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.

Antiviral Treatments

Michael G. Ison, MD, MS

KEYWORDS

• Respiratory virus • Influenza • Respiratory syncytial virus (RSV) • Neuraminidase inhibitor
• Ribavirin

KEY POINTS

- All currently circulating strains of influenza are resistant to the M2 inhibitors amantadine and rimantadine.
- There are 4 approved neuraminidase inhibitors: oseltamivir, laninamivir, peramivir, and zanamivir.
- All of the neuraminidase inhibitors have the greatest clinical impact if started within 24 to 48 hours of symptom onset.
- For hospitalized adults and children, anti-influenza therapy should be initiated as soon as influenza is considered and should not wait for confirmatory testing; there is evidence of reduction in morbidity and mortality among hospitalized adults and children when started up to 5 days, and possibly longer, after symptom onset.
- Aerosol ribavirin is approved for the treatment of respiratory syncytial virus but is generally used in at-risk infants and immunocompromised adults and children.

INTRODUCTION

A wide range of viruses can affect the respiratory tract; in general, these can be divided into viruses for which the primary site of infection is the respiratory tract (classic respiratory viruses, including influenza, respiratory syncytial virus [RSV], human metapneumovirus [hMPV], parainfluenza virus [PIV], rhinovirus, and adenovirus) and viruses that can affect the respiratory tract opportunistically (ie, herpes simplex [HSV], cytomegalovirus [CMV], and measles). The focus of this article is antivirals directed at classic respiratory viruses; excellent reviews of agents for the treatment of HSV and CMV infections can be found elsewhere.[1–3] However, there is significant effort being invested in novel antivirals for respiratory viruses often directed at novel targets, combinations designed to increase potency and reduce resistance emergence, therapeutic antibodies, and immunomodulatory agents selected to mitigate immunopathologic host responses; agents in advanced clinical development are reviewed briefly here, whereas more detailed reviews may be found elsewhere.[4–6] Few antiviral drugs are currently approved for treating respiratory virus infections and most of these are specific inhibitors of influenza viruses. The emergence of new pathogens like Middle East respiratory syndrome coronavirus has also led to screening efforts to identify new therapeutics.[7,8]

M2 Inhibitors

The M2 ion channel allows hydrogen ions to flow into the viral particle and results in release of the

Disclosure Statement: M.G. Ison has received research support, paid to Northwestern University, from Alios, Astellas, Beckman Coulter, Chimerix, Gilead, Jansen/Johnson & Johnson; he has provided compensated consultation to Celltrion, Chimerix, Farmark, Genentech/Roche, Toyama/MediVector, and Shionogi, and uncompensated consultation to BioCryst, Biota, Cellex, GlaxoSmithKlein, Romark, NexBio, Theraclone, Unither Virology, and Vertex; he is also a paid member of data and safety monitor boards related to research activity conducted by Astellas, Jansen/Vertex.

Division of Infectious Diseases, Northwestern University Feinberg School of Medicine, 645 North Michigan Avenue Suite 900, Chicago, IL 60611, USA
E-mail address: mgison@northwestern.edu

Clin Chest Med 38 (2017) 139–153
http://dx.doi.org/10.1016/j.ccm.2016.11.008

RNA segments into the infected cell. Amantadine (Symmetrel) and rimantadine (Flumadine) are symmetric tricyclic amines that specifically inhibit the replication of influenza A viruses at low concentrations (<1.0 μg/mL) by blocking the action of this M2 protein.[9–11] When used against susceptible strains, both agents are 70% to 90% effective in preventing infection and reduce duration of fever and symptoms when used for treatment.[12–14] Although this class of drugs is specifically indicated for the prevention and treatment of influenza A infections, widespread resistance to all M2 inhibitors has been documented in circulating influenza A strains, and this class of agents is not currently recommended for the prevention or treatment of influenza.[15] Cross-resistance to both agents occurs as the result of single amino acid substitutions in the transmembrane portion of the M2 protein.[11] The resistant virus seems to retain wild-type pathogenicity and causes an influenza illness indistinguishable from that caused by susceptible strains.

Both drugs achieve peak levels 3 to 5 hours after ingestion.[16–18] Amantadine and rimantadine come as 100-mg tablets and a syrup formulation (50 mg/5 mL). In adults, the usual dose for treatment or prevention of influenza A infection is 100 mg every 12 hours for both drugs. Amantadine is excreted unchanged by the kidney, whereas rimantadine undergoes extensive metabolism by the liver before being excreted by the kidney; as a result, dose adjustment with renal dysfunction is required. The most common side effects of the M2 inhibitors are minor central nervous system complaints (anxiety, difficulty concentrating, insomnia, dizziness, headache, and jitteriness) and gastrointestinal upset, which are particularly prominent in the elderly and those with renal failure.[17] Patients who receive amantadine may develop antimuscarinic effects, orthostatic hypotension, and congestive heart failure. Rates of adverse effects are lower for rimantadine than amantadine.[17,19] Given drug-drug interactions, care should be used when coadministering either agent with antihistamines or anticholinergic drugs, trimethoprim-sulfamethoxazole, triamterene-hydrochlorothiazide, quinine, quinidine, monoamine oxidase inhibitors, antidepressants, and minor tranquilizers.[20]

Neuraminidase Inhibitors

Influenza A and B viruses possess a surface glycoprotein with neuraminidase activity that cleaves terminal sialic acid residues from various glycoconjugates and destroys the receptors recognized by viral hemagglutinin. This activity is essential for release of virus from infected cells, for prevention of viral aggregates, and for viral spread within the respiratory tract.[21] Oseltamivir (Tamiflu, a prodrug of the active carboxylate), laninamivir (Inavir), peramivir (Rapiacta, Peramiflu) and zanamivir (Relenza) are sialic acid analogues that potently and specifically inhibit influenza A and B neuraminidases by competitively and reversibly interacting with the active enzyme site.[22,23] Oseltamivir and zanamivir are globally available, whereas laninamivir is approved in Japan and peramivir is approved in China, Japan, South Korea, and the United States.

Laninamivir

Laninamivir octanoate (CS-8958) is a prodrug that is converted in the airway to laninamivir (R-125489), the active neuraminidase inhibitor, and is retained at concentrations that exceed the IC_{50} (50% inhibitory concentration) for most influenza neuraminidases for at least 240 hours (10 days) after a single inhalation of 40 mg.[24] Only 15% of the drug is systemically absorbed after inhalation. Dose adjustment is not indicated for renal or hepatic insufficiency. Laninamivir octanoate (CS-8958) is currently only approved in Japan for the treatment and prevention of influenza A and B infection and is available as a 20-mg dry powder inhaler. A single inhalation of 20 mg daily for 2 days is recommended for prophylaxis, whereas a single inhalation of 40 mg for individuals greater than or equal to 10 years of age and 20 mg for children less than 10 years of age are recommended for treatment.

