevents febrile influenza illness during influenza season (84% efficacy),[327] or when used for postexposure prophylaxis in households with or without treatment of the ill index case (82% efficacy).[328,329] In an observational study with limited numbers of patients, orally inhaled zanamivir and oral oseltamivir were not different for prevention of secondary cases during nosocomial outbreaks on pediatric wards.[330] In nursing home residents, 2 weeks of inhaled zanamivir was superior to oral rimantadine in preventing influenza A infection, in part because of a high frequency of rimantadine resistance,[331] and inhaled zanamivir

has been used to curtail transmission of amantadine-resistant influenza A in nursing homes.[297]

Orally inhaled zanamivir has been administered in combination with oral oseltamivir. For postexposure prophylaxis in families, such combined zanamivir-oseltamivir administration was not more efficacious than either agent alone.[332] However, a subgroup analysis suggests greater efficacy of the combination treatment among contacts whose prophylaxis was begun within 24 hours of exposure to the index case compared with oseltamivir or zanamivir alone. For treatment of adults with mainly A/H3N2 influenza, zanamivir-oseltamivir combination treatment was not more efficacious than zanamivir alone and was less efficacious than oseltamivir monotherapy.[333]

Zanamivir has been administered intravenously to treat patients seriously ill with influenza who could not receive or who had failed oral oseltamivir therapy. Immunocompetent[334] and immunocompromised[335,336] patients who were infected with oseltamivir-resistant[337] and oseltamivir-susceptible[336,338] influenza A/H1N1 nonpandemic viruses or oseltamivir-resistant pandemic virus[339] or oseltamivir-sensitive influenza A (H1N1)pdm09 virus[335,340] have been successfully treated with intravenous zanamivir. There is a sense that intravenous zanamivir may be lifesaving.[341] However, an apparent lack of a relationship between intravenous zanamivir treatment–associated reductions in pandemic virus load in upper and lower respiratory tract secretions and mortality have prompted questions about its effectiveness in seriously ill patients.[342] A phase III study comparing intravenous zanamivir and oseltamivir in hospitalized patients is underway.

POLYMERIC ZANAMIVIR CONJUGATES

Polymeric zanamivir conjugates are experimental, high-molecular-weight anti-influenza compounds comprising multiple zanamivir monomers connected at the 7-0 position to backbone or linker molecules of various types and lengths.[343-349] These compounds are potential second-generation inhaled neuraminidase inhibitors for influenza chemoprophylaxis and therapy with enhanced potency and prolonged lung retention time compared with zanamivir. In mice, one of these compounds has been associated with prophylactic efficacy for 7 days after a single intranasal administration.

Spectrum

Polymeric zanamivir conjugates exhibit broad-spectrum anti-influenza activity, inhibiting human influenza A N1, N2, and B viruses and an avian influenza A/H5N1 virus.[343] Inhibitory potency varies according to the length[345] and type of linker molecule[344] and the number of zanamivir derivatives, whether dimeric,[343] trimeric, or tetrameric.[346] The most potent polymeric zanamivir conjugate is a dimer with a 14-carbon linker, which is 10-fold less potent in a neuraminidase assay enzyme inhibition test (IC_{50}, 7.86 nM vs. 0.76 nM for zanamivir) but is 500,000-fold more potent in inhibiting influenza A/WSN/33 (H1N1) in a cytopathic reduction assay (IC_{50}, 0.0001 nM vs. 56 nM for zanamivir).[343] In mice, this dimeric conjugate is 100 times more potent than zanamivir in preventing influenza virus replication in the lung for 7 days after a single intranasal dose of drug and 1 day after intranasal virus challenge (drug doses to reduce lung virus titer by 90% were 0.03 mg/kg and 2.92 mg/kg for the dimeric conjugate and zanamivir). The prophylactic effect is associated with prolonged persistence of dimer conjugate in lung tissue after intranasal administration, as discussed in the section on pharmacokinetics. The specificity of polymeric zanamivir conjugates for influenza A and B neuraminidase is presumed but not yet reported.

A zanamivir polymer can overcome zanamivir resistance. A zanamivir polymer bound to the neuraminidase of zanamivir-resistant avian influenza A viruses possessing a resistance mutation at position 119 bound as much as 2000 times more strongly than did monomeric zanamivir.[350]

Mechanism of Action

The synthesis of polymeric conjugates of zanamivir that retain neuraminidase inhibitory activity is possible because of the unique position of the molecule when it is docked in the enzymatic pocket, with the 7-OH group pointing out and away from the target site, making it accessible to linkage to different backbone molecules. Electron micrographs show influenza virus clumping in the presence of dimeric zanamivir conjugates. The marked potency of some conjugates is postulated to reflect clumping caused by three types of bivalent binding: between two neuraminidase molecules in the tetrameric transmembrane spike protein (intratetramer), binding between sites on different tetramers on the same virion (intravirionic), and head-to-head binding between different neuraminidase sites on separate virions (intervirionic binding).[343]

An additional mechanism for the marked enhancement of potency observed by synthesis of polymer-attached zanamivir is postulated to be the result of interference with intracellular trafficking of endocytosed virus and subsequent virus-endosome fusion.[351]

Resistance

Studies describing attempts to induce resistance in vitro by repeated passage in the presence of drug have not been reported.

Pharmacokinetics

Prolonged retention of polymeric zanamivir compared with monomeric zanamivir in lung tissue accounts for the enhanced antiviral effect of polymeric conjugates. After intratracheal instillation of the same single dose of a polymeric zanamivir conjugate or monomeric zanamivir solution to rats, lung homogenate drug concentrations of the polymeric compound after 48 hours and 168 hours are 35 times and 160 times greater than zanamivir concentrations.[343] Generally, lung retention time is directly related to molecular weight because small polar molecules leave the lung by passing through tight junctions between cells. Prolonged retention of high-molecular-weight polymeric conjugates compared with monomeric zanamivir is expected. However, the prolonged lung retention time of some smaller conjugates indicates that aqueous insolubility and aggregate formation plus partitioning into cell membrane phospholipids may also play a role in the prolonged retention of zanamivir polymeric conjugates in the lung after inhalation.[343]

Interactions and Toxicity

Toxicity studies have been limited to assessments of in vitro cytotoxicity. For a series of dimeric conjugates, concentrations of 100 to 1000 ng/mL caused no cytotoxicity.[345]

Clinical Studies

No clinical studies have been reported.

Key References

The complete reference list is available online at Expert Consult.

5. Hayden FG, Aoki FY. Amantadine, rimantadine, and related agents. In: Yu VL, Merigan TC, White NJ, et al, eds. *Antimicrobial Therapy and Vaccines*. Baltimore: Williams & Wilkins; 1999:1344-1365.
25. Bright RA, Medina MJ, Xu X, et al. Incidence of adamantane resistance among influenza A (H3N2) viruses isolated worldwide from 1994 to 2005: a cause for concern. *Lancet*. 2005;366:1175-1181.
31. Hoopes JD, Driebe EM, Kelley E, et al. Triple combination antiviral drug (TCAD) composed of amantadine, oseltamivir, and ribavirin impedes the selection of drug-resistant influenza A virus. *PLoS One*. 2011;6:E29778.
34. Seo S, Englund JA, Nguyen JT, et al. Combination therapy with amantadine, oseltamivir, and ribavirin for influenza A infection: safety and pharmacokinetics. *Antivir Ther*. 2013;18:377-386.
36. Jefferson T, Demicheli V, DiPietrantorj C, et al. Amantadine and rimantadine for influenza A in adults. *Cochrane Database Syst Rev*. 2006;(2):CD001169.
38. Kimberlin DW, Shalabi M, Abzug MJ, et al. Safety of oseltamivir compared with the adamantanes in children less than 12 months of age. *Pediatr Infect Dis J*. 2010;29:195-198.
50. Alves Galvao MG, Rocha Crispino Santos MA, Alves da Cunha AJ. Amantadine and rimantadine for influenza A in children and the elderly. *Cochrane Database Syst Rev*. 2012;(1):CD002745.
53. Gravenstein S, Drinka P, Osterweil D, et al. Inhaled zanamivir versus rimantadine for the control of influenza in a highly-vaccinated long-term care population. *J Am Med Dir Assoc*. 2005;6:359-366.
64. Ison MG. Expanding the armamentarium against respiratory viral infections: DAS181. *J Infect Dis*. 2012;206:1806-1808.
78. Yamashita M. Laninamivir and its prodrug, CS-8958: long-acting neuraminidase inhibitors for the treatment of influenza. *Antivir Chem Chemother*. 2010;21:71-84.
87. Katsumi Y, Otabe O, Matsui F, et al. Effect of a single inhalation of laninamivir octanoate in children with influenza. *Pediatrics*. 2012;129:e1431-e1436.
102. Kawai N, Ikematsu H, Iwaki N, et al. A comparison of the effectiveness of oseltamivir for the treatment of influenza A and influenza B: a Japanese multicenter study of the 2003-2004 and 2004-2005 influenza seasons. *Clin Infect Dis*. 2006;43:439-444.

112. Whitley RJ, Hayden FG, Reisinger K, et al. Oral oseltamivir treatment of influenza in children. *Pediatr Infect Dis J*. 2001;20:127-133.

121. Kimberlin DW, Acosta EP, Pritchard MN, et al. Oseltamivir pharmacokinetics, dosing and resistance among children aged 2 years with influenza. *J Infect Dis*. 2013;207:709-720.

127. He G, Massarella J, Ward P. Clinical pharmacokinetics of the prodrug oseltamivir and its active metabolite Ro 64-0802. *Clin Pharmacokinet*. 1999;37:471-484.

135. Greer LG, Leff RD, Rogers VL, et al. Pharmacokinetics of oseltamivir according to trimester of pregnancy. *Am J Obstet Gynecol*. 2011;204(suppl 6):S89-S93.

136. Beigi RH, Han K, Venkataramanan R, et al. Pharmacokinetics of oseltamivir among pregnant and nonpregnant women. *Am J Obstet Gynecol*. 2011;204(suppl 1):S84-S88.

167. Jefferson T, Jones M, Doshi P, et al. Neuraminidase inhibitors for preventing and treating influenza in healthy adults: systematic review and meta-analysis. *BMJ*. 2009; 339:b5106.

168. Hsu J, Santesso N, Mustafa R, et al. Antivirals for treatment of influenza: a systematic review and meta-analysis of observational studies. *Ann Intern Med*. 2012;156:512-524.

169a. Muthuru SG, Venkatersan S, Myles PG, et al. Effectiveness of neuraminidase inhibitors in reducing the mortality in patients admitted to hospital with influenza A H1N1pdm09 virus infection: a meta-analysis of individual participant data. *Lancet Respir Med*. 2014;2:395-404.

169b. Jefferson T, Jones MA, Doshi P, et al. Neuraminidase inhibitors for preventing and treating influenza in healthy adults and children. *Cochrane Database Syst Rev*. 2014;4: CD008965.

170. Muthuri SG, Myles PR, Vankatesan S, et al. Impact of neuraminidase inhibitor treatment on outcomes of public health importance during the 2009-2010 influenza A (H1N1) pandemic in a systematic review and metaanalysis in hospitalized patients. *J Infect Dis*. 2013;207:533-563.

172. Siston AM, Rasmussen SA, Honein MA, et al. Pandemic 2009 influenza A (H1N1) virus illness among pregnant women in the United States. *JAMA*. 2010;303:1517-1525.

178. Nichols WG, Guthrie KA, Corey L, et al. Influenza infections after hematopoietic stem cell transplantation: risk factors, mortality and the effect of antiviral therapy. *Clin Infect Dis*. 2004;39:1300-1306.

180. Hayden FG, Atmar RL, Schilling M, et al. Use of the selective oral neuraminidase inhibitor oseltamivir to prevent influenza. *N Engl J Med*. 1999;341:1336-1343.

