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Antiviral Agents Against Respiratory Viruses

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KEY CONCEPTS

- Most circulating strains of influenza are resistant to amantadine and rimantadine.
- There are four approved neuraminidase inhibitors: laninamivir, oseltamivir, peramivir and zanamivir.
- All of the neuraminidase inhibitors have the greatest clinical impact if started within 24–48 hours of symptom onset.
- For hospitalized adults and children, anti-influenza therapy should be initiated as soon as influenza is considered and should not be delayed for confirmatory testing.
- Neuraminidase inhibitors appear to reduce 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 (RSV) but has very limited clinical indications; oral ribavirin is part of a triple drug regimen for influenza undergoing testing.
- Several new antivirals are in advanced development for the treatment of respiratory viral infections including RSV, rhinovirus and adenovirus.
- Neutralizing antibodies in the form of convalescent plasma or monoclonals appear to be promising for treatment in novel influenza and coronavirus infections.

Introduction

Few antiviral drugs are currently approved for treating respiratory virus infections and most of these are specific inhibitors of influenza viruses (Table 154-1). However, considerable progress is being made in the development of new therapeutics for other respiratory viruses.[1] The emergence of new pathogens such as Middle East respiratory syndrome coronavirus (MERS-CoV) has also led to screening efforts to identify new therapeutics.[2,3] Clinical studies to examine novel targets (Table 154-1), combinations designed to increase potency and reduce resistance emergence, therapeutic antibodies, and immunomodulatory agents selected to mitigate immunopathologic host responses, particularly for influenza, are in progress.[4] Neutralizing antibodies have been proven effective for prevention of respiratory syncytial virus (RSV) disease, although not for treatment,[5] but specific neutralizing antibodies (convalescent plasma, monoclonals) appear to be promising for treating novel influenza and coronavirus infections. This chapter reviews the properties and clinical applications of currently approved antiviral agents.

M2 Inhibitors

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 the M2 protein (Figure 154-1).[7–9] Unfortunately, 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.[6]

PHARMACOKINETICS AND DISTRIBUTION

Both drugs achieve peak levels 3-5 hours after ingestion (see detailed pharmacokinetic data in Table 154-2).[10–12] Amantadine is excreted unchanged by the kidney while rimantadine undergoes extensive metabolism by the liver before being excreted by the kidney; as a result, dose adjustment with renal dysfunction is required (Table 154-2).

ROUTE OF ADMINISTRATION AND DOSAGE

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 q12h for both drugs (see Table 154-2).

INDICATIONS

The current recommendations of the Centers for Disease Control and Prevention (CDC) and the World Health Organization (WHO) should be consulted before using this class clinically, including in infections by novel strains of influenza-like avian H5N1. A triple drug regimen (amantadine, ribavirin, oseltamivir) is currently under study for influenza A infections, including those due to adamantane-resistant strains.[6] When used against susceptible strains, both agents are 70–90% effective in preventing infection and reduce duration of fever and symptoms when used for treatment.[15–17] Dosage in special circumstances is summarized in Table 154-1.

ADVERSE REACTIONS AND INTERACTIONS

The most common side-effects of the M2 inhibitors are minor central nervous system (CNS) complaints (anxiety, difficulty concentrating, insomnia, dizziness, headache and jitteriness) and gastrointestinal upset, which are particularly prominent in the elderly and those with renal failure.[11] Patients who receive amantadine may develop antimuscarinic effects, orthostatic hypotension and congestive heart failure. Rates of adverse effects are lower for rimantadine than amantadine.[11,18] Given drug–drug interactions, care should be used when co-administering either agent with antihistamines or anticholinergic drugs, trimethoprim–sulfamethoxazole, triamterene–hydrochlorothiazide, quinine, quinidine, monoamine oxidase inhibitors, antidepressants and minor tranquilizers.[19]

RESISTANCE

Cross-resistance to both agents occurs as the result of single amino acid substitutions in the transmembrane portion of the M2 protein.[9] The resistant virus appears to retain wild-type pathogenicity and causes an influenza illness indistinguishable from susceptible strains. Resistance has emerged within 2–4 days after the start of therapy in up to 30% of patients infected with initially susceptible strains.[11] Emergence of resistant variants may be associated with protracted illness and shedding in immunocompromised hosts[20]; spread to contacts causes failures of antiviral prophylaxis in nursing homes and households.[11]