Laninamivir was associated with more rapid time to alleviation of influenza illness caused by infections by seasonal H1N1 virus with the H275Y substitution in children compared with a standard 5-day oseltamivir regimen, whereas studies in adults showed noninferiority versus oseltamivir in such patients.[25,26] Laninamivir shows a similar duration of fever in ambulatory children compared with patients treated with zanamivir.[27,28] Among household contacts of an index patient with influenza, 2 and 3 days of laninamivir 20 mg daily was associated with a 77% and 78% protective efficacy, respectively, compared with placebo.[29] Common side effects include nausea, vomiting, diarrhea, and dizziness.[25,26] Laninamivir was not associated with significant bronchospasm or other respiratory adverse effects in patients with chronic respiratory disease.[30]

Oseltamivir

Oral oseltamivir ethyl ester is well absorbed and rapidly cleaved by esterases in the gastrointestinal

tract, liver, or blood. The bioavailability of the active metabolite, oseltamivir carboxylate, is estimated to be ~80% in previously healthy persons.[31] The plasma elimination half-life is 6 to 10 hours but is more prolonged in the elderly, although dose adjustments are not generally necessary. Administration with food seems to decrease the risk of gastrointestinal upset without decreasing bioavailability. Both the prodrug and parent are eliminated primarily unchanged through the kidney by glomerular filtration and anionic tubular secretion. The dose should be reduced by half for patients with a creatinine clearance less than 30 mL/min, and further reductions when clearance is less than 10 mL/min.[32] Distribution is not well characterized in humans, but peak bronchoalveolar lavage, middle ear fluid, and sinus fluid levels are similar to plasma levels.[31]

Oseltamivir is indicated for the prevention of influenza A and B in patients greater than or equal to 1 year old, with dosing once a day, and for the treatment of patients greater than or equal to 2 weeks of age who have influenza A and B, with twice-a-day dosing. Oseltamivir is available for oral delivery only. Oseltamivir comes as 30-mg, 45-mg, and 75-mg tablets and as a white tutti-frutti–flavored suspension (360-mg oseltamivir base for a final concentration of 6 mg/mL). The approved adult dose for treatment is 75 mg twice daily for 5 days and for prophylaxis is 75 mg once daily. Pediatric dosing is based on weight and is outlined in **Table 1**. Efficacy of prophylaxis is 84% to 92% in protecting unvaccinated patients when given for 10 days to 8 weeks.[31,33] Caution should be used with prescribing oseltamivir for prophylaxis in patients exposed to an index case because prophylaxis has been associated with emergence of resistant mutants[34]; empiric therapy or monitoring is generally recommended in these cases as a result.

Among ambulatory adults with uncomplicated influenza A or B, oseltamivir 75 mg twice daily for 5 days when started within the first 2 days of symptoms was associated with a shorter time to alleviation of uncomplicated influenza illness (29–35 hours shorter) and with reductions in severity of illness, duration of fever, time to return to normal activity, quantity of viral shedding, duration of impaired activity, and complications leading to antibiotic use, particularly bronchitis, compared with placebo in previously healthy adults.[13,15,35] Pediatric studies enrolling children as young as 2 weeks of age showed that oseltamivir is safe and is associated with significantly reduced illness duration and severity, time to resumption of full activities, and the occurrence of complications leading to antibiotic use (particularly acute otitis media).[36–40] Most existing literature on the safety and efficacy of oseltamivir in hospitalized adults and children suggests that, among such high-risk and hospitalized individuals, there is a benefit to starting antiviral therapy through at least 5 days after symptom onset, with the greatest benefit in patients started within 48 hours after symptom onset.[41–46] All of the studies in hospitalized adults suggest that early therapy is associated with reduced incidence of lower respiratory tract complications, requirement for intensive care unit (ICU)–level care, duration of illness, duration of shedding, and mortality.[13,15,43,44,46] Duration of therapy has not been well studied but data suggest that longer duration of therapy ($\geq$10 days) may be required, particularly in critically ill patients and those with pneumonia. Viral replication in the lower airway does not correlate with quantity or duration of replication in the upper airway. Doubling the treatment dose of oseltamivir in hospitalized patients with influenza does not seem to increase virologic efficacy, except perhaps for influenza B infections, or clinical effectiveness, although one ICU-based randomized controlled trial reported that tripling the standard dose was associated with acceleration of viral RNA clearance from the respiratory tract.[47–49] Doses of oseltamivir should be given after hemodialysis; dosing must be adjusted for renal insufficiency and renal replacement therapy (see **Table 1**). There are conflicting data about optimal dosing of oseltamivir in pregnant women, with some studies suggesting a need for higher doses (75 mg 3 times a day), whereas others suggest that no dose adjustment is needed.[50–52] Current guidelines recommend treating pregnant women with influenza infection with one of the approved neuraminidase inhibitors. The recommended pediatric dosage is listed in **Table 1**.

Oral oseltamivir is generally well tolerated and no serious end-organ toxicity has been found in controlled clinical trials. Oseltamivir is associated with nausea; abdominal discomfort; and, less often, emesis in a minority of treated patients, but this can be ameliorated by giving food with each dose. Other infrequent possible adverse events include insomnia, vertigo, and fever. Postmarketing reports suggest that oseltamivir may be associated, rarely, with skin rash, hepatic dysfunction, or thrombocytopenia. In addition, there have been reports of abnormal neurologic and behavioral symptoms that have, rarely, resulted in deaths, mostly among children; most of these reports have come from Japan. Existing

Table 1
Agents used to prevent and treat influenza

		Usual Adult Dosage[a]			
Class	**Drug**	**Prophylaxis**	**Treatment**	**Dose Adjustment State**	**Suggested Dosage**
M2 Inhibitor	Amantadine	100 mg q 12 h	100 mg q 12 h	Age 1–9 y	5 mg/kg to maximum of 150 mg in 2 divided doses
				CrCl 30–50 mL/min	100 mg q 24 h
				CrCl 15–30 mL/min	100 mg q 24 h
				CrCl 10–15 mL/min	100 mg q week
				CrCl 10 mL/min	100 mg q week
				Age $\geq$ 65 y	100 mg q 24 h
	Rimantadine	100 mg q 12 h	100 mg q 12 h	Age 1–9 y	5 mg/kg to maximum of 150 mg in 2 divided doses
				CrCl <10 mL/min	100 mg q 24 h
				Severe hepatic dysfunction	100 mg q 24 h
				Age $\geq$ 65 y	100 mg q 24 h
Neuraminidase Inhibitor	Laninamivir	20 mg QD $\times$ 2 d	40 mg $\times$ 1	Age <10 y	20 mg $\times$ 1
	Oseltamivir[b]	75 mg q 24 h	75 mg q 12 h	CrCl <30 mL/min[d]	Treatment: 75 mg q 24 h Prophylaxis: 75 mg every other day
				$\leq$15 kg[e]	30 mg q 12 h (5 mL[c])
				15–23 kg[e]	45 mg q 12 h (7.5 mL[c])
				23–40 kg[e]	60 mg q 12 h (10 mL[c])
				>40 kg[e]	75 mg q 12 h (12.5 mL[c])
				Any weight, 2 wk to <1 y	3mg/kg q 12 h (0.5 mL/kg[c])

	Peramivir	NA	300 mg once	For patients with severe infection	600 mg QD as a single-dose or multidose regimen
				Children 6–17 y	10 mg/kg QD for 5 d (maximum of 600 mg QD)
				Children 181 d to 5 y	12 mg/kg QD
				CrCl 31–49 mL/min[e]	Adult: 150 mg QD Age 6–17 y: 2.5 mg/kg QD[e] Age 180 d to 5 y: 3 mg/kg QD
				CrCl 10–30 mL/min[e]	Adult: 100 mg QD Age 6–17 y: 1.6 mg/kg QD[e] Age 180 d to 5 y: 1.9 mg/kg QD
				CrCl <10 mL/min	Adult: 100 mg on day 1 then 15 mg QD Age 6–17 y: 1.6 mg/kg on day 1 then 0.25 mg/kg QD Age 180 d to 5 y: 1.9 mg/kg on day 1 then 0.3 mg/kg
				Intermittent HD (Dose on HD days only)	≥18 y: 100 mg on day 1 then 100 mg 2 h after HD Age 6–17 y: 1.6 mg/kg on day 1 then 1.6 mg/kg 2 h after HD Age 181 d to 6 y: 1.9 mg/kg on day 1 then 1.9 mg/kg 2 h after HD
	Inhaled Zanamivir[f]	2 puffs	2 puffs	No dose adjustment needed	—

Recommendations based on those provided by the Advisory Committee on Immunization Practices.[4]

Abbreviations: CrCl, creatinine clearance; HD, hemodialysis; NA, not available; q, every; QD, every day.