182. Welliver R, Monto AS, Carewicz O, et al. Effectiveness of oseltamivir in preventing influenza in household contacts: a randomized controlled trial. *JAMA*. 2001;285:748-754.

185. Govorkova EA, Ieneva IA, Goloubeva OG, et al. Comparison of efficacies of RWJ-270201, zanamivir, and oseltamivir against H5N1, H9N2, and other avian influenza viruses. *Antimicrob Agents Chemother*. 2001;45:2723.

200. Barrosa L, Treanor J, Gubareva L, et al. Efficacy and tolerability of the oral neuraminidase inhibitor peramivir in experimental human influenza: randomised, controlled trials for prophylaxis and treatment. *Antivir Ther*. 2005;10: 901.

207. Sugaya N, Kohno S, Ishibashi T, et al. Efficacy, safety and pharmacokinetics of intravenous peramivir in children with 2009 pandemic H1N1 influenza virus infection. *Antimicrob Agents Chemother*. 2012;56:369-377.

210. Peramivir. In: *Clinical Pharmacology*. Tampa, FL: Elsevier/Gold Standard; 2009. Available at http://download.thelancet.com/flatcontentassets/H1N1-flu/treatment/treatment-53.pdf.

238. Randolph AG, Wang EE. Ribavirin for respiratory syncytial virus lower respiratory tract infection: a systematic overview. *Arch Pediatr Adolesc Med*. 1996;150:942-947.

248. Boeckh M, Englund J, Li Y, et al. Randomized controlled multicenter trial of aerosolized ribavirin for respiratory syncytial virus upper respiratory tract infection in hematopoietic cell transplant recipients. *Clin Infect Dis*. 2007; 44:245-249.

258. Kim Y, Young Suh G, Huh JW, et al. Triple-combination antiviral drug for pandemic H1N1 influenza virus infection in critically ill patients on mechanical ventilation. *Antimicrob Agents Chemother*. 2011;55:5703-5709.

259. Nichols WG, Corey L, Gooley T, et al. Parainfluenza virus infections after hematopoietic stem cell transplantation: risk factors, response to antiviral therapy, and effect on transplant outcome. *Blood*. 2001;98:573-578.

261. Souza ILA, Schnert L, Goto JM, et al. Oral ribavirin in treatment of adenovirus infection in hematologic patients: experience from a Brazilian university hospital. *Clin Microbiol Infect*. 2010;16:S24.

262. Gavin PJ, Katz BZ. Intravenous ribavirin treatment for severe adenovirus disease in immunocompromised children. *Pediatrics*. 2002;110:E9.

263. Bonney D, Razati H, Turner A, et al. Successful treatment of human metapneumovirus pneumonia using combination therapy with intravenous ribavirin and immune globulin. *Br J Haematol*. 2009;45:667-679.

266. Fuehner T, Dierich M, Duesbert C, et al. Single-centre experience with oral ribavirin in lung transplant recipients with paramyxovirus infections. *Antivir Ther*. 2011;16: 1733-1740.

275. Chapman J, Abbott E, Alber D, et al. RSV604, a novel inhibitor of respiratory syncytial virus replication. *Antimicrob Agents Chemother*. 2007;51:3346-3353.

279. Kawai N, Ikematsu H, Iwaki N, et al. Comparison of the effectiveness of zanamivir and oseltamivir for the treatment of influenza A and B. *J Infect*. 2008;36:51-57.

287. Gubareva LV, Trujillo AA, Okimo-Achiambo M, et al. Comprehensive assessment of 2009 pandemic influenza A(H1N1) virus drug susceptibility in vitro. *Antivir Ther*. 2010;15:1151-1159.

293. Gubareva LV, Matrosovich MN, Brenner MK, et al. Evidence for zanamivir resistance in an immunocompromised child infected with influenza B virus. *J Infect Dis*. 1998; 178:1257-1262.

296. Tamura D, Sugaya N, Ogawa M, et al. Frequency of drug-resistant viruses and virus shedding in pediatric influenza patients treated with neuraminidase inhibitors. *Clin Infect Dis*. 2011;52:e56-e93.

318. Hayden FG, Osterhaus ADME, Treanor JJ, et al. Efficacy and safety of the neuraminidase inhibitor zanamivir in the treatment of influenza virus infections. *N Engl J Med*. 1997;337:874-879.

325. Gukareva LV, Matrosovich MN, Brenner MK, et al. Evidence for zanamivir resistance in an immunocompromised child infected with influenza B virus. *J Infect Dis*. 1998; 178:1257-1262.

327. Monto AS, Robinson DP, Herlocher L, et al. Zanamivir in the prevention of influenza among healthy adults. *JAMA*. 1999;282:31-36.

336. Dohna-Schwake C, Schweiger B, Felderhoff-Muser U, et al. Severe H1N1 infection in a pediatric liver transplant recipient treated with intravenous zanamivir: efficiency and complications. *Transplantation*. 2010;90:223-224.