TABLE 154-1 Agents Used to Prevent and Treat Influenza

Class	Drug	USUAL ADULT DOSAGE*		Dose Adjustment State	Suggested Dosage
		Prophylaxis	Treatment		
M2 inhibitor	Amantadine	100 mg q12h	100 mg q12h	Age 1–9 years (yr) CrCl 30–50 mL/min CrCl 15–30 mL/min CrCl 10–15 mL/min CrCl 10 mL/min Age ≥65 yr	5 mg/kg to max of 150 mg in two divided doses 100 mg q24h 100 mg q24h 100 mg q week 100 mg q week 100 mg q24h
	Rimantadine	100 mg q12h	100 mg q12h	Age 1–9 yr* CrCl <10 mL/min Severe hepatic dysfunction Age ≥65 yr	5 mg/kg to max of 150 mg in two divided doses 100 mg q24h 100 mg q24h 100 mg q24h
Neuraminidase inhibitor	Laninamivir	20 mg QD × 2 days	40 mg once	Age <10 yr	20 mg once
	Oseltamivir†	75 mg q24h	75 mg q12h	CrCl <30 mL/min‡ ≤15 kg§ 15–23 kg§ 23–40 kg§ >40 kg§ Any weight, 2 weeks to <1 yr	Treatment: 75 mg q24h Prophylaxis: 75 mg every other day 30 mg q12h (5 mL¶) 45 mg q12h (7.5 mL¶) 60 mg q12h (10 mL¶) 75 mg q12h (12.5 mL¶) 3 mg/kg q12hr (0.5 mL/kg¶)
	Peramivir	NA	300 mg once	For patients with severe infection Children 6–17 yr Children 180 days–5 yr CrCl 31–49 mL/min§ CrCl 10-30 mL/min§ CrCl <10 mL/min Intermittent hemodialysis (HD) (dose on HD days only)	600 mg QD as a single or multi-dose regimen 10 mg/kg QD for 5 days (max of 600 mg QD) 12 mg/kg QD Adult: 150 mg QD Age 6–17 yr: 2.5 mg/kg QD§ Age 180 days–5 yr: 3 mg/kg QD Adult: 100 mg QD Age 6–17 yr: 1.6 mg/kg QD§ Age 180 days–5 yr: 1.9 mg/kg QD Adult: 100 mg on day 1 then 15 mg QD Age 6–17 yr: 1.6 mg/kg on day 1 then 0.25 mg/kg QD Age 180 days–5 yr: 1.9 mg/kg on day 1 then 0.3 mg/kg ≥18 yr: 100 mg on day 1 then 100 mg 2 hours after HD Age 6–17 yr: 1.6 mg/kg on day 1 then 1.6 mg/kg 2 hours after HD Age 180 days–6 yr: 1.9 mg/kg on day 1 then 1.9 mg/kg 2 hours after HD
	Inhaled zanamivir‖	2 puffs (10 mg) twice a day for 5 days	2 puffs (10 mg) twice a day for 5 days	No dose adjustment needed	
	iv zanamivir	NA	600 mg q12h	Renal insufficiency	Loading dose (all patients): 600 mg Maintenance dosing based on CL_{cr}/CL_{CRRT} values: 80–50 mL/min: 400 mg 30–50 mL/min: 250 mg 15–30 mL/min: 150 mg <15 mL/min: 60 mg The interval between the initial dose and the start of maintenance dosing by CL_{cr}/CL_{CRRT}: 15–30 mL/min: 24 hrs <15 mL/min: 48 hrs

Recommendations based on those provided by the Advisory Committee on Immunization Practices.[4]
*Duration of treatment is usually 5 days. Duration of prophylaxis depends on clinical setting.
†Oseltamivir is indicated for prophylaxis in children ≥1 year old and for treatment in children in ≥2 weeks of age.
‡No treatment or prophylaxis dosing recommendations are available for patients undergoing renal dialysis.
§Initial loading dose of 600 mg or age adjusted equivalent; maximum dose 600 mg QD.
¶Volume of suspension.
‖Zanamivir is indicated for prophylaxis in children ≥5 years old and for treatment in children ≥7 years old.
CL_{cr}/CL_{CRRT}: Ratio of creatinine clearance to continuous renal replacement therapy clearance.

Neuraminidase Inhibitors

Influenza A and B viruses possess a surface glycoprotein with neuraminidase activity whereas influenza C viruses do not (Figure 154-1). This enzyme 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®)

TABLE 154-2 Pharmacokinetic Properties of Antivirals with Activity Against Influenza