[a] Duration of treatment is usually 5 days. Duration of prophylaxis depends on clinical setting.

[b] Oseltamivir is indicated for prophylaxis in children 1 year old and older and for treatment in children in greater than or equal to 2 weeks of age.

[c] Volume of suspension.

[d] No treatment or prophylaxis dosing recommendations are available for patients undergoing renal dialysis.

[e] Initial loading dose of 600 mg or age-adjusted equivalent; maximum dosage 600 mg per day.

[f] Zanamivir is indicated for prophylaxis in children greater than or equal to 5 years old and for treatment in children greater than or equal to 7 years old.

Data from Fiore AE, Fry A, Shay D, et al. Antiviral agents for the treatment and chemoprophylaxis of influenza — recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep 2011;60:1–24.

data suggest that these events are more likely secondary to influenza infections than oseltamivir therapy.[53,54] It is currently recommended that patients be monitored closely for behavioral abnormalities.

No clinically significant drug interactions have been recognized to date, including studies with amoxicillin, aspirin, and acetaminophen. No interactions with the cytochrome P450 enzymes occur in vitro and oseltamivir does not affect the steady-state pharmacokinetics of commonly used immunosuppressive agents.[55] However, probenecid blocks tubular secretion and doubles the half-life of oseltamivir. Protein binding is less than 10%.

Peramivir

Peramivir has low oral bioavailability and is therefore delivered intravenously. Peramivir achieves exceptionally high maximum concentrations (~45,000 ng/mL after 600-mg intravenous dose) with excellent concentrations of drug in the nasal and pharyngeal secretions.[56] Peramivir is predominately eliminated unchanged by renal excretion with a plasma terminal elimination half-life of 12 to 25 hours.[39,57] Outside the United States, peramivir is available in 150-mg and 300-mg solutions for intravenous use, whereas peramivir is available in 200-mg solutions for intravenous use in the United States. Peramivir is approved as a single-dose infusion for the treatment of previously healthy adults with uncomplicated influenza in the United States; nonetheless, it has been studied for treatment of complicated influenza in hospitalized adults and is the only intravenous therapy currently approved for the treatment of influenza. Placebo-controlled studies of a single 300-mg to 600-mg infusion of peramivir was associated with a significantly shorter time to alleviation of symptoms, significantly shorter time to resumption of patients' usual activities, and more rapid clearance of virus.[58] A single 300-mg to 600-mg infusion of peramivir was also noninferior to 5 days of oral oseltamivir 75 mg twice a day in a season when many of the viruses were resistant to oseltamivir as the result of the H275Y mutation; these data challenge the efficacy of peramivir in the management of viruses with the H275Y mutation.[59]

Peramivir has also been investigated in several studies in hospitalized adults and children but is not specifically approved for this indication. In all studies, multiple doses of peramivir were used and findings suggest that single-dose therapy is not appropriate for severely ill patients. The first study, conducted in Japan, randomized 37 high-risk patients (those with diabetes or chronic respiratory tract diseases or patients being treated with drugs that suppress immune function) to receive 300 mg or 600 mg of peramivir daily with the duration of treatment (1–5 days) based on clinical improvement, defined as resolution of fever or judgment by the principal investigator or subinvestigator that continued administration was unnecessary.[60] The median durations of influenza symptoms were 114.4 hours in the 300-mg group and 42.3 hours in the 600-mg group (hazard ratio [90% confidence interval], 0.497 [0.251–0.984]) with a similar trend in time to resolution of fever. All subsequent studies have been larger, randomized, multinational studies. In the phase 2 study, 5 days of 200 mg or 400 mg of peramivir every day was compared with oral oseltamivir 75 mg twice a day in hospitalized adults. There was a trend toward more rapid resumption of usual activities in peramivir-treated patients and greater reductions of influenza B viral titers in the nasopharynx than oseltamivir over the first 48 hours.[61] A phase 3 multidose regimen was an open-label, multinational, randomized study that was started during the 2009 A/H1N1 pandemic (October 2009 to October 2010), and was designed to compare the safety and tolerability of 2 dosing regimens of peramivir in hospitalized patients.[62] Two-hundred and thirty-four patients were randomized to receive 5 days of 300 mg of peramivir twice daily or 600 mg of peramivir once daily. The overall time to clinical resolution (TTCR) was 92 hours in the intent-to-treat infected (ITTI) group with a median time of 42 hours in the 300-mg group and 166 hours in the 600-mg group. The subjects on the 600-mg regimen ITTI analysis were noted to have higher need for supplemental oxygen at randomization, higher baseline APACHE score, and higher need for ICU admission before randomization than the subjects randomized to the 300-mg regimen, and multivariate analysis showed that the difference in TTCR between groups could be explained by differences in severity of illness before randomization. Virologic response, as measured by time-weighted change in virus titer from baseline to 48 hours, was -1.51 $TCID_{50}$ (Median Tissue Culture Infectious Dose)/mL without significant difference between the two doses ($P = .65$). In addition, no treatment differences were seen in the percentage of subjects who remained culture positive or reverse transcription polymerase chain reaction positive at 48, 72, and 96 hours postenrolment. The second phase III study was a double-blind, randomized trail conducted between September 2009 and November 2012 and enrolled 338 patients.[63] Patients were randomized to receive peramivir or

standard of care in a 2:1 ratio. Only 121 patients had confirmed influenza and did not receive an NAI (neuraminidase inhibitor) as part of Standard of Care (SOC) (ITTI–non-NAI group) and were randomized to placebo (n = 43) or peramivir (n = 78) and 217 patients with confirmed influenza received NAI as part of SOC (ITTI-NAI group) and were randomized to placebo (n = 73) or peramivir (n = 144). Of note, there were important differences between the ITTI–non-NAI group and the ITTI-NAI group, namely lower mean body mass index (24.7 vs 29.1 kg/m^2) and lower influenza vaccination rate (5% vs 23%) in the ITTI–non-NAI group. In addition, the non-NAI SOC subjects had shorter symptom duration (32% vs 48% symptoms >48 hours), and were less likely to smoke (13% vs 23%), have abnormal chest radiographs at baseline (27% vs 45%), require supplemental oxygen (26% vs 36%), or have measurable virus titers at baseline (31% vs 50%). The study was terminated for futility after interim analysis. Peramivir-treated subjects in the non-NAI SOC population showed a modest, but not statically significant (P = .97), improvement in TTCR compared with subjects receiving SOC alone (42.5 vs 49.5 hours), with similar results observed in the NAI SOC population (peramivir vs placebo, 41.8 vs 48.9 hours; P = .74).