References

1. Neumayer EM, Haff RF, Hoffman CE. Antiviral activity of amantadine hydrochloride in tissue culture. *Proc Soc Exp Med Biol*. 1965;119:393-396.
2. Webster RG, Kawaoka Y, Bean WJ, et al. Chemotherapy and vaccination: a possible strategy for the control of highly virulent influenza virus. *J Virol*. 1985;55:173-176.
3. He G, Qiao J, Dong C, et al. Amantadine resistance among H5N1 avian influenza viruses isolated in northern China. *Antiviral Res*. 2008;77:72-76.
4. Tumpey TM, Garcia-Sastre A, Mikulasova A, et al. Existing anti-virals are effective against influenza viruses with genes from the 1918 pandemic virus. *Proc Natl Acad Sci U S A*. 2002;99:13849-13854.
5. Hayden FG, Aoki FY. Amantadine, rimantadine, and related agents. In: Yu VL, Merigan TC, White NJ, et al, eds. *Antimicrobial Therapy and Vaccines*. Baltimore: Williams & Wilkins; 1999:1344-1365.
6. Kelly JM, Miles MA, Skinner AC. The anti-influenza virus drug rimantadine has trypanocidal activity. *Antimicrob Agents Chemother*. 1999;43:985-987.
7. Maurin M, Benoliel AM, Bongrand P, et al. Phagolysosomal alkalinization and the bactericidal effect of antibiotics: the *Coxiella burnetii* paradigm. *J Infect Dis*. 1992;166:1097-1102.
8. Chan J, O'Riordan K, Wiley TE. Amantadine's viral kinetics in chronic hepatitis C infection. *Dig Dis Sci*. 2002;47:438-442.
9. Smee DF, Hurst BL, Wong MH, et al. Effects of double combinations of amantadine, oseltamivir, and ribavirin on influenza A (H5N1) virus infections in cell culture and in mice. *Antimicrob Agents Chemother*. 2009;53:2120-2128.
10. Bantia S, Kellogg D, Parker C, et al. Combination of peramivir and rimantadine demonstrate synergistic antiviral effects in sub-lethal influenza A (H3N2) virus mouse model. *Antiviral Res*. 2010;88:276-280.
11. Simeonova L, Gegova G, Galabov AS. Prophylactic and therapeutic combination effects of rimantadine and oseltamivir against influenza virus A (H3N2) infection in mice. *Antiviral Res*. 2012;95:172-181.
12. Madren LK, Shipman C Jr, Hayden FG. In vitro inhibitory effects of combinations of anti-influenza agents. *Antivir Chem Chemother*. 1995;6:109-113.
13. Takeda M, Pekosz A, Shuck K, et al. Influenza A virus M2 ion channel activity is essential for efficient replication in tissue culture. *J Virol*. 2002;76:1391-1399.
14. Hay AJ. Amantadine and rimantadine: mechanisms. In: Richman DD, ed. *Antiviral Drug Resistance*. Chichester, UK: Wiley; 1996:43-58.
15. Pinto LH, Holsinger LJ, Lamb RA. Influenza virus M2 protein has ion channel activity. *Cell*. 1992;69:517-528.
16. Griffin SD, Beales LP, Clarke DS, et al. The p7 protein of hepatitis C virus forms an ion channel that is blocked by the antiviral drug, amantadine. *FEBS Lett*. 2003;535:34-38.
17. Jubin R, Murray MG, Howe AY, et al. Amantadine and rimantadine have no direct inhibitory effects against hepatitis C viral protease, helicase, ATPase, polymerase, and internal ribosomal entry site-mediated translation. *J Infect Dis*. 2000;181:331-334.
18. Ziegler T, Hemphill ML, Ziegler ML, et al. Low incidence of rimantadine resistance in field isolates of influenza A viruses. *J Infect Dis*. 1999;180:935-939.
19. Hayden FG. Amantadine and rimantadine: clinical aspects. In: Richman DD, ed. *Antiviral Drug Resistance*. Chichester, UK: Wiley; 1996:59-77.
20. Englund JA, Champlin RE, Wyde PR, et al. Common emergence of amantadine and rimantadine resistant influenza A viruses in symptomatic immunocompromised adults. *Clin Infect Dis*. 1998;26:1418-1424.
21. Shiraishi K, Mitamura K, Sakai-Tagawa Y, et al. High frequency of resistant viruses harboring different mutations in amantadine-treated children with influenza. *J Infect Dis*. 2003;188:57-61.
22. Hayden FG, Sperber SJ, Belshe RB, et al. Recovery of drug-resistant influenza A virus during therapeutic use of rimantadine. *Antimicrob Agents Chemother*. 1991;35:1741-1747.
23. Galbraith AW, Oxford JS, Schild GC, et al. Protective effect of 1-adamantanamine hydrochloride on influenza A2 infections in the family environment. *Lancet*. 1969;2:1026-1028.
24. Mast EE, Harmon MW, Gravenstein S, et al. Emergence and possible transmission of amantadine-resistant viruses during nursing home outbreaks of influenza A (H3N2). *Am J Epidemiol*. 1991;134:988-997.
25. Bright RA, Medina MJ, Xu X, et al. Incidence of adamantane resistance among influenza A (H3N2) viruses isolated worldwide from 1994 to 2005: a cause for concern. *Lancet*. 2005;366:1175-1181.
26. Deyde VM, Xu X, Bright RA, et al. Surveillance of resistance to adamantanes among influenza A (H3N2) and A (H1N1) viruses isolated worldwide. *J Infect Dis*. 2007;196:249-257.
27. Centers for Disease Control and Prevention. Update drug susceptibility of swine-origin influenza A (H1N1) viruses. *MMWR Morb Mortal Wkly Rep*. 2009;58:433-435.
28. Cho HG, Choi JH, Kim WH, et al. High prevalence of amantadine-resistant influenza A virus isolated in Gyeonggi Province, South Korea, during 2005-2010. *Arch Virol*. 2013;158:241-245.
29. Lan Y, Zhang Y, Dong L, et al. A comprehensive surveillance of adamantane resistance among human influenza A virus isolated from mainland China between 1956 and 2009. *Antivir Ther*. 2010;15(6):853-859.
30. Weinstock DM, Zuccotti G. Adamantane resistance in influenza A. *JAMA*. 2006;295:934-936.
31. Hoopes JD, Driebe EM, Kelley E, et al. Triple combination antiviral drug (TCAD) composed of amantadine, oseltamivir, and ribavirin impedes the selection of drug-resistant influenza A virus. *PLoS One*. 2011;6:E29778.
32. Nguyen JT, Hoopes JD, Le MH, et al. Triple combination of amantadine, ribavirin, and oseltamivir is highly active and synergistic against drug resistant influenza virus strains in vitro. *PLoS One*. 2010;5:e9332.
33. Goralski KB, Bose R, Sitar DS. $NH4^+$ modulates renal tubule amantadine transport independently of intracellular pH changes. *Eur J Pharmacol*. 2006;541:87-94.
34. Seo S, Englund JA, Nguyen JT, et al. Combination therapy with amantadine, oseltamivir, and ribavirin for influenza A infection: safety and pharmacokinetics. *Antivir Ther*. 2013;18:377-386.
35. Morrison D, Roy S, Rayner C, et al. A randomized, crossover study to evaluate the pharmacokinetics of amantadine and oseltamivir administered alone and in combination. *PLoS One*. 2007;2:e1305.
36. Jefferson T, Demicheli V, DiPietrantorj C, et al. Amantadine and rimantadine for influenza A in adults. *Cochrane Database Syst Rev*. 2006;(2):CD001169.
37. Strange KC, Little DW, Blatnik B. Adverse reactions to amantadine prophylaxis in a retirement home. *J Am Geriatr Soc*. 1991;39:700-705.
38. Kimberlin DW, Shalabi M, Abzug MJ, et al. Safety of oseltamivir compared with the adamantanes in children less than 12 months of age. *Pediatr Infect Dis J*. 2010;29:195-198.
39. Greer LG, Sheffield JS, Rogers VL, et al. Maternal and neonatal outcomes after antepartum treatment of influenza with antiviral medications. *Obstet Gynecol*. 2010;115:711-716.
40. Douglas RGJ. Prophylaxis and treatment of influenza. *N Engl J Med*. 1990;322:443-450.
41. Keyser LA, Karl M, Nafziger AN, et al. Comparison of central nervous system adverse effects of amantadine and rimantadine used as sequential prophylaxis of influenza A in elderly nursing home patients. *Arch Intern Med*. 2000;160:1485-1488.