Drug	Dose	Route	C_{max} (μg/L)	T_{max} (h)	$AUC_{0-12\ h}$ (mg/mL•h)	$T_{1/2}$ (h)	Bioavailability (Oral, %)	Protein Binding (%)
Amantadine[5,6]*	200 mg 200 mg	Oral (young) Oral (elderly)	510 (140) 800 (200)	2.1 (1) 2.2 (2.1)	10.2 (3.4) 17.6 (6.5)	14.4 (6) 19 (9.1)	62–93 54–100	67
Rimantadine[5,6]*	200 mg 200 mg	Oral (young) Oral (elderly)	240 (70) 250 (50)	4.6 (2.1) 4.0 (2.4)	9.8 (4.5) 11.5 (3.0)	36.5 (17.3) 36.5 (14.5)	75–93 NA	40
Laninamivir	40 mg	Inhaled	NA	NA	NA	3	~15	NA
Oseltamivir[8]*	100 mg q12h 100 mg q12h	Oral (18–55 years) Oral (≥65 years)	439 (40.8) 575 (83.8)	3.5 (1) 3.5 (1.4)	3.85 (0.6) 4.94 (1.0)	6–10 –	79 –	42
Peramivir	600 mg	Intravenous	46.8	NA	102.7	20	NA	<30
Zanamivir[7]†	16 mg 16 mg	Inhaled Inhaled	29 (23–69) 54 (34–96)	0.75 (0.08–2) 0.75 (0.25–1)	0.03 (0.02–0.06) 0.16 (0.02–0.32)	3.6 (2.2–9.4) –	4–17 4–17	10

C_{max}, maximum serum drug concentration; T_{max}, time to C_{max}; $T_{1/2}$, serum elimination half-life; AUC, area under the curve for serum drug concentration versus time for the dose interval; bioavailability, percentage of intravenous C_{max}.
*Values are mean (SD).
†Values are median (range).

