Antiviral Treatments

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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

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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