42. Degelau J, Somani SK, Cooper SL, et al. Occurrence of adverse effects and high amantadine concentrations with influenza prophylaxis in the nursing home. *J Am Geriatr Soc*. 1990;38:428.
43. Stange KC, Little DW, Blatnik B. Adverse reactions to amantadine prophylaxis of influenza in a retirement home. *J Am Geriatr Soc*. 1991;39:700-705.
44. Kolbe F, Sitar DS, Papaioannou A, et al. An amantadine hydrochloride dosing program adjusted for renal function during an influenza outbreak in elderly institutionalized patients. *Can J Clin Pharmacol*. 2003;10:119-122.
45. Pimentel L, Hughes B. Amantadine toxicity presenting with complex ventricular ectopy and hallucinations. *Pediatr Emerg Care*. 1991;7:89-92.
46. Singer C, Papapetropoulos S, Gonzalez MA, et al. Rimantadine in Parkinson's disease patients experiencing peripheral adverse effects from amantadine: report of a case series. *Mov Disord*. 2005;20:873-877.
47. Monto AS, Ohmit SE, Hornbuckle K, et al. Safety and efficacy of long-term use of rimantadine for prophylaxis of type A influenza in nursing homes. *Antimicrob Agents Chemother*. 1995;39:2224-2228.
48. Pandit PB, Chitayat D, Jefferies AL, et al. Tibial hemimelia and tetralogy of Fallot associated with first trimester exposure to amantadine. *Reprod Toxicol*. 1994;8:89-92.
49. Wintermeyer SM, Nahata MC. Rimantadine: a clinical perspective. *Ann Pharmacother*. 1995;29:299-310.
50. Alves Galvao MG, Rocha Crispino Santos MA, Alves da Cunha AJ. Amantadine and rimantadine for influenza A in children and the elderly. *Cochrane Database Syst Rev*. 2012;(1):CD002745.
51. Hayden FG. Perspectives on antiviral use during pandemic influenza. *Philos Trans R Soc Lond B Biol Sci*. 2001;356:1877-1884.
52. Libow LS, Neufeld RR, Olson E, et al. Sequential outbreak of influenza A and B in a nursing home: efficacy of vaccine and amantadine. *J Am Geriatr Soc*. 1996;44:1153-1157.
53. Gravenstein S, Drinka P, Osterweil D, et al. Inhaled zanamivir versus rimantadine for the control of influenza in a highly-vaccinated long-term care population. *J Am Med Dir Assoc*. 2005;6:359-366.
54. Brady MT, Sears SD, Pacini DL, et al. Safety and prophylactic efficacy of low-dose rimantadine in adults during an influenza A epidemic. *Antimicrob Agents Chemother*. 1990;34:1633-1636.
55. La Rosa AM, Malik S, Englund JA, et al. Influenza A in hospitalized adults with leukemia and hematopoietic stem cell transplant (HSCT) recipients: risk factors for progression to pneumonia [abstract 418]. Presented at the 39th Annual Meeting of the Infectious Diseases Society of America. San Francisco, October 25-28, 2001.
56. Nichols WG, Guthrie KA, Corey L, et al. Influenza infections after hematopoietic stem cell transplantation: risk factors, mortality and the effect of antiviral therapy. *Clin Infect Dis*. 2004;39:1300-1306.
57. Clover RD, Waner JL, Becker L, et al. Effect of rimantadine on the immune response to influenza A infections. *J Med Virol*. 1991;34:68-73.
58. Zeuzem S, Teuber G, Naumann U, et al. Randomized, double-blind, placebo-controlled trial of interferon alfa2a with and without amantadine as initial treatment for chronic hepatitis C. *Hepatology*. 2000;32:835-841.
59. Helbling B, Stamenic I, Viani F, et al. Interferon and amantadine in naive chronic hepatitis C: a double-blind, randomized, placebo-controlled trial. *Hepatology*. 2002;35:447-454.
60. Berg T, Kronenberger B, Hinrichsen H, et al. Triple therapy with amantadine in treatment-naive patients with chronic hepatitis C: a placebo-controlled trial. *Hepatology*. 2003;37:1359-1367.
61. Younossi ZM, Mullen KD, Zakko W, et al. A randomized, double-blind controlled trial of interferon alpha-2b and ribavirin vs. interferon alpha-2b and amantadine for treatment of chronic hepatitis C non-responder to interferon monotherapy. *J Hepatol*. 2001;34:128-133.
62. Adinolfi LE, Utili R, Tonziello A, et al. Effects of alpha interferon induction plus ribavirin with or without amantadine in the treatment of interferon non-responsive chronic hepatitis C: a randomised trial. *Gut*. 2003;52:701-705.
63. Keating GM, Curran MP. Peginterferon-alpha-2a (40kD) plus ribavirin: a review of its use in the management of chronic hepatitis C. *Drugs*. 2003;63:701-730.
64. Ison MG. Expanding the armamentarium against respiratory viral infections: DAS181. *J Infect Dis*. 2012;206:1806-1808.
65. Malakhov MP, Aschenbrenner LM, Smee DF, et al. Sialidase fusion protein as a novel broad-spectrum inhibitor of influenza virus infection. *Antimicrob Agents Chemother*. 2006;50:1470-1479.
66. Moscona A, Porotto M, Palmer S, et al. A recombinant sialidase fusion protein effectively inhibits human parainfluenza viral infection in vitro and in vivo. *J Infect Dis*. 2010;202:234-241.
67. Triana-Baltzer G, Gubareva L, Nicholls J, et al. Novel pandemic influenza A (H1N1) viruses are potently inhibited by DAS181, a sialidase fusion protein. *Plos One*. 2009;4:e7788.
68. Chan R, Chan M, Wong A, et al. DAS181 inhibits H5N1 influenza virus infection of human lung tissue. *Antimicrob Agents Chemother*. 2009;53:3935-3941.
69. Zhang H. DAS181 and H5N1 virus infection. *J Infect Dis*. 2009;199:1250, author reply 1250-1251.
70. Boltz D, Aldridge JR Jr, Webster R, Govorkova E. Drugs in development for influenza. *Drugs*. 2010;70:1349-1362.
71. Triana-Baltzer G, Gubareva L, Klimov A, et al. Inhibition of neuraminidase inhibitor-resistant influenza virus by DAS181, a novel sialidase fusion protein. *PloS One*. 2009;4:e7838.
72. Triana-Baltzer G, Sanders R, Hedlund M, et al. Phenotypic and genotypic characterization of influenza virus mutants selected with the sialidase fusion protein DAS181. *J Antimicrob Chemother*. 2011;66:15-28.
73. Moss R, Hansen C, Sanders R, et al. A phase II study of DAS181, a novel host directed antiviral for the treatment of influenza infection. *J Infect Dis*. 2012;206:1844-1851.
74. Chen Y, Driscoll J, McAfee S, et al. Treatment of parainfluenza 3 infection with DAS181 in a patient after allogeneic stem cell transplantation. *Clin Infect Dis*. 2011;53:e77-e80.
75. Guzman-Suarez B, Buckley M, Gilmore E, et al. Clinical potential of DAS181 for treatment of parainfluenza-3 infections in transplant recipients. *Transpl Infect Dis*. 2012;14:427-433.
76. Yamashita M, Tomozawa T, Kakuta M, et al. CS-8958, a prodrug of the new neuraminidase inhibitor R-125489, shows long-acting anti-influenza virus activity. *Antimicrob Agents Chemother*. 2009;53:186-192.
77. Reviriego C. Laninamivir octanoate: neuraminidase inhibitor treatment of influenza. *Drugs Future*. 2010;35:537-545.
78. Yamashita M. Laninamivir and its prodrug, CS-8958: long-acting neuraminidase inhibitors for the treatment of influenza. *Antivir Chem Chemother*. 2010;21:71-84.
79. Kubo S, Tomozawa T, Kakuta M, et al. Laninamivir prodrug CS-8958, a long-acting neuraminidase inhibitor, shows superior anti-influenza virus activity after a single administration. *Antimicrob Agents Chemother*. 2010;54:1256-1264.
80. Ishizuka H, Toyama K, Yoshiba S, et al. Intrapulmonary distribution and pharmacokinetics of laninamivir, a neuraminidase inhibitor, after a single inhaled administration

of its prodrug, laninamivir octanoate, in healthy volunteers. *Antimicrob Agents Chemother*. 2012;56:3873-3878.