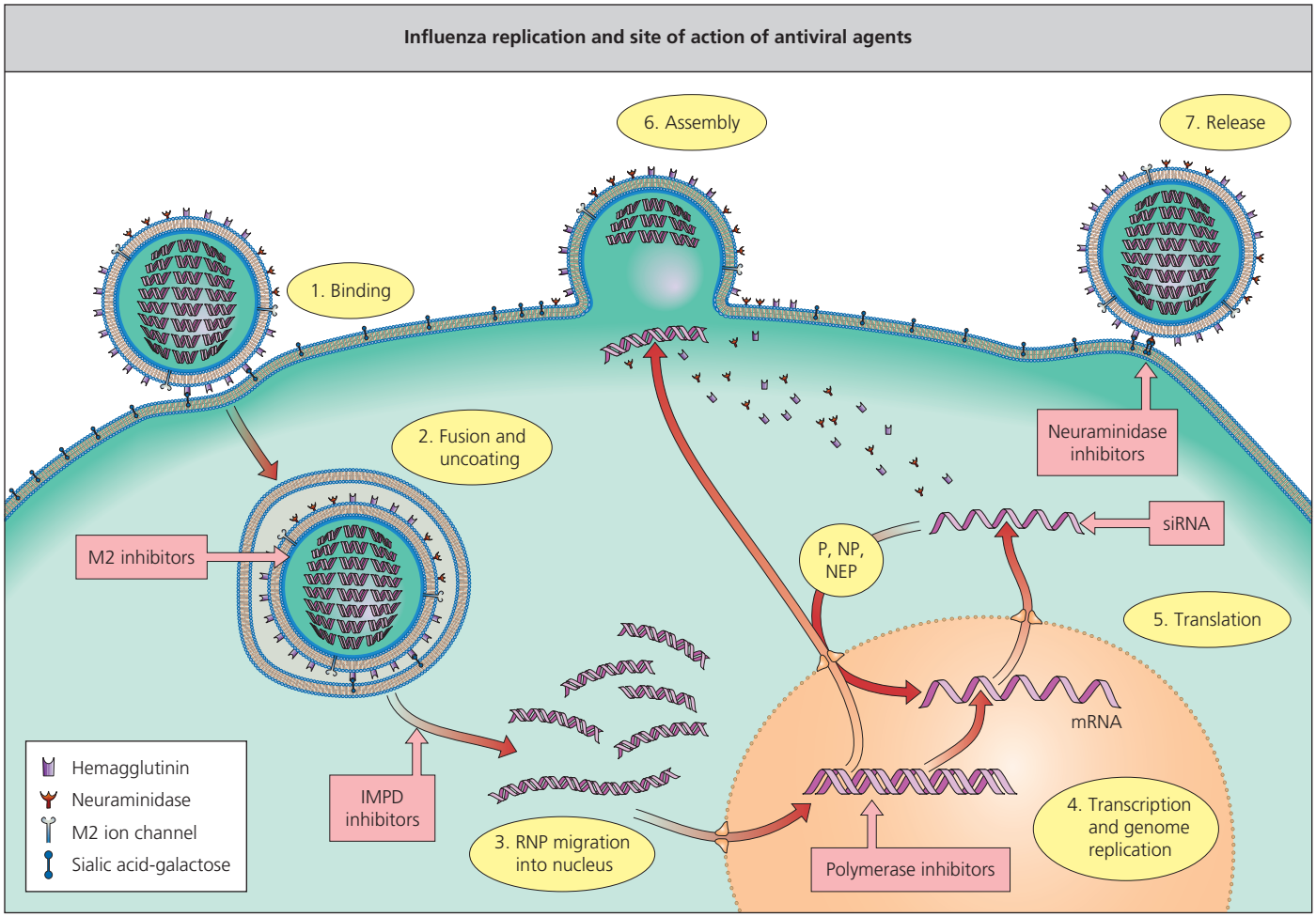

Figure 154-1 Influenza replication and site of action of antiviral agents. IMPD, inosine monophosphate dehydrogenase; NEP, nuclear export protein; NP, nucleoprotein; P, polymerase; RNP, ribonuclear protein; siRNA, small inhibitory ribonucleic acid. *(Reprinted from Beigel J, Bray M. Current and future antiviral therapy of severe seasonal and avian influenza. Antiviral Res 2008; 78:91–102.)*

and zanamivir (Relenza®) are sialic acid analogs that potently and specifically inhibit influenza A and B neuraminidases by competitively and reversibly interacting with the active enzyme site.[22,23] These drugs are active against all nine influenza neuraminidase subtypes in nature. Oseltamivir and zanamivir are globally available, while laninamivir is approved in Japan and peramivir is approved in China, Japan, South Korea and the USA.

Laninamivir

PHARMACOKINETICS AND DISTRIBUTION

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} 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. Laninamivir has excellent *in vitro* activity against wild-type influenza A and B viruses currently circulating, including those H1N1 viruses containing H275Y mutations in the neuraminidase.

ROUTE OF ADMINISTRATION AND DOSAGE

Laninamivir octanoate (CS-8958) is currently only approved in Japan and is available as a 20 mg dry powder inhaler. It is undergoing clinical investigation outside of Japan at present.

INDICATIONS

Prophylaxis

Laninamivir is approved for the prevention of influenza in adults and children ≥ 10 years of age; a single inhalation of 20 mg daily for 2 days is recommended for this indication. 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.[25]

Treatment

Laninamivir is approved for the treatment and prevention of influenza A and B infection in Japan. For treatment, laninamivir is approved as a single inhalation of 40 mg for individuals ≥10 years of age and 20 mg for children less than 10 years of age. Laninamivir was associated with more rapid time to alleviation of influenza illness due to infections by seasonal H1N1 virus with the H275Y substitution in children compared to a standard 5-day oseltamivir regimen, while studies in adults demonstrated noninferiority versus oseltamivir in such patients.[26,27] Laninamivir demonstrates a similar duration of fever in ambulatory children when compared to patients treated with zanamivir.[28,29]

Dosage in Special Circumstances

No dose adjustment is currently indicated in any patient population.

Adverse Reactions and Interactions

Clinical studies in Asia found similar rates of nausea in laninamivir octanoate- and oseltamivir- treated patients, lower rates of vomiting in the laninamivir octanoate arm, and similar to slightly higher rates of diarrhea in laninamivir octanoate arms.[26,27] Dizziness was seen in 0.9–1.8% of laninamivir octanoate-treated patients but not oseltamivir-treated patients.[26] Laninamivir was not associated with significant bronchospasm or other respiratory adverse effects in patients with chronic respiratory disease.[30]

Oseltamivir

PHARMACOKINETICS AND DISTRIBUTION

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 (see Table 154-3).[13] The plasma elimination half-life is 6–10 hours but is more prolonged in the elderly, although dose adjustments are not generally necessary. Administration with food appears 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 below 10 mL/min.[31] Distribution is not well characterized in humans, but peak bronchoalveolar lavage, middle ear fluid and sinus fluid levels are similar to plasma levels.[13] Recent data suggest that significant relationships exist between oseltamivir carboxylate AUC_{0-24} and area under the curve (AUC) of symptom scores, time to alleviation of composite symptom scores, and time to cessation of viral shedding in experimentally infected volunteers.[32]

ROUTE OF ADMINISTRATION AND DOSAGE

Oseltamivir is available for oral delivery only. Oseltamivir comes as 30, 45, 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 154-2.