The largest pediatric study was a multicenter, open-labeled, uncontrolled study during the 2009 A/H1N1 pandemic.[64] One-hundred and six pediatric subjects, aged 125 days to 15 years, with confirmed A/H1N1 influenza received intravenous peramivir infusion at 10 mg/kg (500 mg maximum) once daily and clinical response, adverse events, and pharmacokinetics were assessed. Median time to resolution of fever was 20.6 hours, time to resolution of symptoms was 29.1 hours, and 92.9% had viral clearance by day 6 of treatment. Of note, TTCR in this pediatric study was shorter than the time noted in the adult trials. Taken together, these results suggest that intravenous peramivir likely has similar efficacy to oral oseltamivir and can be considered as an alternative to oral therapy in patients who cannot take oral therapy or in whom oral absorption is in question.

Because peramivir is renally cleared, dosing must be adjusted based on renal function (see **Table 1**).[65,66] There are limited data to guide dosing of peramivir in children, particularly among neonates.[65] No dose adjustments are needed for hepatic impairment. Recognized adverse events associated with the administration of peramivir are diarrhea, nausea, vomiting, and decreased neutrophil count; other less common adverse events observed in studies to date include dizziness, headache, somnolence, nervousness, insomnia, feeling agitated, depression, nightmares, hyperglycemia, hyperbilirubinemia, increased blood pressure, cystitis, electrocardiogram abnormalities, anorexia, and proteinuria.[67]

Zanamivir

The oral bioavailability of zanamivir is low (<5%), and most clinical trials have used intranasal or dry powder inhalation delivery. Following inhalation of the dry powder, approximately 7% to 21% is deposited in the lower respiratory tract and the remainder in the oropharynx.[68,69] Median zanamivir concentrations are more than 1000 ng/mL in induced sputum 6 hours after inhalation and remain detectable up to 24 hours. The peak plasma concentration averages 46 μg/L after a single 16-mg inhalation of zanamivir. The proprietary inhaler device for delivering zanamivir is breath actuated and requires a cooperative patient.[70]

Intravenous zanamivir displays linear dosing kinetics and the volume of distribution is approximately equivalent to that of extracellular water (16 L).[68] Intravenous zanamivir provides high peak plasma concentrations (~35,000 ng/mL after 600-mg dose in adults).[71] Ninety percent of the drug is excreted unchanged in the urine with an elimination half-life of approximately 2 hours. Intravenous zanamivir clearance is highly correlated with renal function.[72] Zanamivir is approved for the prevention and treatment of acute, uncomplicated influenza in ambulatory adults and children and is delivered by inhalation with a proprietary breath-activated device (Diskhaler). The usual adult treatment dose is 2 inhalations (10 mg) twice a day for 5 days and once a day for 10 days for prophylaxis. Intravenous zanamivir is currently only available by compassionate use.

Once-daily inhaled zanamivir for 10 days to 4 weeks is between 79% and 84% effective in preventing laboratory-confirmed symptomatic influenza.[69] Zanamivir is indicated for the treatment of uncomplicated acute illness caused by influenza A and B viruses in adults and pediatric patients 7 years of age and older who have been symptomatic for no more than 2 days.[15] Inhaled zanamivir in adults has consistently shown at least 1 less day of disabling influenza symptoms, and most studies have found a reduction in the number of nights of disturbed sleep, in time to resumption of normal activities, and in the use of symptom relief medications.[13,15] Similar therapeutic benefits have also been shown in children aged 5 to 12 years.[73] Zanamivir has also been associated with a 40% reduction in lower respiratory tract complications of influenza leading to antibiotics, particularly bronchitis and pneumonia.[74] Zanamivir seems generally well tolerated and effective in

treating influenza in patients with mild to moderate asthma or, less often, chronic obstructive pulmonary disease.[74,75]

Intravenous zanamivir is in advanced clinical development and has been used in seriously ill patients with influenza, especially those with suspected oseltamivir-resistant variants. Most of the emergency investigational new drug uses of intravenous zanamivir were in patients who were clinically failing other antiviral therapy, with at least 25% of patients having proven or clinically suspected resistance to oseltamivir; 10.5% of patients died.[76] A phase 2 study in critically ill patients with pandemic 2009 H1N1 found that treatment was associated with significant antiviral effects, even though therapy was initiated a median of 4.5 days after symptom onset. Of patients with influenza detected on initial sample, 2 days of therapy were associated with a median 1.42 $\log_{10}$ copies per milliliter decline in viral load.[71] There were no drug-related trends in safety parameters identified. The 14-day and 28-day all-cause mortalities were 13% and 17%, respectively.[71] A phase 3 study comparing intravenous zanamivir and oral oseltamivir in hospitalized adults was recently completed but results are not available at the time of the writing.

Dose adjustment is not necessary for renal or hepatic dysfunction. Certain populations, particularly very young, frail, or cognitively impaired patients, may have difficulty using the drug delivery system.[70] Intravenous zanamivir requires dose adjustment for renal insufficiency. All patients should receive an initial 600-mg loading dose. The maintenance dose and dosing interval are reduced with worsening renal function and it should be dosed according to updated guidance provided with the compassionate use drug.[71,72]

Topically applied zanamivir is generally well tolerated in controlled studies, including those involving patients with asthma and chronic obstructive pulmonary disease.[75] Postmarketing reports indicate that bronchospasm may be an uncommon but potentially severe problem, particularly in patients with acute influenza and underlying reactive airway disease.[15] Anecdotal reports of hospitalization and fatality indicate that inhaled zanamivir should be used cautiously in such patients.[15] The currently available inhaled formulation cannot be used in patients on ventilators because obstruction of filters and death of patients has been reported. One randomized controlled trial in ambulatory adults found that the combination of inhaled zanamivir and oral oseltamivir was less effective than oseltamivir monotherapy.[77] Zanamivir is not associated with teratogenic effects in preclinical studies (US Food and Drug Administration pregnancy category C) and should be considered as an option in pregnant women with proven influenza.[15]

Ribavirin

Ribavirin (Virazole, Rebetol) is a guanosine analogue with a wide range of antiviral activity, including influenza viruses, RSV, and parainfluenza viruses. Ribavirin is rapidly phosphorylated by intracellular enzymes and the triphosphate inhibits influenza virus RNA polymerase activity and competitively inhibits the guanosine triphosphate–dependent 5′ capping of influenza viral messenger RNA. In addition, ribavirin depletes cellular guanine pools[78,79] and may inhibit virus replication by lethal mutagenesis. Oral ribavirin has a bioavailability of 33% to 45% in adults and children and achieves peak plasma concentration of 0.6 μg/mL 1 to 2 hours after ingestion of a 400-mg dose in adults. Ribavirin has a short initial (0.3–0.7 hour) and a long terminal (18–36 hours) phase half-life and is eliminated by hepatic metabolism and renal clearance.[80] After aerosol administration, plasma levels increase with exposure and range from 0.2 to 1 μg/mL. Respiratory secretions have levels up to 1000 μg/mL, which decline with a half-life of 1.4 to 2.5 hours.

Ribavirin is available in 3 formulations: oral (approved for combined use in hepatitis C), intravenous (investigational in the United States), and aerosol. Ribavirin for aerosolization is available as a solution of 6 g/100 mL, which is diluted to a final concentration of 20 mg/mL and delivered by small particle aerosol for 12 to 18 hours with a proprietary device (SPAG-2 nebulizer). A higher concentration of aerosol solution (60 mg/mL) has been given over 2 hours 3 times daily in some studies and seems well tolerated.[81] Ribavirin also comes in 200-mg tablets and sterile solution for injection.