81. Koyama K, Nakai D, Takahashi M, et al. Pharmacokinetic mechanism involved in the prolonged high retention of laninamivir in mouse respiratory tissues after intranasal administration of its prodrug laninamivir octanoate. *Drug Metab Dispos*. 2013;41:180-187.
82. Kubo S, Tokumitsu A, Tomazawa T, et al. High and continuous exposure of laninamivir, an anti-influenza drug, may work suppressively to generate low-susceptibility mutants in animals. *J Infect Chemother*. 2012;18:69-74.
83. Ishizuka H, Yoshiba S, Okabe H, et al. Clinical pharmacokinetics of laninamivir, a novel long-acting neuraminidase inhibitor, after single and multiple inhaled doses of its prodrug, CS-8958, in healthy male volunteers. *J Clin Pharmacol*. 2010;50:1319-1329.
84. Honda T, Kubo S, Masuda T, et al. Synthesis and in vivo influenza-virus inhibitory effect of ester prodrug of 4-guanidino-7-O-methyl-neu5Ac2en. *Bioorg Med Chem Lett*. 2009;19:2938-2940.
85. Ishizuka H, Yoshiba S, Yoshihara K, et al. Assessment of the effects of renal impairment on the pharmacokinetic profile of laninamivir, a novel neuraminidase inhibitor, after a single inhaled dose of its prodrug, CS-8958. *J Clin Pharmacol*. 2011;51:243-251.
86. Gibaldi M, Perrier D. *Pharmacokinetics*. 2nd ed. New York: Dekker; 1982.
87. Katsumi Y, Otabe O, Matsui F, et al. Effect of a single inhalation of laninamivir octanoate in children with influenza. *Pediatrics*. 2012;129:e1431-e1436.
88. Sugaya N, Ohashi Y. Long-acting neuraminidase inhibitor laninamivir octanoate (CS-8958) versus oseltamivir as treatment for children with influenza virus infection. *Antimicrob Agents Chemother*. 2010;54:2575-2582.
89. Watanabe A, Chang SC, Kim MJ, et al. Long-acting neuraminidase inhibitor laninamivir octanoate versus oseltamivir for treatment of influenza: a double-blind, randomized, noninferiority clinical trial. *Clin Infect Dis*. 2010;51:1167-1175.
90. Nakano T, Okumura A, Tanabe T, et al. Safety evaluation of laninamivir octanoate hydrate through analysis of adverse events reported during early post-marketing phase vigilance. *Scand J Infect Dis*. 2013;45:469-477.
91. Kashiwagi S, Yoshida S, Yamaguchi H, et al. Safety of the long-acting neuraminidase inhibitor laninamivir octanoate hydrate in post-marketing surveillance. *Int J Antimicrob Agents*. 2012;40:381-388.
92. Shobugawa Y, Saito R, Sato I, et al. Clinical effectiveness of neuraminidase inhibitors—oseltamivir, zanamivir, laninamivir, and peramivir—for treatment of influenza A (H3N2) and A (H1N1)pdm09 infection: an observational study in the 2010-2011 influenza season in Japan. *J Infect Chemother*. 2012;18:858-864.
93. Kim CU, Lew W, Williams MA, et al. Influenza neuraminidase inhibitors possessing a novel hydrophobic interaction in the enzyme active site: design, synthesis, and structural analysis of carbocyclic sialic acid analogues with potent anti-influenza activity. *J Am Chem Soc*. 1997;119:681-690.
94. Mendel DB, Tai CY, Escarpe PA, et al. Oral administration of a prodrug of the influenza virus neuraminidase inhibitor GS4071 protects mice and ferrets against influenza infection. *Antimicrob Agents Chemother*. 1998;42:640-646.
95. Li W, Escarpe PA, Eisenberg EJ, et al. Identification of GS 4104 as an orally bioavailable prodrug of the influenza virus neuraminidase inhibitor GS 4071. *Antimicrob Agents Chemother*. 1998;42:647.
96. Wetherall NT, Trivedi T, Zeller J, et al. Evaluation of neuraminidase enzyme assays using different substrates to measure susceptibility of influenza virus clinical isolates to neuraminidase inhibitors: report of the neuraminidase inhibitor susceptibility network. *J Clin Microbiol*. 2003;41:742-750.
97. McClellan K, Perry CM. Oseltamivir: a review of its use in influenza. *Drugs*. 2001;61:263-283.
98. Tisdale M. Monitoring of viral susceptibility: new challenges with the development of influenza NA inhibitors. *Rev Med Virol*. 2000;10:45-55.
99. Leneva IA, Roberts N, Govorkova EA, et al. The neuraminidase inhibitor GS4104 (oseltamivir phosphate) is efficacious against A/Hong Kong/156/97 (H5N1) and A/Hong Kong/1074/99 (H9N2) influenza viruses. *Antiviral Res*. 2000;48:101-115.
100. Yen HL, McKimm-Breschkin JL, Choy K, et al. Resistance to neuraminidase inhibitors conferred by an R292K mutation in a human influenza virus H7N9 isolate can be masked by a mixed R/K viral population. *MBio*. 2013;4:e00396-13.
101. Kawai N, Ikematsu H, Iwaki N, et al. Longer virus shedding in influenza B than in influenza A among outpatients treated with oseltamivir. *J Infect*. 2007;55:267-272.
102. Kawai N, Ikematsu H, Iwaki N, et al. A comparison of the effectiveness of oseltamivir for the treatment of influenza A and influenza B: a Japanese multicenter study of the 2003-2004 and 2004-2005 influenza seasons. *Clin Infect Dis*. 2006;43:439-444.
103. Sato M, Saito R, Sato I, et al. Effectiveness of oseltamivir treatment among children with influenza A or B virus infections during successive winters in Niigata City, Japan. *Tokoku J Exp Med*. 2008;214:113-120.
104. Boltz DA, Rehg JE, McClaren J, et al. Oseltamivir prophylactic regimens prevent H5N1 influenza morbidity and mortality in a ferret model. *J Infect Dis*. 2008;197:1315-1323.
105. Smee DF, Wong MH, Bailey KW, et al. Activities of oseltamivir and ribavirin used alone and in combination against infection in mice with recent isolates of influenza A (H1N1) and B viruses. *Antiviral Chem Chemother*. 2006;17:185-192.
106. Ilyushina NA, Hay A, Yilmaz N, et al. Oseltamivir-ribavirin combination therapy for highly pathogenic H5N1 influenza infections in mice. *Antimicrob Agents Chemother*. 2008;52:3889-3897.
107. Smee DF, Hurst BL, Wong MH, et al. Effects of double combinations of amantadine, oseltamivir and ribavirin on influenza A (H5N1) virus infections in cell culture and in mice. *Antimicrob Agents Chemother*. 2009;53:2120-2128.
108. Ilyushina NA, Bovin NV, Webster RG, et al. Combination chemotherapy, a potential strategy for reducing the emergence of drug-resistant influenza A variants. *Antiviral Res*. 2006;70:121-131.
109. Colman PM. Influenza virus neuraminidase: structure, antibodies, and inhibitors. *Protein Sci*. 1994;3:1687-1696.
110. Zambon M, Hayden FG. Position statement: global neuraminidase inhibitor susceptibility network. *Antiviral Res*. 2001;49:147-156.
111. Carr J, Ives J, Kelly L, et al. Influenza virus carrying neuraminidase with reduced sensitivity to oseltamivir carboxylate has altered properties in vitro and is compromised for infectivity and replicative ability in vivo. *Antiviral Res*. 2002;54:79-88.
112. Whitley RJ, Hayden FG, Reisinger K, et al. Oral oseltamivir treatment of influenza in children. *Pediatr Infect Dis J*. 2001;20:127-133.
113. Jackson HC, Roberts N, Wang Z, et al. Management of influenza: use of new antivirals and resistance in perspective. *Clin Drug Invest*. 2000;20:447-454.
114. Weinstock DM, Gubareva LV, Zuccotti G. Prolonged shedding of multidrug-resistant influenza A virus in an immunocompromised patient. *N Engl J Med*. 2003;348:867-868.
115. Hurt AC, Hardie K, Wilson NJ, et al. Community transmission of oseltamivir-resistant A(H1N1)pdm09 influenza. *N Engl J Med*. 2011;365:2541-2542.
116. Hurt AC, Hardi K, Wilson NJ, et al. Characteristics of a widespread community cluster of H275Y oseltamivir-resistant A(H1N1)pdm09 influenza in Australia. *J Infect Dis*. 2012;206:148-157.
117. Hauge SH, Blix HS, Borgen K, et al. Sales of oseltamivir in Norway prior to the emergence of oseltamivir resistant influenza A(H1N1) viruses in 2007-2008. *Virol J*. 2009;6:54.
118. Longtin J, Patel S, Eshaghi A, et al. Neuraminidase-inhibitor resistance testing for pandemic influenza A(H1N1) 2009 in Ontario, Canada. *J Clin Virol*. 2011;50:257-261.
119. Storms AD, Gubareva LV, Su S, et al. Oseltamivir-resistant pandemic (H1N1) 2009 virus infections, United States, 2010-2011. *Emerg Infect Dis*. 2012;18:308-311.
120. Hurt AC, Deng YM, Ernest J, et al. Oseltamivir-resistant influenza viruses circulating during the first year of the influenza A(H1N1) 2009 pandemic in the Asia-Pacific region, March 2009 to March 2010. *Euro Surveill*. 2011;16:19770.
121. Kimberlin DW, Acosta EP, Pritchard MN, et al. Oseltamivir pharmacokinetics, dosing and resistance among children aged 2 years with influenza. *J Infect Dis*. 2013;207:709-720.
122. Wong DD, Choy KT, Chan RW, et al. Comparable fitness and transmissibility between oseltamivir-resistant pandemic 2009 and seasonal H1N1 influenza viruses with the H275Y neuraminidase mutation. *J Virol*. 2012;86:10558-10570.
123. Hamelin ME, Baz M, Abed Y, et al. Oseltamivir-resistant pandemic A/H1N1 virus is as virulent as its wild-type counterpart in mice and ferrets. *PLoS Pathog*. 2010;6:e1001015.
124. Saito R, Sato I, Suzuki Y, et al. Reduced effectiveness of oseltamivir in children infected with oseltamivir-resistant influenza A(H1N1) viruses with His275Tyr mutation. *Pediatr Infect Dis*. 2010;29:898-904.
125. Stephenson I, Democratis J, Lackenby A, et al. Neuraminidase inhibitor resistance after oseltamivir treatment of acute influenza A and B in children. *Clin Infect Dis*. 2009;48:389-396.
126. Rath B, von Kleist M, Tief F, et al. Virus load kinetics and resistance development during oseltamivir treatment in infants and children infected with influenza A(H1N1) 2009 and influenza B viruses. *Pediatr Infect Dis J*. 2012;31:899-905.
127. He G, Massarella J, Ward P. Clinical pharmacokinetics of the prodrug oseltamivir and its active metabolite Ro 64-0802. *Clin Pharmacokinet*. 1999;37:471-484.
128. Wattanagoon Y, Stepniewska K, Lindegardl N, et al. Pharmacokinetics of high-dose oseltamivir in healthy volunteers. *Antimicrob Agents Chemother*. 2009;53:945-952.
129. Zhu HJ, Markowitz JS. Activation of the antiviral prodrug oseltamivir is impaired by two newly identified carboxylesterase 1 variants. *Drug Metab Disp*. 2009;37:264-267.
130. Taylor WR, Thinh BN, Anh GT, et al. Oseltamivir is adequately absorbed following nasogastric administration to adults with severe H5N1 influenza. *PLoS One*. 2008;3:3410.
131. Ariano RE, Sitar DS, Zelenitsky SA, et al. Enteric absorption and pharmacokinetics of oseltamivir in critically ill patients with pandemic (H1N1) influenza. *Can Med Assoc J*. 2010;182:357-363.
132. Oo C, Barrett J, Hill G, et al. Pharmacokinetics and dosage recommendations for an oseltamivir oral suspension for the treatment of influenza in children. *Paediatr Drugs*. 2001;3:229-236.
133. Tamiflu USA Product Monograph. Revised December, 2012.
134. Thorne-Humphrey LM, Goralski KB, Slayter KL, et al. Oseltamivir pharmacokinetics in morbid obesity (OPTIMO trial). *J Antimicrob Chemother*. 2011;66:2083-2091.
135. Greer LG, Leff RD, Rogers VL, et al. Pharmacokinetics of oseltamivir according to trimester of pregnancy. *Am J Obstet Gynecol*. 2011;204(suppl 6):S89-S93.
136. Beigi RH, Han K, Venkataramanan R, et al. Pharmacokinetics of oseltamivir among pregnant and nonpregnant women. *Am J Obstet Gynecol*. 2011;204(suppl 1):S84-S88.
137. Eisenberg G, Bidgood A, Lynch G, et al. Penetration of GS4071, a novel influenza neuraminidase inhibitor, into rat bronchoalveolar lining fluid following oral administration of the prodrug GS4104. *Antimicrob Agents Chemother*. 1997;41:1949-1952.
138. Kurowski M, Oo C, Wiltshire H, et al. Oseltamivir distributes to influenza virus replication sites in the middle ear and sinuses. *Clin Drug Investig*. 2004;24:49-53.
139. Wentges-van Holthe N, Van Eijkeren M, van der Laan J. Oseltamivir and breastfeeding [letter]. *Int J Infect Dis*. 2008;12:451-452.
140. Worley KC, Roberts SW, Bawdon RE. The metabolism and transplacental transfer of oseltamivir in the ex vivo human model. *Infect Dis Obstet Gynecol*. 2008;2008:927574.
141. Straumanis JP, Tapia M, King J. Influenza B infection associated with encephalitis: treatment with oseltamivir. *Pediatr Infect Dis J*. 2003;21:173-175.
142. Jhee SS, Yen M, Ereshefsky L, et al. Low penetration of oseltamivir and its carboxylate into cerebrospinal fluid in healthy Japanese and Caucasian volunteers. *Antimicrob Agents Chemother*. 2008;52:3687-3693.
143. Aoki FY, Allen UD, Stiver HG, et al. The use of antiviral drugs for influenza: guidance for practitioners 2012/2013. *Can J Infect Dis Med Microbiol*. 2012;23:e79-e92.
144. Jullien V, Hubert D, Launay G, et al. Pharmacokinetics and diffusion into sputum of oseltamivir and oseltamivir carboxylate in adults with cystic fibrosis. *Antimicrob Agents Chemother*. 2011;55:4183-4187.
145. Holodniy M, Penzak SR, Straight TM, et al. Pharmacokinetics and tolerability of oseltamivir combined with probenecid. *Antimicrob Agents Chemother*. 2008;52:3013-3021.
146. Wells Q, Hardin B, Raj SR, et al. Sotalol-induced torsades de pointes precipitated during treatment with oseltamivir for H1N1 influenza. *Heart Rhythm*. 2010;7:1454-1457.
147. Lam H, Jeffery JR, Sitar DS, et al. Oseltamivir, an influenza neuraminidase inhibitor drug, does not affect the steady-state pharmacokinetic characterstics of cyclosporine, mycophenolate or tacrolimus in adult renal transplant patients. *Ther Drug Monit*. 2011;33:699-704.
148. Davies BE, Aceves Baldo P, Lennon-Chrimes S, et al. Effect of oseltamivir treatment on anticoagulation: a cross-over study in warfarinized patients. *Br J Clin Pharmacol*. 2010;70:834-843.
149. Atiee G, Lasseter K, Baughman S, et al. Absence of pharmacokinetic interaction between intravenous peramivir and oral oseltamivir or rimantadine in humans. *J Clin Pharmacol*. 2012;52:1410-1419.
150. Donner B, Niranjan V, Hoffmann G. Safety of oseltamivir in pregnancy: a review of preclinical and clinical data. *Drug Saf*. 2010;33:631-642.
151. Greer LG, Sheffield JS, Rogers VL, et al. Maternal and neonatal outcomes after antepartum treatment of influenza with antiviral medications. *Obstet Gynecol*. 2010;115:711-716.
152. Enger C, Nordstrom BL, Thakrar B, et al. Health outcomes among patients receiving oseltamivir. *Pharmacoepidemiol Drug Saf*. 2003;12:1-11.
153. Donner B, Bader-Weder S, Schwarz R, et al. Safety profile of oseltamivir during the 2009 influenza pandemic. *Pharmacoepidemiol Drug Saf*. 2011;20:532-543.
154. Kara A, Karadag-Oncel E, Ozkaya-OParlakay A, et al. Oseltamivir use in infants under one year of age: are there still unanswered questions? *Turk J Pediatr*. 2012;54:25-29.