INDICATIONS

Prophylaxis

Oseltamivir is indicated for the prevention of influenza infection in patients ≥1 year, with dosing once a day. The efficacy of once-daily oseltamivir 75 mg for 6 weeks in preventing influenza illness in healthy, nonimmunized adults was 84% and in preventing influenza infection irrespective of symptoms was 50%.[13] In immunized nursing home residents, the efficacy of prophylaxis was 92% against illness compared to placebo.[23] Somewhat lower efficacy was seen in a household-contact prophylaxis study, and protection against influenza has been shown in children.[33] Seasonal prophylaxis of high-risk immunocompromised patients was documented to provide ~80% protective efficacy against RT-PCR-confirmed influenza illness.[34] Caution should be used when prescribing oseltamivir for prophylaxis in patients exposed to an index case as prophylaxis has been associated with emergence of resistant mutants;[35] empiric therapy or monitoring is generally recommended in these cases as a result.

Postexposure prophylaxis in nursing home influenza outbreaks is advised for 14 days or for at least 7 days after the last culture-confirmed illness in the ward or building is effective; this regimen should be given with concomitant influenza vaccination for those not previously provided. Seasonal prophylaxis, during the 4–8 weeks of peak influenza virus circulation within the community, can be used for protection of high-risk patients who cannot tolerate immunization, who do not develop an adequate immune response to vaccine, or when the strain circulating in the community does not match the vaccine strain.

Treatment

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 to placebo in previously healthy adults.[6,16,36] One recent study in Bangladesh suggests that oseltamivir may have efficacy up to 72 hours after symptom onset in children.[37] Pediatric studies enrolling children as young as 2 weeks of age demonstrated 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.[38–42] Most existing literature on the safety and efficacy of oseltamivir in elderly or high-risk persons, including those with underlying cardiopulmonary conditions or immunodeficiency comes from observational studies[43–46] and 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.[47]

TABLE 154-3 Summary of Antiviral Agents in Advanced Clinical Development for Respiratory Viruses

Drug	Spectrum	Target of Antiviral Action	Antiviral Resistance in Clinical Isolates	Route of Dosing	Pharmacokinetic Properties	Principal Adverse Effects	Clinical Effectiveness
Zanamivir	Influenza A + B	Enzymatic action of viral NA	Rare	iv	Renal excretion with plasma elimination half-life of ~2 hrs; dose adjustment required for renal insufficiency	iv delivery avoids bronchospasm risk with aerosol treatment	Significant antiviral effects in severely ill A(H1N1)pdm09-infected patients not responding to oseltamivir.
Favipiravir/ T-705	Influenza A, B, C and other RNA viruses	Influenza RNA polymerase; lethal mutagenesis	Not reported to date	Oral	Intracellular ribosylation and phosphorylation to its active triphosphate form. Good oral bioavailability; parent compound metabolized to inactive moiety by and also inhibitor of aldehyde oxidase >65% renally excreted as metabolite by 48 hrs	Dose-related hyperuricemia; teratogenic in preclinical testing – restricted use in pregnancy	BID dosing regimen more effective than TID regimen. Approved in Japan for use in novel or drug-resistant influenza infections. No data from severe influenza
DAS181	Influenza A + B, PIV	Host cell receptor for viral HA. Sialidase removes both the human-like a2,6- and avian-like a2,3-linked sialic acids from cellular receptors	Not reported to date	Inhaled	In *ex vivo* human airway epithelium and human bronchial tissue, the inhibitory effect of DAS181 treatment lasts ≥2 days. Tracheobronchial delivery and degree of systemic absorption dependent on particle size	Elevated alkaline phosphatase due to reduced clearance, no associated increases in transaminases	Reduced pharyngeal influenza virus detection but little clinical benefit in treating uncomplicated influenza; unstudied in serious influenza. Case reports of antiviral effectiveness and clinical improvement in serious PIV illness in transplant recipients; RCT in progress
Nitazoxanide	A + B and other RNA viruses	Influenza HA maturation; possible immune-modulatory and other antiviral mechanism of action	Not reported to date	Oral	Metabolized by plasma esterases metabolize to its active desacetyl derivative tizoxanide, which undergoes glucuronidation and urinary elimination with elimination half-life of ~7 hrs. Tizoxanide is highly bound by (>99%) plasma proteins. Need for dose adjustments uncertain	GI; respiratory distress	Shorter duration of viral replication and illness compared to placebo in phase 2 RCT in uncomplicated influenza; evidence for clinical benefit in influenza-like illness without detectable virus by RT-PCR
VX-787	Influenza A	Influenza RNA polymerase	Common	Oral		Not reported	Antiviral efficacy and associated reduction in illness measures in experimentally infected volunteers; no studies in natural influenza reported to date
AVI-7100	Influenza A	M1 (matrix) and M2 (ion channel) genes	Not reported	iv	Phosphorodiamidate morpholino oligomer with three modified linkages; active after topical or iv dosing in ferrets	Not reported	Phase 1 study of iv formulation in progress