Ribavirin aerosol is currently indicated for the treatment of severe RSV in children. Trials of aerosolized ribavirin for the treatment of severe RSV infection in infants have shown no consistent effect on duration of hospitalization time, mortality, or pulmonary functions.[13] Current guidelines recommend that aerosolized ribavirin be considered in the treatment of high-risk infants and young children, as defined by congenital heart disease, chronic lung disease, immunodeficiency states, prematurity, and age less than 6 weeks, as well as for those hospitalized with severe illness.[13] Aerosolized ribavirin has shown minimal efficacy in treating influenza in hospitalized children.[82]

Ribavirin has also been studied for the treatment of RSV and parainfluenza virus infections in

immunocompromised patients. Intravenous ribavirin seems to be ineffective in reducing RSV-associated mortality in hematopoietic stem cell transplant (HSCT) patients with RSV pneumonia; there may be benefit among lung transplant recipients.[83] Aerosolized ribavirin may provide benefit in selected patient groups with less severe RSV disease. Survival was improved when treatment was started before respiratory failure or when infection was limited to the upper respiratory tract.[84] Observational studies suggest that combination therapy with antibodies (either intravenous immunoglobulin, RespiGam, or palivizumab) seems more effective, particularly when started before severe respiratory distress.[84] Oral ribavirin has been tried in the management of RSV with variable success.[85] In the management of parainfluenza virus in bone marrow transplant recipients, 2 case series found that aerosolized ribavirin failed to improve 30-day mortality or reduce the duration of viral replication relative to no treatment.[86] Ribavirin has not been clearly shown to have consistent clinical activity for the treatment of adenovirus infections and is not recommended for this indication.[87]

Systemic ribavirin is contraindicated in patients with creatinine clearance less than 50 mL/min and the dose should be reduced by one-third for patients less than 10 years of age. Dose adjustment is needed if there is a substantial decline in hematocrit and the drug should be discontinued if the hemoglobin level decreases to less than 8.5 g/dL. Systemic ribavirin can cause a dose-related extravascular hemolytic anemia and, at higher doses, suppression of bone marrow release of erythroid elements. Aerosolized ribavirin can cause bronchospasm, mild conjunctival irritation, rash, psychological distress if administered in an oxygen tent, and (rarely) acute water intoxication. Bolus intravenous administration may cause rigors. Antagonism of both drugs may occur when ribavirin is combined with zidovudine. Ribavirin is contraindicated in pregnant women and in male partners of women who are pregnant because of teratogenicity of the drug. Pregnancy should be avoided during therapy and for 6 months after completion of therapy in both female patients and in female partners of male patients taking ribavirin (pregnancy category X).

Nitazoxanide

Nitazoxanide is an antiparasitic agent with apparent antiviral activities, including influenza virus and norovirus.[88,89] The mechanism of action of nitazoxanide against influenza viruses is through blockage of maturation of the viral hemagglutinin at the posttranslational stage.[89] Nitazoxanide reduced symptom duration in phase 2b/3 trials in adults and adolescents with uncomplicated influenza[90]; a phase 3 trial is underway.[91] The drug also showed clinical efficacy in a small randomized trial of viral gastroenteritis.[92,93]

Cidofovir

No antiviral agents are specifically approved for the treatment of adenovirus. Cidofovir, which is a potent inhibitor of adenovirus in cell culture, has been used (either 5 mg/kg weekly for 2 weeks then every other week or 1 mg/kg 3 times a week), but data suggest that its efficacy/toxicity (predominantly nephrotoxicity) ratio is narrow. As a result, its use is limited generally to patients with significant evidence of disseminated adenovirus disease, preemptive treatment in pediatric HSCT patients with persistent replication. Earlier onset of therapy generally is associated with the best results and failure to develop a significant (1 log or greater) reduction in adenovirus load within 2 weeks of initiation of therapy is generally associated with poor outcomes.[87,94]

Combination Therapy

Combination therapy has been studied using a variety of combinations of antivirals and adjunctive therapies with the hope of improving antiviral activity, improving clinical outcomes, and reducing the risk of development of antiviral resistance for influenza.[95] There is evidence of in vitro synergy or additive effects with oseltamivir and amantadine; oseltamivir and favipiravir; peramivir and rimantadine; peramivir and oseltamivir; and a triple combination of amantadine, ribavirin, and oseltamivir.[95–99] In a study of oral rimantadine and nebulized zanamivir in an era with virus susceptible to M2 inhibitors, the combination was associated with trends toward faster cough resolution and lesser risk of adamantane resistance emergence.[100] The combination of oseltamivir and either convalescent plasma or hyperimmune globulin is associated with reduced mortality compared with patients treated with oseltamivir alone.[95,101] A study of oseltamivir, sirolimus, and corticosteroids was likewise associated with reduced mortality among critically ill patients.[102] The triple combination of amantadine, ribavirin, and oseltamivir was found to have similar PKs (pharmacokinetics) to each individual antiviral during monotherapy following a single dose and can be administered safely in immunocompromised patients; additional clinical studies of this triple combination are currently underway (NCT01227967). Likewise, the combination of oseltamivir and nitazoxanide has been studied; at the

time of writing, the study is complete but results have not been made public (NCT01610245). Despite their theoretic benefits, the optimal use of combination therapy is still under investigation.[95] Similarly, combinations of therapy, typically ribavirin plus antibody preparations, have also been studied for the treatment of RSV and parainfluenza virus in immunocompromised patients. For RSV, the lowest rate of progression to lower tract disease and lowest mortality has been observed with the combination of aerosolized ribavirin and an antibody preparation (either RSV immunoglobulin, intravenous immunoglobulin, or palivizumab).[84]

Investigational Agents

Favipiravir (T-705)

Favipiravir is a broad antiviral that seems to inhibit RNA-dependent RNA polymerase but not mammalian RNA or DNA synthesis. It is approved in Japan for treatment of influenza in selected circumstances and phase 3 studies from ex-Japan for the treatment of acute uncomplicated influenza have recently been completed but results are pending.[103] The antiviral has in vitro activity against several RNA viruses, including West Nile virus, dengue virus, yellow fever virus, and Ebola.

FluDase (DAS181)

DAS181 is a recombinant fusion protein that cleaves sialic acid residues from respiratory epithelial cell surfaces, and prevents influenza and parainfluenza viral infection.[104–107] A phase 2 trial showed reduction in influenza viral load in healthy adults but had a more limited impact on symptoms.[108] DAS181 has also been used to treat several immunocompromised patients with PIV infection with a complete or partial response shown in 81% of patients.[109–113] A phase 2 randomized trial of DAS181 in immunocompromised hosts with PIV lower respiratory tract infection is ongoing.

Presatovir (GS-5806)

GS-5806 is an oral RSV entry inhibitor that showed reductions in viral load and clinical severity in phase 1 studies.[114–116] Phase 2 trials are underway in hospitalized patients and adult HSCT and lung transplant recipients.[117–120]

ALS-8176

ALS-8176, a nucleoside analogue targeting RSV polymerase, showed reduction of viral load and decreased disease severity in a human challenge model.[121] Studies in hospitalized infants are ongoing.[122]

ALN-RSV01

ALN-RSV01, a small interfering RNA, was effective in a challenge model[123] and reduced cumulative daily symptom scores and incidence of progressive bronchiolitis obliterans syndrome in lung transplant recipients.[124,125] There is currently no ongoing clinical development.