155. Dutkowski R, Smith JR, Davies BE. Safety and pharmacokinetics of oseltamivir at standard and high dosages. *Int J Antimicrob Agents*. 2010;35:461-467.
156. Ison MG, Szakaly P, Shapira MY, et al. Efficacy and safety of oral oseltamivir for influenza prophylaxis in transplant recipients. *Antivir Ther*. 2012;17:955-964.
157. Tamiflu 2006 Product Monograph.
158. Casscells SW, Granger E, Kress AM, et al. The association between oseltamivir use and adverse neuropsychiatric outcomes among TRICARE beneficiaries, ages 1 through 21 years diagnosed with influenza. *Int J Adolesc Med Health*. 2009;21:79-89.
159. Smith JR, Sacks S. Incidence of neuropsychiatric and adverse events in influenza patients treated with oseltamivir or no antiviral treatment. *Int J Clin Pract*. 2009;63:596-605.
160. Greene SK, Li L, Shay DK, et al. Risk of adverse events following oseltamivir treatment in influenza outpatients, Vaccine Safety Datalink Project, 2007-2010. *Pharmacoepidemiol Drug Saf*. 2013;22:335-344.
161. Urushihara H, Doi Y, Arai M, et al. Oseltamivir prescription and regulatory actions vis-à-vis abnormal behavior risk in Japan: drug utilization study using a nationwide pharmacy database. *PLoS One*. 2011;6:e28483.
162. Treanor JJ, Hayden FG, Vrooman PS, et al. Efficacy and safety of the oral neuraminidase inhibitor oseltamivir in treating acute influenza. *JAMA*. 2000;283:1016-1024.
163. Cooper NJ, Sutton AJ, Abrams KR, et al. Effectiveness of neuraminidase inhibitors in treatment and prevention of influenza A and B: systematic review and meta-analyses of randomised controlled trials. *BMJ*. 2003;326:1235-1239.
164. Boivin G, Coulombe Z, Wat C. Quantification of the influenza virus load by real-time polymerase chain reaction in nasopharyngeal swabs of patients treated with oseltamivir. *J Infect Dis*. 2003;188:578-580.
165. Aoki FY, Macleod MD, Paggiaro P, et al. Early administration of oral oseltamivir increases the benefits of influenza treatment. *J Antimicrob Chemother*. 2003;51:123-129.
166. Kaiser L, Wat C, Mills T, et al. Impact of oseltamivir treatment on influenza-related lower respiratory tract complications and hospitalizations. *Arch Intern Med*. 2003;163:1667-1672.
167. Jefferson T, Jones M, Doshi P, et al. Neuraminidase inhibitors for preventing and treating influenza in healthy adults: systematic review and meta-analysis. *BMJ*. 2009;339:b5106.
168. Hsu J, Santesso N, Mustafa R, et al. Antivirals for treatment of influenza: a systematic review and meta-analysis of observational studies. *Ann Intern Med*. 2012;156:512-524.
169. McGeer A, Green KA, Plevneshi A, et al. Antiviral therapy and outcomes of influenza requiring hospitalization in Ontario, Canada. *Clin Infect Dis*. 2007;45:1568-1575.
169a. Muthuru SG, Venkatersan S, Myles PG, et al. Effectiveness of neuraminidase inhibitors in reducing the mortality in patients admitted to hospital with influenza A H1N1pdm09 virus infection: a meta-analysis of individual participant data. *Lancet Respir Med*. 2014;2:395-404.
169b. Jefferson T, Jones MA, Doshi P, et al. Neuraminidase inhibitors for preventing and treating influenza in healthy adults and children. *Cochrane Database Syst Rev*. 2014;4:CD008965.
170. Muthuri SG, Myles PR, Vankatesan S, et al. Impact of neuraminidase inhibitor treatment on outcomes of public health importance during the 2009-2010 influenza A (H1N1) pandemic in a systematic review and metaanalysis in hospitalized patients. *J Infect Dis*. 2013;207:553-563.
171. Yang S-G, Cao B, Liang L-R, et al. Antiviral therapy and outcomes of patients with pneumonia caused by influenza A pandemic (H1N1) virus. *PLoS One*. 2012;7:29652.
172. Siston AM, Rasmussen SA, Honein MA, et al. Pandemic 2009 influenza A (H1N1) virus illness among pregnant women in the United States. *JAMA*. 2010;303:1517-1525.
173. Halloran ME, Hayden FG, Yang Y, et al. Antiviral effects in influenza viral transmission and pathogenicity: observations from household based trials. *Am J Epidemiol*. 2006;165:212-221.
174. Ng S, Cowling BJ, Fang VJ, et al. Effects of oseltamivir treatment on duration of clinical illness and viral shedding and household transmission of influenza virus. *Clin Infect Dis*. 2009;50:707-714.
175. Sugaya N, Mitamura K, Yamazaki M, et al. Lower clinical effectiveness of oseltamivir against influenza B contrasted with influenza A infection in children. *Clin Infect Dis*. 2007;44:197-202.
176. Kawai N, Ikematsu H, Iwaki N, et al. A comparison of the effectiveness of oseltamivir for the treatment of influenza A and influenza B: a Japanese multicenter study of the 2003-2004 and 2004-2005 influenza seasons. *Clin Infect Dis*. 2006;43:439-444.
177. Adisasmito W, Chan PKS, Lee N, et al. Effectiveness of antiviral treatment in human influenza A (H5N1) infections: analysis of a global registry. *J Infect Dis*. 2010;202:1154-1160.
178. Nichols WG, Guthrie KA, Corey L, et al. Influenza infections after hematopoietic stem cell transplantation: risk factors, mortality and the effect of antiviral therapy. *Clin Infect Dis*. 2004;39:1300-1306.
179. Chemaly RF, Torres HA, Aguilera EA, et al. Neuraminidase inhibitors improve outcome of patients with leukemia and influenza: an observational study. *Clin Infect Dis*. 2007;44:964-967.
180. Hayden FG, Atmar RL, Schilling M, et al. Use of the selective oral neuraminidase inhibitor oseltamivir to prevent influenza. *N Engl J Med*. 1999;341:1336-1343.
181. Peters PH, Gravenstein S, Norwood P, et al. Long-term use of oseltamivir for the prophylaxis of influenza in a vaccinated frail older population. *J Am Geriatr Soc*. 2001;49:1-7.
182. Welliver R, Monto AS, Carewicz O, et al. Effectiveness of oseltamivir in preventing influenza in household contacts: a randomized controlled trial. *JAMA*. 2001;285:748-754.
183. Hayden FG, Belshe R, Villanueva C, et al. Management of influenza in households: a prospective, randomized comparison of oseltamivir treatment with or without post-exposure prophylaxis. *J Infect Dis*. 2004;189:440-449.
184. Bowles SK, Lee W, Simor AE, et al. Use of oseltamivir during influenza outbreaks in Ontario nursing homes, 1999-2000. *J Am Geriatr Soc*. 2002;50:608-616.
185. Govorkova EA, Ieneva IA, Goloubeva OG, et al. Comparison of efficacies of RWJ-270201, zanamivir, and oseltamivir against H5N1, H9N2, and other avian influenza viruses. *Antimicrob Agents Chemother*. 2001;45:2723.
186. Gubareva LV, Triujillo AA, Okomo-Adhiambo M, et al. Comprehensive assessment of 2009 pandemic influenza A (H1N1) virus drug susceptibility in vitro. *Antivir Ther*. 2010;14:1151-1159.
187. Gubareva LG, Webster RG, Hayden FG. Comparison of the activities of zanamivir, oseltamivir and RWJ-270201 against clinical isolates of influenza virus and neuraminidase inhibitor-resistant variants. *Antimicrob Agents Chemother*. 2001;45:3403.
188. Mishin VP, Hayden FG, Gubareva LV. Susceptibilities of antiviral-resistant influenza viruses to novel neuraminidase inhibitors. *Antimicrob Agents Chemother*. 2005;49:4515.
189. Bantia S, Parker CD, Anath SL, et al. Comparison of the anti-influenza virus activity of RWJ-270201 with those of oseltamivir and zanamivir. *Antimicrob Agents Chemother*. 2001;45:1162-1167.
190. Smee DF, Huffman JH, Morrison AC, et al. Cyclopentane neuraminidase inhibitors with potent in vitro anti-influenza virus activities. *Antimicrob Agents Chemother*. 2001;45:734-738.
191. Smee DF, Bailey KW, Morrison AC, et al. Combination treatment of influenza A virus infections in cell culture and in mice with the cyclopentane neuraminidase inhibitor RWJ-270201 and ribavirin. *Chemotherapy*. 2002;48:88.
192. Govorkova EA, Fang HB, Tan M, et al. Neuraminidase inhibitor-rimantadine combinations exert additive and synergistic anti-influenza virus effects in MDCK cells. *Antimicrob Agents Chermother*. 2004;48:4855.
193. Bantia S, Kellogg D, Parker CD, et al. Combination of peramivir and rimantadine demonstrate synergistic antiviral effects in sub-lethal influenza A (H3N2) virus mouse model. *Antivir Res*. 2010;88:276-280.
194. Chand P, Bantia S, Kotian PL, et al. Comparison of the anti-influenza activity of cyclopentane derivatives with oseltamivir and zanamivir in vivo. *Bioorg Med Chem*. 2005;13:4071-4077.
195. Sidwell RW, Smee DF, Hoffman DH, et al. In vivo influenza virus inhibitory effects of the cyclopentane neuraminidase inhibitor RWJ-270201. *Antimicrob Agents Chemother*. 2001;45:749-757.
196. Bantia S, Arnold CS, Parker CD, et al. Anti-influenza virus activity of peramivir in mice with single intramuscular injection. *Antivir Res*. 2006;69:39-45.
197. Bantia S, Ananth SL, Horn L, et al. Generation and characterization of a mutant of influenza A virus selected with a neuraminidase inhibitor, RWJ-270201. *Antivir Res*. 2000;46:A60.
198. Smee DF, Sidwell RW, Morrison AC, et al. Characterisation of an influenza A (H3N2) virus resistant to the cyclopentane neuraminidase inhibitor RWJ-270201. *Antivir Res*. 2001;52:251.
199. Sidwell RW, Bailey KW, Morrison AC, et al. Inability to select in vivo for influenza A resistance to the orally administered neuraminidase inhibitor RWJ-270201. Presented at the Third International Symposium on Respiratory Viral Infections. St. Lucia, Windward Islands, 2000.
200. Barrosa L, Treanor J, Gubareva L, et al. Efficacy and tolerability of the oral neuraminidase inhibitor peramivir in experimental human influenza: randomised, controlled trials for prophylaxis and treatment. *Antivir Ther*. 2005;10:901.
201. Renaud C, Pergam SA, Polyak C, et al. Early emergence of an H275Y mutation in a hematopoietic cell transplant recipient treated with intravenous peramivir. *Transpl Infect Dis*. 2010;12:513-517.
202. Pizzorno A, Abed Y, Bouhy X, et al. Impact of mutations at residue I223 of the neuraminidase protein on the resistance profile, replication level, and virulence of the 2009 pandemic influenza virus. *Antimicrob Agents Chemother*. 2012;56:1208-1214.
203. Abed Y, Pizzorno A, Boivin G. Therapeutic activity of intramuscular peramivir in mice infected with a recombinant influenza A/WSN/33 (H1N1) virus containing the H27Y neuraminidase mutation. *Antimicrob Agents Chemother*. 2012;56:4375-4379.
204. Kohno S, Kida H, Mizugichi M, et al. Intravenous peramivir for treatment of influenza A and B virus infection in high-risk patients. *Antimicrob Agents Chemother*. 2011;55:2803-2812.
205. World Health Organization. WHO Guidelines for Pharmacologic Management of Pandemic Influenza A (H1N1) 2009 and Other Influenza Viruses. Available at: http://www.who.int/csr/resources/publications/swineflu/h1n1_guidelines_pharmaceutical_mngt.pdf. Accessed November 9, 2010.
206. Peramivir Investigator Brochure. Cary, NC: Biocryst Pharmaceuticals; 2007.
207. Sugaya N, Kohno S, Ishibashi T, et al. Efficacy, safety and pharmacokinetics of intravenous peramivir in children with 2009 pandemic H1N1 influenza virus infection. *Antimicrob Agents Chemother*. 2012;56:369-377.
208. Kohno S, Kida H, Mizuguchi M, et al. Efficacy and safety of intravenous peramivir for treatment of seasonal influenza virus infection. *Antimicrob Agents Chemother*. 2010;54:4568-4574.
209. Drusano GL, Preston SL, Smee D, et al. Pharmacodynamic evaluation of RWJ-270-201, a novel neuraminidase inhibitor, in a lethal murine model predicts efficacy for once daily dosing. *Antimicrob Agents Chemother*. 2001;45:2115-2118.
210. Peramivir. In: *Clinical Pharmacology*. Tampa, FL: Elsevier/Gold Standard; 2009. Available at http://download.thelancet.com/flatcontentassets/H1N1-flu/treatment/treatment-53.pdf.
211. Ison MG, Hui DS, Clezy K, et al. A clinical trial of intravenous peramivir compared with oral oseltamivir for the treatment of seasonal influenza in hospitalized adults. *Antivir Ther*. 2013;18:651-661.
212. Alexander JW. *Peramivir:* An investigational antiviral therapy for seasonal and pandemic influenza. Presented at the Xth International Symposium on Respiratory Viral Infections. Singapore, February 28-March 2, 2008.
213. Kohno S, Yen M-Y, Cheong M-J, et al. Phase III randomized, double-blind study comparing single-dose intravenous peramivir with oral oseltamivir in patients with seasonal influenza virus infection. *Antimicrob Agents Chemother*. 2011;55:5267-5276.
214. Morfin F, Dupuis-Girod S, Carrington D, et al. Adenovirus susceptibility to antiviral drugs is genogroup-dependent. Poster V-282. Presented at the 43rd Interscience Conference on Antimicrobial Agents and Chemotherapy. Chicago, September 14-17, 2003.
215. Ison MG, Fraiz J, Heller B, et al. Intravenous peramivir for treatment of influenza in hospitalized patients. *Antivir Ther*. 2013; Aug 28 [Epub ahead of print].
216. BioCryst Pharmaceuticals, Inc. BioCryst Announces Outcome from the Peramivir Phase 3 Interim Analysis [Press release]. 2012. Available at http://www.businesswire.com/news/home/20121107006831/en/BioCryst-Announces-Outcome-Peramivir-Phase-3-Interim.
217. Crance JM, Scaramozzino N, Jouan A, et al. Interferon, ribavirin, 6-azauridine and glycyrrhizin: antiviral compounds active against pathogenic flaviviruses. *Antiviral Res*. 2003;58:73-79.
218. Cinatl J, Morgenstern B, Bauer G, et al. Glycyrrhizin, an active component of liquorice roots, and replication of SARS-associated coronavirus. *Lancet*. 2003;361:2045-2046.
219. Heagy W, Crumpacker C, Lopez PA, et al. Inhibition of immune functions by antiviral drugs. *J Clin Invest*. 1991;87:1916-1924.
220. Meier V, Burger E, Mihm S, et al. Ribavirin inhibits DNA, RNA, and protein synthesis in PHA-stimulated human peripheral blood mononuclear cells: possible explanation for therapeutic efficacy in patients with chronic HCV infection. *J Med Virol*. 2003;69:50-58.
221. Tam RC, Lau JY, Hong Z. Mechanisms of action of ribavirin in antiviral therapies. *Antivir Chem Chemother*. 2002;12:261-272.
222. Graci JD, Cameron CE. Quasispecies, error catastrophe, and the antiviral activity of ribavirin. *Virology*. 2002;298:175-180.
223. Hong Z, Cameron CE. Pleiotropic mechanisms of ribavirin antiviral activities. *Prog Drug Res*. 2002;59:41-69.
224. Vo NV, Young KC, Lai MM. Mutagenic and inhibitory effects of ribavirin on hepatitis C virus RNA polymerase. *Biochemistry*. 2003;42:10462-10471.
225. Fernandez-Larsson R, Patterson JL. Ribavirin is an inhibitor of human immunodeficiency virus reverse transcriptase. *Mol Pharmacol*. 1990;38:766-770.