Brincidofovir (CMX-001)	Adenovirus, other DNA viruses	Viral DNA polymerase	Infrequent	Oral	Infrequent dosing (weekly or bi-weekly) possible due to high intracellular concentration and long intracellular half-life (up to 4-6.5 days) of the active antiviral cidofovir-diphosphate	Diarrhea, other GI symptoms; transaminase elevations	Antiviral effects in case series of transplant recipients intolerant of or failing cidofovir for serious adenovirus infection and with bi-weekly dosing in RCT for pre-emptive treatment of adenoviremia; follow-up RCT in progress
GS-5806	RSV	F protein-fusion	Not reported but common in preclinical studies with other fusion inhibitors	Oral	Fusion inhibitor	Limited clinical data	Protective effects in experimentally infected volunteers; placebo-controlled RCTs in progress for treating elderly hospitalized with RSV and for transplant recipients with upper or lower respiratory illness due to RSV
ALS-8176	RSV	Polymerase	Not reported	Oral	Nucleoside analog	Not reported	Phase 1 studies in healthy adults completed; phase 2 in progress
MDT-637 (formerly VP-14637)	RSV	F protein-fusion	Not reported but common in preclinical studies with other fusion inhibitors	Inhaled	Fusion inhibitor	Not reported	Phase 1 studies up to 10 days dosing in healthy adults completed
ALN-RSV01	RSV	Nucleocapsid gene	Not reported	Inhaled	Small interfering RNA	Generally well-tolerated in studies to date	Protective against RSV infection in experimental human RSV challenge. Two placebo-controlled phase 2 RCTs in RSV-infected lung transplant patients found reduced incidence of new or progressive BOS

Note: this table summarizes small molecular weight inhibitors in active clinical development and does not include combinations, biologics like therapeutic antibodies, or immunomodulators.
Abbreviations: BOS, bronchiolitis obliterans syndrome; CNS, central nervous system; GI, gastrointestinal; HA, hemagglutinin; NA, neuraminidase; NAI, neuraminidase inhibitor; PIV, parainfluenza virus; RCT, randomized, controlled trial.

All of the studies in hospitalized adults suggest that early therapy is associated with reduced incidence of lower respiratory tract complications, requirement for ICU-level care, duration of illness, duration of shedding and mortality.[6,16,45,46,48]

DOSAGE IN SPECIAL CIRCUMSTANCES

The usual oseltamivir dose should be reduced to 75 mg once a day for treatment and 75 mg every other day or 30 mg of suspension daily for prophylaxis when a patient has a creatinine clearance of <30 mL/min. Doses of oseltamivir should be given after hemodialysis; detailed dosing for renal insufficiency and renal replacement therapy is available in Table 154-3. The safety and pharmacokinetics in patients with hepatic impairment have not been evaluated. Several studies in pregnancy suggest that oseltamivir is likely safe and provides clear therapeutic benefit to pregnant women infected with influenza.[49–51] There are conflicting data about optimal dosing of oseltamivir in pregnant women, with some studies suggesting need for higher doses (75 mg TID), while others suggest no dose adjustment is needed.[52–54] Current guidelines recommend treating pregnant women with influenza infection with one of the approved neuraminidase inhibitors. The recommended pediatric dosage is listed in Table 154-2.

Doubling the treatment dose of oseltamivir in hospitalized influenza patients does not appear to increase virologic efficacy, except perhaps for influenza B infections, or clinical effectiveness, although one ICU-based RCT reported that tripling the standard dose was associated with acceleration of viral RNA clearance from the respiratory tract.[55–57]

ADVERSE REACTIONS AND INTERACTIONS

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. Nausea and vomiting occur at approximately 10–15% excess frequency in oseltamivir recipients. Gastrointestinal complaints are typically mild-to-moderate in intensity, usually resolve despite continued dosing, and are ameliorated by administration with food. Clinical studies comparing 75 mg and 150 mg twice daily found similar frequencies of adverse events with the two doses. 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. Additionally, there have been reports of abnormal neurologic and behavioral symptoms which have rarely resulted in deaths among mostly children; most of these reports have come from Japan. Existing data suggest that these events are more likely secondary to influenza infections than oseltamivir therapy.[58,59] 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 steady-state pharmacokinetics of commonly used immunosuppressive agents.[60] However, probenecid blocks tubular secretion and doubles the half-life of oseltamivir. Protein binding is below 10%. Oseltamivir does not affect the immunogenicity of concomitant inactivated virus vaccine but might impair the immunogenicity of concurrent live-attenuated intranasal influenza vaccine.