REFERENCES

1. Limaye AP, Boeckh M. CMV in critically ill patients: pathogen or bystander? Rev Med Virol 2010;20:372–9.
2. Luyt CE, Combes A, Trouillet JL, et al. Virus-induced acute respiratory distress syndrome: epidemiology, management and outcome. Presse Med 2011;40:e561–8.
3. Travi G, Pergam SA. Cytomegalovirus pneumonia in hematopoietic stem cell recipients. J Intensive Care Med 2014;29:200–12.
4. Hayden FG. Newer influenza antivirals, biotherapeutics and combinations. Influenza Other Respir Viruses 2013;7(Suppl 1):63–75.
5. Hurt AC, Hui DS, Hay A, et al. Overview of the 3rd isirv-Antiviral Group Conference–advances in clinical management. Influenza Other Respir Viruses 2015;9:20–31.
6. McKimm-Breschkin JL, Fry AM. Meeting report: 4th ISIRV antiviral group conference: novel antiviral therapies for influenza and other respiratory viruses. Antiviral Res 2016;129:21–38.
7. Chan JF, Chan KH, Kao RY, et al. Broad-spectrum antivirals for the emerging Middle East respiratory syndrome coronavirus. J Infect 2013;67:606–16.
8. de Wilde AH, Jochmans D, Posthuma CC, et al. Screening of an FDA-approved compound library identifies four small-molecule inhibitors of Middle East respiratory syndrome coronavirus replication in cell culture. Antimicrobial Agents Chemother 2014;58:4875–84.
9. Hay AJ, Wolstenholme AJ, Skehel JJ, et al. The molecular basis of the specific anti-influenza action of amantadine. EMBO J 1985;4:3021–4.
10. Pinto LH, Holsinger LJ, Lamb RA. Influenza virus M2 protein has ion channel activity. Cell 1992;69:517–28.
11. Hay AJ, Zambon MC, Wolstenholme AJ, et al. Molecular basis of resistance of influenza A viruses to amantadine. J Antimicrob Chemother 1986;18(Suppl B):19–29.
12. 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.
13. 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;156:512–24.
14. Kaiser L, Hayden FG. Hospitalizing influenza in adults. In: Swartz MN, editor. Current clinical topics

in infectious diseases. Malden (MA): Blackwell Science; 1999. p. 112–34.
15. Fiore AE, Fry A, Shay D, et al. Antiviral agents for the treatment and chemoprophylaxis of influenza –- recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep 2011;60:1–24.
16. Aoki FY, Sitar DS. Clinical pharmacokinetics of amantadine hydrochloride. Clin Pharmacokinet 1988;14:35–51.
17. Hayden FG, Aoki FY. Amantadine, rimantadine and related agents. In: Barriere SL, editor. Antimicrobial therapy and vaccines. Baltimore (MD): Williams and Wilkins; 1999. p. 1344–65.
18. Hayden FG, Minocha A, Spyker DA, et al. Comparative single-dose pharmacokinetics of amantadine hydrochloride and rimantadine hydrochloride in young and elderly adults. Antimicrobial Agents Chemother 1985;28:216–21.
19. 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;160:1485–8.
20. Wills RJ. Update on rimatadine's clinical pharmacokinetics. J Respir Dis 1989;10:s20–5.
21. Colman PM. Influenza virus neuraminidase: structure, antibodies, and inhibitors. Protein Sci 1994;3:1687–96.
22. Moscona A. Neuraminidase inhibitors for influenza. N Engl J Med 2005;353:1363–73.
23. Kamali A, Holodniy M. Influenza treatment and prophylaxis with neuraminidase inhibitors: a review. Infect Drug Resist 2013;6:187–98.
24. Yamashita M. Laninamivir and its prodrug, CS-8958: long-acting neuraminidase inhibitors for the treatment of influenza. Antivir Chem Chemother 2010;21:71–84.
25. 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;51:1167–75.
26. Sugaya N, Ohashi Y. Long-acting neuraminidase inhibitor laninamivir octanoate (CS-8958) versus oseltamivir as treatment for children with influenza virus infection. Antimicrobial Agents Chemother 2010;54:2575–82.
27. Koseki N, Kaiho M, Kikuta H, et al. Comparison of the clinical effectiveness of zanamivir and laninamivir octanoate for children with influenza A(H3N2) and B in the 2011-2012 season. Influenza Other Respir Viruses 2014;8:151–8.
28. Katsumi Y, Otabe O, Matsui F, et al. Effect of a single inhalation of laninamivir octanoate in children with influenza. Pediatrics 2012;129:e1431–6.
29. Kashiwagi S, Watanabe A, Ikematsu H, et al. Laninamivir octanoate for post-exposure prophylaxis of influenza in household contacts: a randomized double blind placebo controlled trial. J Infect Chemother 2013;19:740–9.
30. Watanabe A. A randomized double-blind controlled study of laninamivir compared with oseltamivir for the treatment of influenza in patients with chronic respiratory diseases. J Infect Chemother 2013;19:89–97.
31. McClellan K, Perry CM. Oseltamivir: a review of its use in influenza. Drugs 2001;61:263–83.
32. He G, Massarella J, Ward P. Clinical pharmacokinetics of the prodrug oseltamivir and its active metabolite Ro 64-0802. Clin Pharmacokinet 1999; 37:471–84.
33. Ison MG, Szakaly P, Shapira MY, et al. Efficacy and safety of oral oseltamivir for influenza prophylaxis in transplant recipients. Antivir Ther 2012;17:955–64.
34. Baz M, Abed Y, Papenburg J, et al. Emergence of oseltamivir-resistant pandemic H1N1 virus during prophylaxis. N Engl J Med 2009;361:2296–7.
35. 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;163:1667–72.
36. Acosta EP, Jester P, Gal P, et al. Oseltamivir dosing for influenza infection in premature neonates. J Infect Dis 2010;202:563–6.
37. Kamal MA, Acosta EP, Kimberlin DW, et al. The posology of oseltamivir in infants with influenza infection using a population pharmacokinetic approach. Clin Pharmacol Ther 2014;96(3):380–9.
38. Kimberlin DW, Acosta EP, Prichard MN, et al. Oseltamivir pharmacokinetics, dosing, and resistance among children aged <2 years with influenza. J Infect Dis 2013;207:709–20.
39. Whitley RJ, Hayden FG, Reisinger KS, et al. Oral oseltamivir treatment of influenza in children. Pediatr Infect Dis J 2001;20:127–33.
40. Piedra PA, Schulman KL, Blumentals WA. Effects of oseltamivir on influenza-related complications in children with chronic medical conditions. Pediatrics 2009;124:170–8.
41. Kumar D, Michaels MG, Morris MI, et al. Outcomes from pandemic influenza A H1N1 infection in recipients of solid-organ transplants: a multicentre cohort study. Lancet Infect Dis 2010;10:521–6.
42. Reid G, Huprikar S, Patel G, et al. A multicenter evaluation of pandemic influenza A/H1N1 in hematopoietic stem cell transplant recipients. Transpl Infect Dis 2013;15:487–92.
43. Lee N, Ison MG. Diagnosis, management and outcomes of adults hospitalized with influenza. Antivir Ther 2012;17:143–57.
44. Lee N, Ison MG. Editorial commentary. "Late" treatment with neuraminidase inhibitors for severely ill patients with influenza: better late than never? Clin Infect Dis 2012;55:1205–8.