226. Young KC, Lindsay KL, Lee KJ, et al. Identification of a ribavirin-resistant NS5B mutation of hepatitis C virus during ribavirin monotherapy. *Hepatology*. 2003;38: 869-878.
227. Glue P. The clinical pharmacology of ribavirin. *Semin Liver Dis*. 1999;19(suppl 1):17-24.
228. Preston SL, Drusano GL, Glue P, et al. Pharmacokinetics and absolute bioavailability of ribavirin in healthy volunteers as determined by stable-isotope methodology. *Antimicrob Agents Chemother*. 1999;43:2451-2456.
229. Laskin OL, Longstreth JA, Hart CC, et al. Ribavirin disposition in high-risk patients for acquired immunodeficiency syndrome. *Clin Pharmacol Ther*. 1987;41:546-555.
230. Glue P, Schenker S, Gupta S, et al. The single dose pharmacokinetics of ribavirin in subjects with chronic liver disease. *J Clin Pharmacol*. 2000;49:417-421.
231. Jen JF, Glue P, Gupta S, et al. Population pharmacokinetic and pharmacodynamic analysis of ribavirin in patients with chronic hepatitis C. *Ther Drug Monit*. 2000;22: 555-565.
232. ICN Pharmaceuticals ICMC. Investigational Drug Brochure, Intravenous Ribavirin IND 9,076. February 2001.
233. Dieterich DT, Spivak JL. Hematologic disorders associated with hepatitis C virus infection and their management. *Clin Infect Dis*. 2003;37:533-541.
234. Di Bisceglie AM, Conjeevaram HS, Fried MW, et al. Ribavirin as therapy for chronic hepatitis C: a randomized, double-blind, placebo-controlled trial. *Ann Intern Med*. 1995;123:897-903.
235. Knowles SR, Phillips EJ, Dresser L, et al. Common adverse events associated with the use of ribavirin for severe acute respiratory syndrome in Canada. *Clin Infect Dis*. 2003;37: 1139-1142.
236. Bradley JS, Connor JD, Compogiannis LS, et al. Exposure of health care workers to ribavirin during therapy for respiratory syncytial virus infections. *Antimicrob Agents Chemother*. 1990;34:668-670.
237. Deleted in proofs.
238. Randolph AG, Wang EE. Ribavirin for respiratory syncytial virus lower respiratory tract infection: a systematic overview. *Arch Pediatr Adolesc Med*. 1996;150:942-947.
239. Guerguerian AM, Gauthier M, Lebel MH, et al. Ribavirin in ventilated respiratory syncytial virus bronchiolitis: a randomized, placebo-controlled trial. *Am J Respir Crit Care Med*. 1999;160:829-834.
240. Englund JA, Piedra PA, Jefferson LS, et al. High-dose, short-duration ribavirin aerosol therapy in children with suspected respiratory syncytial virus infection. *J Pediatr*. 1990;117:313-320.
241. American Academy of Pediatrics. Respiratory syncytial virus. In: Pickering LK, Baker CJ, Kimberlin W, et al, eds. *Red Book. 2012 Report of the Committee on Infectious Diseases*. Elk Grove Village, IL: American Academy of Pediatrics; 2012:609-618.
242. Long CE, Voter KZ, Barker WH, et al. Long term follow-up of children hospitalized with respiratory syncytial virus lower respiratory tract infection and randomly treated with ribavirin or placebo. *Pediatr Infect Dis J*. 1997;16: 1023-1028.
243. Small TN, Casson A, Malak SF, et al. Respiratory syncytial virus infection following hematopoietic stem cell transplantation. *Bone Marrow Transplant*. 2002;29:321-327.
244. Boeckh M, Berrey MM, Bowden RA, et al. Phase 1 evaluation of the respiratory syncytial virus–specific monoclonal antibody palivizumab in recipients of hematopoietic stem cell transplants. *J Infect Dis*. 2001;184:350-354.
245. Krilov LR. Respiratory syncytial virus disease: update on treatment and prevention. *Expert Rev Anti Infect Ther*. 2011;9:27-32.
246. Llungman P, Ward KN, Crooks RN, et al. Respiratory tract infection after stem cell transplantation: a prospective study from the Infectious Diseases Working Group of the European Group for Blood and Marrow Transplantation. *Bone Marrow Transplant*. 2001;28:479-484.
247. Lewinsohn DM, Bowden RA, Mattson D, et al. Phase I study of intravenous ribavirin treatment of respiratory syncytial virus pneumonia after marrow transplantation. *Antimicrob Agents Chemother*. 1996;40:2555-2557.
248. Boeckh M, Englund J, Li Y, et al. Randomized controlled multicenter trial of aerosolized ribavirin for respiratory syncytial virus upper respiratory tract infection in hematopoietic cell transplant recipients. *Clin Infect Dis*. 2007; 44:245-249.
249. Chemaly RF, Torres HA, Munsell MF, et al. An adaptive randomized trial of an intermittent dosing schedule of aerosolized ribavirin in patients with cancer and respiratory syncytial virus infection. *J Infect Dis*. 2012;206:136-171.
250. McCoy D, Wong E, Kuyumjian AG, et al. Treatment of respiratory syncytial virus infection in adult patients with hematologic malignancies based on an institution-specific guideline. *Transpl Infect Dis*. 2011;13:117-121.
251. Khanna N, Widmer AF, Decker M, et al. Respiratory syncytial virus infection in patients with hematological diseases: single-center study and review of the literature. *Clin Infect Dis*. 2008;46:402-412.
252. Gueller S, Duenzinger U, Wolf T, et al. Treatment of respiratory syncytial virus–induced tracheobronchitis and pneumonia occurring pre-engagement in allogeneic hematopoietic stem cell transplant recipients can be safely treated with high-dose ribavirin. *Bone Marrow Transpl*. 2010;45:S215.
253. Li L, Avery R, Budev M, et al. Oral versus inhaled ribavirin therapy for respiratory syncytial virus infection after lung transplantation. *J Heart Lung Transpl*. 2012;31:839-844.
254. Pelaez A, Lyon GM, Force SD, et al. Efficacy of oral ribavirin in lung transplant patients with respiratory syncytial virus lower respiratory tract infection. *J Heart Lung Transpl*. 2009;28:67-71.
255. Hayden FG, Sable CA, Connor JD, et al. Intravenous ribavirin by constant infusion for serious influenza and parainfluenzavirus infection. *Antiviral Ther*. 1996;1:51-56.
256. Chan-Tack KM, Murray JS, Birnkrant DB. Use of ribavirin to treat influenza. *N Engl J Med*. 2009;361:1713-1714.
257. Rodriguez WJ, Hall CB, Welliver R, et al. Efficacy and safety of aerosolized ribavirin in young children hospitalized with influenza: a double-blind, multicenter, placebo-controlled trial. *J Pediatr*. 1994;125:129-135.
258. Kim Y, Young Suh G, Huh JW, et al. Triple-combination antiviral drug for pandemic H1N1 influenza virus infection in critically ill patients on mechanical ventilation. *Antimicrob Agents Chemother*. 2011;55:5703-5709.
259. Nichols WG, Corey L, Gooley T, et al. Parainfluenza virus infections after hematopoietic stem cell transplantation: risk factors, response to antiviral therapy, and effect on transplant outcome. *Blood*. 2001;98:573-578.
260. Chakrabarti S, Collingham KE, Holder K, et al. Pre-emptive oral ribavirin therapy of paramyxovirus infections after haematopoietic stem cell transplantation: a pilot study. *Bone Marrow Transplant*. 2001;28:759-763.
261. Souza ILA, Schnert L, Goto JM, et al. Oral ribavirin in treatment of adenovirus infection in hematologic patients: experience from a Brazilian university hospital. *Clin Microbiol Infect*. 2010;16:S24.
262. Gavin PJ, Katz BZ. Intravenous ribavirin treatment for severe adenovirus disease in immunocompromised children. *Pediatrics*. 2002;110:E9.
263. Bonney D, Razati H, Turner A, et al. Successful treatment of human metapneumovirus pneumonia using combination therapy with intravenous ribavirin and immune globulin. *Br J Haematol*. 2009;45:667-679.
264. Raza K, Ismailjee SB, Crespo M, et al. Successful outcome of human metapneumovirus (hMPV) pneumonia in a lung transplant recipient treated with intravenous ribavirin. *J Heart Lung Transpl*. 2007;26:862-864.
265. Schachor-Meyouhas Y, Ben-Barak A, Kassis I. Treatment with oral ribavirin and IVIG of severe human metapneumovirus pneumonia in immune compromised child. *Pediatr Blood Cancer*. 2011;57:350-351.
266. Fuehner T, Dierich M, Duesbert C, et al. Single-centre experience with oral ribavirin in lung transplant recipients with paramyxovirus infections. *Antivir Ther*. 2011;16: 1733-1740.
267. Shima T, Yoshimoto G, Nonami A, et al. Successful treatment of parainfluenza virus 3 pneumonia with oral ribavirin and methylprednisolone in a bone marrow transplant recipient. *Int J Hematol*. 2008;88:336-340.
268. Wright JJ, O'Driscoll G. Treatment of parainfluenza virus 3 pneumonia in a cardiac transplant recipient with intravenous ribavirin and methylprednisone. *J Heart Lung Transpl*. 2005;24:343-346.
269. Kanji J, Vaudry W. Successful cardiac transplantation in a 4-year-old child with active parainfluenza-3 infection: experience with systemic ribavirin therapy. *Can J Infect Dis Med Microbiol*. 2011;22:16A.
270. Mazzulli T, Farcas GA, Poutanen SM, et al. Severe acute respiratory syndrome–associated coronavirus in lung tissue. *Emerg Infect Dis*. 2004;10:20-24.
271. Chapman LE, Mertz GJ, Peters CJ, et al. Intravenous ribavirin for hantavirus pulmonary syndrome: safety and tolerance during 1 year of open-label experience. Ribavirin Study Group. *Antivir Ther*. 1999;4:211-219.
272. Safronetz D, Haddock E, Feldmann H, et al. In vitro and in vivo activity against Andes virus infection. *PLoS One*. 2011;6:e23560.
273. Henderson E, Alber D, Baxter R, et al. 1,4-Benzodiazepines as inhibitors of respiratory syncytial virus: the identification of a clinical candidate. *J Med Chem*. 2007;50: 1685-1692.
274. Olszewska W, Openshaw P. Emerging drugs for respiratory syncytial virus infection. *Expert Opin Emerg Drugs*. 2009;14:207-217.
275. Chapman J, Abbott E, Alber D, et al. RSV604, a novel inhibitor of respiratory syncytial virus replication. *Antimicrob Agents Chemother*. 2007;51:3346-3353.
276. von Itzstein M, Wu WY, Kok GB, et al. Rational design of potent sialidase-based inhibitors of influenza virus replication. *Nature*. 1993;363:418-423.
277. Cheer SM, Wagstaff AJ. Zanamivir: an update of its use in influenza. *Drugs*. 2002;62:71-106.
278. Woods JM, Bethell RC, Coates JA, et al. 4-Guanidino-2,4-dideoxy-2,3-dehydro-N-acetylneuraminic acid is a highly effective inhibitor both of the sialidase (neuraminidase) and of growth of a wide range of influenza A and B viruses in vitro. *Antimicrob Agents Chemother*. 1993;37: 1473-1479.
279. Kawai N, Ikematsu H, Iwaki N, et al. Comparison of the effectiveness of zanamivir and oseltamivir for the treatment of influenza A and B. *J Infect*. 2008;36:51-57.
280. McKimm-Breschkin J, Trivedi T, Hampson A, et al. Neuraminidase sequence analysis and susceptibilities of influenza virus clinical isolates to zanamivir and oseltamivir. *Antimicrob Agents Chemother*. 2003;47:2264-2272.
281. Govorkova FA, Fang H-B, Tam M, et al. Neuraminidase inhibitor-rimantadine combinations exert additive and synergistic anti-influenza virus effects in MDCK cells. *Antimicrob Agents Chemother*. 2004;48:4855.
282. Hata K, Koseki K, Yamaguchi K, et al. Limited inhibitory effect of oseltamivir and zanamivir on human sialadases. *Antimicrob Agents Chemother*. 2008;52:3484-3491.
283. Murrell M, Porotto M, Weber T, et al. Mutations in human parainfluenza virus type 3 hemagglutinin-neuraminidase causing increased receptor binding activity and resistance to the transition state sialic acid analog 4-GU-DANA (Zanamivir). *J Virol*. 2003;77:309-317.
284. Thorlund K, Awad T, Boivin G, et al. Systematic review of influenza resistance to the neuraminidase inhibitors. *BMC Infect Dis*. 2011;11:134. Also available at http://www.biomedcentral.com/1471-2334/11/134.
285. World Health Organization. Influenza A (H1N1) virus resistance to oseltamivir—2008/2009 influenza season, northern hemisphere, 18 March 2009. Available at http://www.who.int/influenza/resources/documents/H1N1webupdate20090318_ed_ns.pdf. Accessed February 23, 2012.
286. Hurt AC, Holien JK, Parker M, et al. Zanamivir-resistant influenza viruses with a novel neuraminidase mutation. *J Virol*. 2009;83:10366-10373.
287. Gubareva LV, Trujillo AA, Okimo-Achiambo M, et al. Comprehensive assessment of 2009 pandemic influenza A(H1N1) virus drug susceptibility in vitro. *Antivir Ther*. 2010;15:1151-1159.
288. World Health Organization. Weekly update on oseltamivir resistance to influenza A (H1N1) 2009 viruses. Available at http://www.who.int/csr/disease/swineflu/oseltamivirresistant20/00820pdf. Accessed December 30, 2010.
289. McKimm-Breschkin JL, Selleck PW, Usman TB, et al. Reduced sensitivity of influenza A (H5N1) to oseltamivir. *Emerg Infect Dis*. 2007;13:1354-1357.
290. Wang D, Sleeman K, Huang W, et al. Neuraminidase inhibitor susceptibility testing of influenza type B viruses in China during 2010 and 2011 identifies viruses with reduced susceptibility to oseltamivir and zanamivir. *Antiviral Res*. 2013;97:240-244.
291. Hurt AC, Lee RT, Leang SK, et al. Increased detection in Australia and Singapore of a novel influenza A (H1N1) 2009 variant with reduced oseltamivir and zanamivir sensitivity due to a S274N neuraminidase mutation. *Euro Surveill*. 2011;16:19884.
292. LeGoff J, Rousset D, Abou-Jaoude G, et al. I223R mutation in influenza A(H1N1)pdm09 neuraminidase confers reduced susceptibility to oseltamivir and zanamivir and enhanced resistance with H275Y. *PLoS One*. 2012;7:e37095.
293. Gubareva LV, Matrosovich MN, Brenner MK, et al. Evidence for zanamivir resistance in an immunocompromised child infected with influenza B virus. *J Infect Dis*. 1998; 178:1257-1262.
294. Pizzorno A, Abed Y, Bouhy X, et al. Impact of mutations at residue I223 of the neuraminidase protein on the resistance profile, replication level, and virulence of the 2009 pandemic influenza virus. *Antimicrob Agents Chemother*. 2012;56:1208-1214.
295. Ilyushina NA, Seiler JP, Rehg JE, et al. Effect of neuraminidase inhibitor–resistant mutations on pathogenicity of clade 2.2 A/Turkey/15/06/(H5N1) influenza virus in ferrets. *PLos Pathog*. 2010;6:e1000933.
296. Tamura D, Sugaya N, Ogawa M, et al. Frequency of drug-resistant viruses and virus shedding in pediatric influenza patients treated with neuraminidase inhibitors. *Clin Infect Dis*. 2011;52:e56-e93.
297. Lee C, Loeb M, Phillips A, et al. Zanamivir use during transmission of amantadine-resistant influenza A in a nursing home. *Infect Control Hosp Epidemiol*. 2000;21:700-704.
298. Diggory P, Fernandez C, Humphrey A, et al. Comparison of elderly people's technique in using two dry powder inhalers to deliver zanamivir: randomised controlled trial. *BMJ*. 2001;322:1-4.
299. Shelton MJ, Lovern M, Bg-Cashin J, et al. Zanamivir pharmacokinetics and pulmonary penetration into epithelial lung fluid following intravenous or oral inhaled administration to healthy adult subjects. *Antimicrob Agents Chemother*. 2011;55:5178-5184.
300. Peng AW, Milleri S, Stein DS. Direct measurement of the anti-influenza agent zanamivir in the respiratory tract following inhalation. *Antimicrob Agents Chemother*. 2000;44: 1974-1976.