Peramivir

PHARMACOKINETICS AND DISTRIBUTION

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 secrections.[61] Peramivir is predominately eliminated unchanged by renal excretion with a plasma terminal elimination half-life of 12–25 hours.[41,62] Peramivir has comparable or lower activity *in vitro* against influenza A and B viruses than oseltamivir carboxylate and zanamivir.[63]

ROUTE OF ADMINISTRATION AND DOSAGE

Peramivir is available in 150 mg and 300 mg solutions for intravenous use.

INDICATIONS

Peramivir randomized clinical trials have been conducted in previously healthy adults and children infected with uncomplicated influenza. When compared to placebo, a single 300–600 mg infusion of peramivir was associated with a significantly shorter time to alleviation of symptoms, significantly shorter time to resumption of their usual activities, and more rapid clearance of virus.[64] Another study found that a single 300–600 mg infusion of peramivir was noninferior to 5 days of oral oseltamivir 75 mg BID in a season when many of the viruses were resistant to oseltamivir as the result of the H275Y mutation; these data question the efficacy of peramivir in the management of viruses with the H275Y mutation.[65] In a study comparing 5 days of 200 mg or 400 mg QD of peramivir with oral oseltamivir 75 mg BID 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 h.

DOSAGE IN SPECIAL CIRCUMSTANCES

Since peramivir is renally cleared, dosing must be adjusted based on renal function (see Table 154-3). There are limited data to guide dosing of peramivir in children, particularly among neonates.[66] Available data and models suggest that patients receiving intermittent hemodialysis need dose adjustment (see Table 154-3).[66] Dosing of patients on continuous renal replacement therapy (CRRT) should be based on CRRT clearance.[67] There is limited dosing information for patients on extracorporeal membrane oxygenation (ECMO). Based on modeling data and predicted drug concentrations, it is recommended that children ≥181 days and ≤ 5 years receive 12 mg/kg daily (daily maximum of 600 mg/dose), infants 91–180 days receive 10 mg/kg daily, infants 31–90 days receive 8 mg/kg daily, and neonates ≤30 days receive 6 mg/kg daily. No dose adjustments are needed for hepatic impairment.

ADVERSE REACTIONS AND INTERACTIONS

Recognized adverse events associated with the administration of peramivir are diarrhea, nausea, vomiting, and neutrophil count decreased; other less common adverse events observed in studies to date include dizziness, headache, somnolence, nervousness, insomnia, feeling agitated, depression, nightmares, hyperglycemia, hyperbilirubinemia, elevated blood pressure, cystitis, ECG abnormalities, anorexia, and proteinuria.[68]

Zanamivir

PHARMACOKINETICS AND DISTRIBUTION

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 7–21% is deposited in the lower respiratory tract and the remainder in the oropharynx.[14,69] Median zanamivir concentrations are above 1000 ng/mL in induced sputum 6 hours after inhalation and remain detectable up to 24 hours later. 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 (16L).[14] Intravenous zanamivir provides high peak plasma concentrations (~35 000 ng/mL after 600 mg dose in adults).[71] 90% 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 (CL ≅ 7.08 + 0.826 · CLCR).[72]

ROUTE OF ADMINISTRATION AND DOSAGE

Zanamivir is delivered by inhalation with a proprietary breath-activated device (Diskhaler®). The usual adult treatment dose is two inhalations (10 mg) twice a day for 5 days. Intravenous zanamivir is currently in advanced clinical development and available by compassionate use.

INDICATIONS

Prophylaxis

Zanamivir is indicated as once-daily inhalations for the prevention of influenza in patients >5 years old. Once-daily inhaled zanamivir for 4 weeks was 84% efficacious in preventing laboratory-confirmed illness with fever and 31% effective in preventing influenza infections, irrespective of symptoms.[69] When used for postexposure prophylaxis, inhaled zanamivir for 10 days reduced the risk of secondary influenza illness by 79% in households.[69] In nursing homes experiencing influenza outbreaks, inhaled zanamivir was more effective for prevention of influenza A illness than oral rimantadine, in part because of frequent resistance emergence to the M2 inhibitor.[69]

Treatment

In the USA, zanamivir is indicated for the treatment of uncomplicated acute illness due to influenza A and B viruses in adults and pediatric patients 7 years and older who have been symptomatic for no more than 2 days.[9] Inhaled zanamivir in adults has consistently shown at least 1 fewer 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.[6,16] Similar therapeutic benefits have also been shown in children aged 5–12 years old.[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 appears 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 influenza patients, especially those with suspected oseltamivir-resistant variants. Most of the emergency IND (eIND) use 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.[76] Available data from patients who were treated under eIND demonstrated that among those with reported outcomes, 10.5% died despite therapy.[76] A phase 2 study in critically ill pandemic 2009 H1N1 patients found that treatment was associated with significant antiviral effects, even though therapy was initiated a median of 4.5 days after symptom onset. In patients with influenza detected on initial sample, 2 days of therapy was associated with a median 1.42 $\log_{10}$ copies/mL decline in viral load.[71] There were no drug-related trends in safety parameters identified. The 14- and 28-day all-cause mortality rates were 13% and 17%, respectively.[71] A phase 3 study comparing iv zanamivir and oral oseltamivir in hospitalized adults is currently in progress.