45. Louie JK, Yang S, Acosta M, et al. Treatment with neuraminidase inhibitors for critically ill patients with influenza A (H1N1)pdm09. Clin Infect Dis 2012;55:1198–204.
46. Muthuri SG, Venkatesan S, Myles PR, et al. Effectiveness of neuraminidase inhibitors in reducing 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.
47. Lee N, Hui DS, Zuo Z, et al. A prospective intervention study on higher-dose oseltamivir treatment in adults hospitalized with influenza a and B infections. Clin Infect Dis 2013;57:1511–9.
48. South East Asia Infectious Disease Clinical Research Network. Effect of double dose oseltamivir on clinical and virological outcomes in children and adults admitted to hospital with severe influenza: double blind randomised controlled trial. BMJ 2013;346:f3039.
49. Kumar A. Viral clearance with standard or triple dose oseltamivir therapy in critically ill patients with pandemic (H1N1) 2009 influenza. Denver (CO): ICAAC; 2013. p. B-1470.
50. Beigi RH, Han K, Venkataramanan R, et al. Pharmacokinetics of oseltamivir among pregnant and nonpregnant women. Am J Obstet Gynecol 2011; 204:S84–8.
51. Greer LG, Leff RD, Rogers VL, et al. Pharmacokinetics of oseltamivir according to trimester of pregnancy. Am J Obstet Gynecol 2011;204:S89–93.
52. Greer LG, Leff RD, Rogers VL, et al. Pharmacokinetics of oseltamivir in breast milk and maternal plasma. Am J Obstet Gynecol 2011;204:524.e1-4.
53. Toovey S, Prinssen EP, Rayner CR, et al. Post-marketing assessment of neuropsychiatric adverse events in influenza patients treated with oseltamivir: an updated review. Adv Ther 2012;29:826–48.
54. Hoffman KB, Demakas A, Erdman CB, et al. Neuropsychiatric adverse effects of oseltamivir in the FDA adverse event reporting system, 1999-2012. BMJ 2013;347:f4656.
55. Lam H, Jeffery J, Sitar DS, et al. Oseltamivir, an influenza neuraminidase inhibitor drug, does not affect the steady-state pharmacokinetic characteristics of cyclosporine, mycophenolate, or tacrolimus in adult renal transplant patients. Ther Drug Monit 2011;33:699–704.
56. Boltz DA, Aldridge JR Jr, Webster RG, et al. Drugs in development for influenza. Drugs 2010;70:1349–62.
57. Chairat K, Tarning J, White NJ, et al. Pharmacokinetic properties of anti-influenza neuraminidase inhibitors. J Clin Pharmacol 2012;53(2):119–39.
58. Kohno S, Kida H, Mizuguchi M, et al. Efficacy and safety of intravenous peramivir for treatment of seasonal influenza virus infection. Antimicrobial Agents Chemother 2010;54:4568–74.
59. Kohno S, Yen MY, Cheong HJ, et al. Phase III randomized, double-blind study comparing single-dose intravenous peramivir with oral oseltamivir in patients with seasonal influenza virus infection. Antimicrobial Agents Chemother 2011;55:5267–76.
60. Kohno S, Kida H, Mizuguchi M, et al. Intravenous peramivir for treatment of influenza A and B virus infection in high-risk patients. Antimicrobial Agents Chemother 2011;55:2803–12.
61. 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;18:651–61.
62. Ison MG, Fraiz J, Heller B, et al. Intravenous peramivir for treatment of influenza in hospitalized patients. Antivir Ther 2014;19:349–61.
63. de Jong MD, Ison MG, Monto AS, et al. Evaluation of intravenous peramivir for treatment of influenza in hospitalized patients. Clin Infect Dis 2014;59: e172–85.
64. Sugaya N, Kohno S, Ishibashi T, et al. Efficacy, safety, and pharmacokinetics of intravenous peramivir in children with 2009 pandemic H1N1 influenza A virus infection. Antimicrobial Agents Chemother 2012;56:369–77.
65. Arya V, Carter WW, Robertson SM. The role of clinical pharmacology in supporting the emergency use authorization of an unapproved anti-influenza drug, peramivir. Clin Pharmacol Ther 2010;88: 587–9.
66. Thomas B, Hollister AS, Muczynski KA. Peramivir clearance in continuous renal replacement therapy. Hemodialysis Int 2010;14:339–40.
67. Centers for Disease Control and Prevention. Emergency use authorization of Peramivir IV: fact sheet for health care providers. 2009.
68. Cass LM, Efthymiopoulos C, Bye A. Pharmacokinetics of zanamivir after intravenous, oral, inhaled or intranasal administration to healthy volunteers. Clin Pharmacokinet 1999;36(Suppl 1):1–11.
69. Dunn CJ, Goa KL. Zanamivir: a review of its use in influenza. Drugs 1999;58:761–84.
70. 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;322:577–9.
71. Marty FM, Man CY, van der Horst C, et al. Safety and pharmacokinetics of intravenous zanamivir treatment in hospitalized adults with influenza: an open-label, multicenter, single-arm, phase II study. J Infect Dis 2014;209:542–50.
72. Weller S, Jones LS, Lou Y, et al. Pharmacokinetics of zanamivir following intravenous administration to subjects with and without renal impairment. Antimicrobial Agents Chemother 2013;57:2967–71.
73. 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;19:410–7.
74. Lalezari J, Campion K, Keene O, et al. Zanamivir for the treatment of influenza A and B infection in high-risk patients - a pooled analysis of randomized controlled trials. Arch Intern Med 2001;161: 212–7.
75. Murphy KR, 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 - a double-blind, randomised, placebo-controlled, multicentre study. Clin Drug Invest 2000;20: 337–49.
76. Chan-Tack KM, Gao A, Himaya AC, et al. Clinical experience with intravenous zanamivir under an emergency investigational new drug program in the United States. J Infect Dis 2013;207:196–8.
77. 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.
78. Wray SK, Gilbert BE, Knight V. Effect of ribavirin triphosphate on primer generation and elongation during influenza virus transcription in vitro. Antiviral Res 1985;5:39–48.
79. Wray SK, Gilbert BE, Noall MW, et al. Mode of action of ribavirin: effect of nucleotide pool alterations on influenza virus ribonucleoprotein synthesis. Antiviral Res 1985;5:29–37.
80. Paroni R, Del Puppo M, Borghi C, et al. Pharmacokinetics of ribavirin and urinary excretion of the major metabolite 1,2,4-triazole-3-carboxamide in normal volunteers. Int J Clin Pharmacol Ther Toxicol 1989;27:302–7.
81. 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;206:1367–71.
82. 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;125:129–35.
83. Glanville AR, Scott AI, Morton JM, et al. Intravenous ribavirin is a safe and cost-effective treatment for respiratory syncytial virus infection after lung transplantation. J Heart Lung Transplant 2005;24:2114–9.
84. Shah JN, Chemaly RF. Management of RSV infections in adult recipients of hematopoietic stem cell transplantation. Blood 2011;117:2755–63.
85. Marcelin JR, Wilson JW, Razonable RR, Mayo Clinic Hematology/Oncology and Transplant Infectious Diseases Services. Oral ribavirin therapy for respiratory syncytial virus infections in moderately to severely immunocompromised patients. Transpl Infect Dis 2014;16:242–50.
86. Ison MG. Respiratory viral infections in transplant recipients. Antivir Ther 2007;12:627–38.
87. Ison MG. Adenovirus infections in transplant recipients. Clin Infect Dis 2006;43:331–9.