301. Weller S, Thamlikitkul V, Francois B, et al. Pharmacokinetics of intravenous zanamivir in hospitalized adults with influenza: interim results from open-label phase II study NAI 113678 [abstract 764]. Presented at the Annual Meeting of the Infectious Diseases Society of America. Vancouver, Canada, October 21-24, 2010.
302. Cass LMR, Efthymiopoulas C, March J, et al. Effect of renal impairment on the pharmacokinetics of intravenous zanamivir. *Clin Pharmacokinet*. 1999;36(suppl 1):13-19.
303. European Medicines Agency. Conditions of Use, Conditions for Distribution and Patients Targeted and Conditions for Safety Monitoring Addressed to Member States for IV Zanamivir Available for Compassionate Use. June 23, 2011. Available at http://www.ema.europa.eu/docs/en_GB/document_library/Other/2010/02/WC500074124.pdf. Accessed January 15, 2014.
304. Pukrittayakamee S, Jittamala P, Stepniewska K, et al. An op-label crossover study to evaluate potential pharmacokinetic interactions between oral oseltamivir and intravenous zanamivir in healthy Thai adults. *Antimicrob Agents Chemother*. 2011;55:4050-4057.
305. Centers for Disease Control and Prevention. Recommendation of the Advisory Committee on Immunization Practices (ACIP), 2008: prevention and control of influenza. *MMWR Recomm Rep*. 2008;157(RR):1-60.
306. Freund B, Gravenstein S, Elliott M, et al. Zanamivir: a review of clinical safety. *Drug Saf*. 1999;21:267-281.
307. Hedrick JA, Barzilai A, Behre U, et al. Zanamivir for treatment of symptomatic influenza A and B infection in children five to twelve years of age: a randomized controlled trial. *Pediatr Infect Dis J*. 2000;19:410-417.
308. Anekthananon T, Pukritayakamee S, Ratanasuwan W, et al. Oseltamivir and inhaled zanamivir as influenza prophylaxis in Thai health workers: a randomized, double-blind, placebo-controlled safety trial over 16 weeks. *J Antimicrob Chemother*. 2013;68:697-707.
309. Gravenstein S, Johnston SL, Loeschel E, et al. Zanamivir: a review of clinical safety in individuals at high risk of developing influenza-related complications. *Drug Saf*. 2001;24:1113-1125.
310. Murphy K, Eivindson A, Pauksens K, et al. Efficacy and safety of inhaled zanamivir for the treatment of influenza in patients with asthma or chronic obstructive pulmonary disease. *Clin Drug Invest*. 2000;20:337-349.
311. FDA Public Health Advisory. Safe and Appropriate Use of Influenza Drugs. Available at http://www.fda.gov/cder/drug/advisory/influenza.htm. Accessed January 12, 2000.
312. Fleming DM. Zanamivir in the treatment of influenza. *Expert Opin Pharmacother*. 2003;4:799-805.
313. Ison MG, Gnann JW Jr, Nagy-Agren S, et al. Safety and efficacy of nebulized zanamivir in hospitalized patients with serious influenza. *Antivir Ther*. 2003;8:183-190.
314. Kiatboonsri S, Kiatboonsri C, Theerawit P. Fatal respiratory events caused by zanamivir nebulization. *Clin Infect Dis*. 2010;50:620.
315. Cass LMR, Efthymiopoulas C, Bye A. Pharmacokinetics of zanamivir after intravenous, oral, inhaled or intranasal administration in healthy volunteers. *Clin Pharmcokinet*. 1999;36(suppl 1):1-11.
316. Poster 1626: Safety, tolerability and pharmacokinetics of intravenous zanamivir treatment in hospitalized adults with influenza: a phase 2 open-label, multicenter, single-arm study. Presented at ID Week, Infectious Diseases Society of America. San Diego, CA, October 17-21, 2012.
317. Walker JB, Hussey EK, Treanor JJ, et al. Effects of the neuraminidase inhibitor zanamivir on otologic manifestations of experimental human influenza. *J Infect Dis*. 1997;176:1417-1422.
318. Hayden FG, Osterhaus ADME, Treanor JJ, et al. Efficacy and safety of the neuraminidase inhibitor zanamivir in the treatment of influenza virus infections. *N Engl J Med*. 1997;337:874-879.
319. MIST (Management of Influenza in the Southern Hemisphere Trialists) Study Group. Randomized trial of efficacy and safety of inhaled zanamivir in treatment of influenza A and B virus infections. *Lancet*. 1998;352:1877-1881.
320. Monto AS, Webster A, Keene O. Randomized, placebo-controlled studies of inhaled zanamivir in the treatment of influenza A and B: pooled efficacy analysis. *J Antimicrob Chemother*. 1999;44:23-29.
321. Kaiser L, Keene ON, Hammond J, et al. Impact of zanamivir on antibiotics use for respiratory events following acute influenza in adolescents and adults. *Arch Intern Med*. 2000;160:3234-3240.
322. Kawai N, Ikematsu H, Iwaki N, et al. Zanamivir treatment is equally effective for both influenza A and influenza B [letter]. *Clin Infect Dis*. 2007;44:1666.
323. Lalezari JP, Elliott M, Keene O. Zanamivir for the treatment of influenza A and B infection in high-risk patients [abstract]. *Arch Intern Med*. 2001;161:212-217.
324. Johny AA, Clark A, Price N, et al. The use of zanamivir to treat influenza A and B infection after allogeneic stem cell transplantation. *Bone Marrow Transplant*. 2002;29:113-115.
325. Gukareva LV, Matrosovich MN, Brenner MK, et al. Evidence for zanamivir resistance in an immunocompromised child infected with influenza B virus. *J Infect Dis*. 1998;178:1257-1262.
326. Kawai N, Ikematsu H, Hirotsu N. Clinical effectiveness of oseltamivir and zanamivir for treatment of influenza A virus subtype H1N1 with the H274Y mutation: a Japanese, multicenter study of the 2007-2008 and 2008-2009 influenza seasons. *Clin Infect Dis*. 2009;49:1828-1835.
327. Monto AS, Robinson DP, Herlocher L, et al. Zanamivir in the prevention of influenza among healthy adults. *JAMA*. 1999;282:31-36.
328. Hayden FG, Gubareva LV, Monto AS, et al. Inhaled zanamivir for preventing influenza in families. *N Engl J Med*. 2000;343:1282-1289.
329. Monto AS, Pichichero ME, Blanckenberg SJ, et al. Zanamivir prophylaxis: an effective strategy for the prevention of influenza types A and B within households. *J Infect Dis*. 2002;186:1582-1588.
330. Shinjoh M, Takano Y, Takahashi T, et al. Postexposure prophylaxis for influenza in pediatric wards: oseltamivir or zanamivir after rapid antigen detection. *Pediatr Infect Dis J*. 2012;31:1119-1123.
331. Gravenstein S, Drinka P, Osterweil D, et al. A multicenter prospective double-blind randomized controlled trial comparing the relative safety and efficacy of zanamivir to rimantadine for nursing home influenza outbreak control [abstract 1155]. Presented at the 40th Interscience Conference on Antimicrobial Agents and Chemotherapy. Toronto, September 17-20, 2000.
332. Carrat F, Duval X, Tubach F, et al. Effect of oseltamivir, zanamivir, or oseltamivir-zanamivir combination treatments on transmission of influenza in households. *Antivir Ther*. 2012;17:1085-1090.
333. Duval X, van der Werf S, Blanchon T, et al. Efficacy of oseltamivir-zanamivir combination compared to each monotherapy for seasonal influenza: a randomized placebo-controlled trial. *PLoS Med*. 2010;7:e1000362.
334. Biatto JF, Costa EL, Pastore L, et al. Prone position ventilation, recruitment maneuver and intravenous zanamivir in severe refractory hypoxemia caused by influenza A (H1N1). *Clinics (Sao Paulo, Brazil)*. 2010;65:1211-1213.
335. Ghosh S, Adams O, Schuster FR, et al. Efficient control of pandemic 2009 H1N1 virus infection with intravenous zanamivir despite the lack of immune function. *Transpl Infect Dis*. 2012;14:657-659.
336. Dohna-Schwake C, Schweiger B, Felderhoff-Muser U, et al. Severe H1N1 infection in a pediatric liver transplant recipient treated with intravenous zanamivir: efficiency and complications. *Transplantation*. 2010;90:223-224.
337. Guar AH, Bagga B, Barman S, et al. Intravenous zanamivir for oseltamivir-resistant 2009 H1N1 influenza. *N Engl J Med*. 2010;362:88-89.
338. Kidd IM, Down J, Nastouli E, et al. H1N1 pneumonitis treated with intravenous zanamivir. *Lancet*. 2009;374:1036.
339. Dulek DE, Williams JV, Creech CB, et al. Use of intravenous zanamivir after development of oseltamivir resistance in a critically ill immune-suppressed child infected with 2009 pandemic influenza A (H1N1) virus. *Clin Infect Dis*. 2010;50:1493-1496.
340. Harter G, Zimmermann O, Maier L, et al. Intravenous zanamivir for patients with pneumonitis due to pandemic (H1N1) 2009 influenza virus. *Clin Infect Dis*. 2010;50:1249-1251.
341. Uhl D. [New influenza: zanamivir intravenous administration seems life-saving]. *Dtsch Apoth Ztg*. 2009;149:47 [in German].
342. Fry AM, Perez A, Finelli L. Use of intravenous neuraminidase inhibitors during the 2009 pandemic: results from population-based surveillance. *JAMA*. 2011;306:160-162.
343. Macdonald SJF, Cameron R, Demaine DA, et al. Dimeric zanamivir conjugates with various linking groups are potent long-lasting inhibitors of influenza neuraminidase dose including H5N1 avian influenza. *J Med Chem*. 2005;48:2964-2971.
344. Masuda T, Yoshida S, Arai M, et al. Synthesis and anti-influenza evaluation of polyvalent sialadose inhibitors bearing 4-quanidino-Neu5Acw2en derivatives. *Chem Pharm Bull*. 2003;51:1386-1398.
345. Macdonald SJF, Watson KG, Cameron R, et al. Potent and long-acting dimeric inhibitors of influenza virus neuraminidase are effective at a once-weekly dosing regimen. *Antimicrob Agents Chemother*. 2004;48:4542-4549.
346. Watson KG, Cameron R, Fenton RJ, et al. Highly potent and long-acting trimeric and tetrameric inhibitors of influenza virus neuraminidase. *Bioorg Med Chem Lett*. 2004;14:1589-1592.
347. Honda T, Masuda T, Yoshida S, et al. Synthesis and anti-influenza virus activity of 4-quanidino-7-substituted Neu5A-c2en derivatives. *Bioorg Med Chem Lett*. 2002;12:1921-1924.
348. Honda T, Toshida S, Arai M, et al. Synthesis and anti-influenza evaluation of polyvalent sialidase inhibitors bearing 4-quanidino-Neu5Ac2en derivatives. *Bioorg Med Chem Lett*. 2002;12:1929-1932.
349. Honda T, Masuda T, Yoshida S, et al. Synthesis and anti-influenza virus activity of 7-0-alkylated derivatives related to zanamivir. *Bioorg Med Chem Lett*. 2002;12:1925-1928.
350. Weight AK, Haldar J, Alvarez de Cienfuegos L, et al. Attaching zanamivir to a polymer markedly enhances its activity against drug-resistant strains of influenza A virus. *J Pharm Sci*. 2011;100:831-835.
351. Lee CM, Weight AK, Haldar J, et al. Polymer-attached zanamivir inhibits synergistically both early and late stages of influenza virus infection. *Proc Natl Acad Sci U S A*. 2012;109:20385-20390.