DOSAGE IN SPECIAL CIRCUMSTANCES

Although the plasma elimination half-life increases with creatinine clearance ≤70 mL/min, drug accumulation is negligible after inhalation and 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 (see Table 154-2).[71,72]

ADVERSE REACTIONS AND INTERACTIONS

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.[6] Anecdotal reports of hospitalization and fatality indicate that inhaled zanamivir should be used cautiously in such patients.[6]

Low bioavailability is associated with low exposure to circulating zanamivir, and no clinically significant drug interactions have been recognized. *In vitro* studies suggest that zanamivir does not inhibit or induce cytochrome P450 enzymes. The drug does not affect the immunogenicity of concomitant immunization with inactivated virus vaccines but effects on intranasal, live-attenuated vaccine have not been studied. One randomized control 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 (FDA pregnancy category C) and should be considered as an option in pregnant women with proven influenza.[78]

NEURAMINIDASE INHIBITOR RESISTANCE

Neuraminidase inhibitor resistance *in vitro* results from mutations in the viral hemagglutinin and/or neuraminidase.[79,80] In the hemagglutinin variants, mutations in or near the receptor binding site make the virus less dependent on neuraminidase action, whereas neuraminidase mutations directly affect interaction with the inhibitors. The altered neuraminidases typically show reduced activity or stability, and the mutated viruses usually have decreased infectivity in animals.[79,80] The particular neuraminidase mutation determines the degree of resistance and cross-resistance (i.e. H275Y cause high-level resistance to oseltamivir but not zanamivir; R292K results in reduced susceptibility to both oseltamivir and zanamivir).[79,80] Oseltamivir-resistant variants have been recovered from <1% of treated adults and about 4% of treated children.[22] Assessment for resistance can be assessed by sequencing of the HA or NA gene or phenotypic testing.[79,80]

Ribavirin

Ribavirin (Virazole®, Rebetol®) is a guanosine analog 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[81,82] and may inhibit virus replication by lethal mutagenesis.

PHARMACOKINETICS AND DISTRIBUTION

Oral ribavirin has a bioavailability of 33–45% in adults and children and achieves peak plasma concentration of 0.6 μg/mL 1–2 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.[83] 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 1.4–2.5 hours.

ROUTE OF ADMINISTRATION AND DOSAGE

Ribavirin comes in three formulations: oral (approved for combined use in hepatitis C), intravenous (investigational in USA) and aerosol. Ribavirin for aerosolization is available as a 6 g/100 mL solution which is diluted to a final concentration of 20 mg/mL and delivered by small particle aerosol for 12–18 hours with a proprietary device (SPAG-2 nebulizer). A higher concentration of aerosol solution (60 mg/mL) has been given over 2 hours three times daily in some studies and appears

well tolerated.[84] Ribavirin also comes in 200 mg tablets and sterile solution for injection.

INDICATIONS

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 on pulmonary functions.[85] 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 <6 weeks, as well as for those hospitalized with severe illness.[85] Aerosolized ribavirin has shown minimal efficacy in treating influenza in hospitalized children.[86]

Ribavirin has also been studied for the treatment of RSV and parainfluenza virus infections in immunocompromised patients. Intravenous ribavirin appears 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.[87] 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.[88] Observational studies suggest that combination therapy with antibodies (either intravenous immunoglobulin, RespiGam or palivizumab) appears more effective, particularly when started before severe respiratory distress.[88] Oral ribavirin has been tried in the management of RSV with variable success.[89] In the management of parainfluenza virus in bone marrow transplant recipients, two case series found that aerosolized ribavirin failed to improve 30-day mortality or reduce the duration of viral replication relative to no treatment.[90]

DOSAGE IN SPECIAL CIRCUMSTANCES

Systemic ribavirin is contraindicated in patients with creatinine clearance <50 mL/min and the dose should be reduced by one-third for patients under 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 drops below 8.5 g/dL. There is a fixed combination of oseltamivir, amantadine and ribavirin that is active *in vitro* against susceptible and resistant strains and shows promise in clinical management of influenza infections.[91,92]

ADVERSE REACTIONS AND INTERACTIONS

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).

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