88. Rossignol JF. Nitazoxanide: a first-in-class broad-spectrum antiviral agent. Antiviral Res 2014;110: 94–103.
89. Rossignol JF, La Frazia S, Chiappa L, et al. Thiazolides, a new class of anti-influenza molecules targeting viral hemagglutinin at the post-translational level. J Biol Chem 2009;284:29798–808.
90. Haffizulla J, Hartman A, Hoppers M, et al. Effect of nitazoxanide in adults and adolescents with acute uncomplicated influenza: a double-blind, randomised, placebo-controlled, phase 2b/3 trial. Lancet Infect Dis 2014;14:609–18.
91. Romark Laboratories. A phase III randomized double-blind placebo controlled trial to evaluate the efficacy and safety of nitazoxanide in the treatment of acute uncomplicated influenza. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US); 2015 [cited 22 Dec 2015].
92. Rossignol JF, Abu-Zekry M, Hussein A, et al. Effect of nitazoxanide for treatment of severe rotavirus diarrhoea: randomised double-blind placebo-controlled trial. Lancet 2006;368:124–9.
93. Rossignol JF, El-Gohary YM. Nitazoxanide in the treatment of viral gastroenteritis: a randomized double-blind placebo-controlled clinical trial. Aliment Pharmacol Ther 2006;24:1423–30.
94. Ison MG, Green M. Practice ASTIDCo. Adenovirus in solid organ transplant recipients. Am J Transplant 2009;9(Suppl 4):S161–5.
95. Dunning J, Baillie JK, Cao B, et al, International Severe Acute Respiratory and Emerging Infection Consortium (ISARIC). Antiviral combinations for severe influenza. Lancet Infect Dis 2014;14: 1259–70.
96. 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: 1410–9.
97. Pukrittayakamee S, Jittamala P, Stepniewska K, et al. An open-label crossover study to evaluate potential pharmacokinetic interactions between oral oseltamivir and intravenous zanamivir in healthy Thai adults. Antimicrobial Agents Chemother 2011;55:4050–7.
98. 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.
99. 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;18:377–86.
100. 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: 183–90.
101. Hung IF, To KK, Lee CK, et al. Convalescent plasma treatment reduced mortality in patients with severe pandemic influenza A (H1N1) 2009 virus infection. Clin Infect Dis 2011;52:447–56.
102. Wang CH, Chung FT, Lin SM, et al. Adjuvant treatment with a mammalian target of rapamycin inhibitor, sirolimus, and steroids improves outcomes in patients with severe H1N1 pneumonia and acute respiratory failure. Crit Care Med 2014;42:313–21.
103. MDVI, LLC. Phase 3 efficacy and safety study of favipiravir for treatment of uncomplicated influenza in adults. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US); 2015 [cited 21 Dec 2015].
104. Malakhov MP, Aschenbrenner LM, Smee DF, et al. Sialidase fusion protein as a novel broad-spectrum inhibitor of influenza virus infection. Antimicrobial Agents Chemother 2006;50:1470–9.
105. Belser JA, Lu X, Szretter KJ, et al. DAS181, a novel sialidase fusion protein, protects mice from lethal avian influenza H5N1 virus infection. J Infect Dis 2007;196:1493–9.
106. Triana-Baltzer GB, Gubareva LV, Klimov AI, et al. Inhibition of neuraminidase inhibitor-resistant influenza virus by DAS181, a novel sialidase fusion protein. PLoS One 2009;4:e7838.
107. Triana-Baltzer GB, Gubareva LV, Nicholls JM, et al. Novel pandemic influenza A(H1N1) viruses are potently inhibited by DAS181, a sialidase fusion protein. PLoS One 2009;4:e7788.
108. Moss RB, Hansen C, Sanders RL, et al. A phase II study of DAS181, a novel host directed antiviral for the treatment of influenza infection. J Infect Dis 2012;206:1844–51.
109. Waghmare A, Wagner T, Andrews R, et al. Successful treatment of parainfluenza virus respiratory tract infection with DAS181 in 4 immunocompromised children. J Pediatr Infect Dis Soc 2015;4: 114–8.
110. Chalkias S, Mackenzie MR, Gay C, et al. DAS181 treatment of hematopoietic stem cell transplant patients with parainfluenza virus lung disease requiring mechanical ventilation. Transpl Infect Dis 2014;16:141–4.
111. Drozd DR, Limaye AP, Moss RB, et al. DAS181 treatment of severe parainfluenza type 3 pneumonia in a lung transplant recipient. Transpl Infect Dis 2013;15:E28–32.
112. Guzman-Suarez BB, Buckley MW, Gilmore ET, et al. Clinical potential of DAS181 for treatment of parainfluenza-3 infections in transplant recipients. Transpl Infect Dis 2012;14:427–33.
113. Salvatore M, Satlin MJ, Jacobs SE, et al. DAS181 for the treatment of parainfluenza virus infections in 16 hematopoietic stem cell transplant recipients at a single center. Biol Blood Marrow Transplant 2016;22(5):965–70.
114. DeVincenzo JP, Whitley RJ, Mackman RL, et al. Oral GS-5806 activity in a respiratory syncytial virus challenge study. N Engl J Med 2014;371:711–22.
115. Mackman RL, Sangi M, Sperandio D, et al. Discovery of an oral respiratory syncytial virus (RSV) fusion inhibitor (GS-5806) and clinical proof of concept in a human RSV challenge study. J Med Chem 2015;58:1630–43.
116. Samuel D, Xing W, Niedziela-Majka A, et al. GS-5806 inhibits pre- to postfusion conformational changes of the respiratory syncytial virus fusion protein. Antimicrobial Agents Chemother 2015;59:7109–12.
117. Gilead Sciences. Efficacy, pharmacokinetics, and safety of GS-5806 in hospitalized adults with respiratory syncytial virus (RSV) infection. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US); 2015 [cited 2015 Nov 24].
118. Gilead Sciences. GS-5806 in lung transplant (LT) recipients with respiratory syncytial virus (RSV) infection. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US); 2015 [cited 2015 Nov 24].
119. Tylden GD, Hirsch HH, Rinaldo CH. Brincidofovir (CMX001) inhibits BK polyomavirus replication in primary human urothelial cells. Antimicrobial Agents Chemother 2015;59:3306–16.
120. Gilead Sciences. GS-5806 in hematopoietic cell transplant recipients with respiratory syncytial virus (RSV) infection of the lower respiratory tract. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US); 2015 [cited 2015 Nov 24].
121. DeVincenzo JP, McClure MW, Symons JA, et al. Activity of oral ALS-008176 in a respiratory syncytial virus challenge study. N Engl J Med 2015;373: 2048–58.
122. Parker S, Crump R, Foster S, et al. Co-administration of the broad-spectrum antiviral, brincidofovir (CMX001), with smallpox vaccine does not compromise vaccine protection in mice challenged with ectromelia virus. Antiviral Res 2014; 111:42–52.

123. DeVincenzo J, Lambkin-Williams R, Wilkinson T, et al. A randomized, double-blind, placebo-controlled study of an RNAi-based therapy directed against respiratory syncytial virus. Proc Natl Acad Sci U S A 2010;107:8800–5.
124. Zamora MR, Budev M, Rolfe M, et al. RNA interference therapy in lung transplant patients infected with respiratory syncytial virus. Am J Respir Crit Care Med 2011;183:531–8.
125. Gottlieb J, Zamora MR, Hodges T, et al. ALN-RSV01 for prevention of bronchiolitis obliterans syndrome after respiratory syncytial virus infection in lung transplant recipients. J Heart Lung Transplant 2016;35(2):213–21.