Journal of Antimicrobial Chemotherapy (1999) **44**, 6–10

JAC

Leading article

Chemotherapeutic control of influenza

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Influenza is an important epidemic and pandemic viral illness with over 26,000 deaths attributed to the last major outbreak in England and Wales in 1989–90.[1] It produces an acute febrile respiratory illness with cough, headache and myalgia for 3–4 days with symptoms that may persist for up to 2 weeks.[2] The majority of deaths, usually in patients of 65 years or older, are caused by pneumonia or the exacerbation of pre-existing cardiopulmonary conditions. Primary viral and secondary bacterial pneumonia with *Staphylococcus aureus*, *Haemophilus influenzae* or *Streptococcus pneumoniae* may occur.[2,3] Diagnosis is made on clinical grounds with laboratory confirmation by serology, direct immunofluorescence or viral isolation and culture. Antigen detection by ELISA and gene amplification provide a more rapid diagnostic approach, but are mostly used as research tools.[4]

Surveillance has shown that influenza A or B (or both) circulate annually, producing outbreaks of varying severity, resulting in lost school- and work-hours and severe, occasionally fatal complications in high-risk groups. These include those of all ages, but especially the elderly, who have: chronic respiratory disease, including asthma; chronic heart disease; chronic renal failure; diabetes mellitus; immunosuppression due to disease or treatment; and those living in residential care homes and long-stay facilities where rapid spread of influenza is likely to follow the introduction of infection.

Control aims are to prevent infection by vaccination and/or chemoprophylaxis. Inactivated vaccines represent the primary means of preventing influenza and its complications. They provide considerable benefits in reducing the complications of influenza, including hospitalizations for pneumonia and influenza, all respiratory conditions and congestive cardiac failure, and in reducing deaths from all causes. However, vaccine coverage is poor in many countries and a substantial proportion of people in high-risk groups remain unprotected during outbreaks. Drug therapy is also available: amantadine and rimantadine may be used for chemoprophylaxis and acute treatment during infection outbreaks and two neuraminidase inhibitors are being evaluated in Phase III clinical studies.

Amantadine, the only anti-influenza agent that is licensed in the UK, and its analogue, rimantadine, are tricyclic structures that inhibit viral uncoating through their effects on the M_2 ion channel. This is a tetrametric membrane channel that is important in the regulation of the internal pH of the virus. By promoting acidification of the virion interior, the M_2 channel plays a pivotal role in uncoating of viral ribonucleoprotein—an important step in viral replication. Both amantadine and rimantadine are active against influenza A but clinically toxic doses are required if these are to be of benefit against influenza B and other respiratory pathogens, limiting their use to the prevention and treatment of influenza A.[6,7] Amantadine, which is renally excreted, is well absorbed with good penetration into nasal and salivary secretions. It is associated with a number of minor reversible CNS disturbances, including insomnia and reduced concentration, which are especially prominent in the elderly, and lowered seizure threshold in epileptic patients.[8,9] It is embryotoxic and teratogenic in rats at 50 mg/kg daily (about 15 times the usual human dose), and use in pregnant women should be restricted to life-threatening influenza pneumonia. It is contraindicated in patients who are subject to convulsions and those with severe renal impairment and must be used with caution in patients with renal insufficiency, liver disease and congestive cardiac failure—i.e. many of those with high-risk conditions. Rimantadine has a larger volume of distribution than amantadine with nasal mucus concentrations reaching 50% higher than plasma concentrations and is better tolerated with fewer side effects reported.[10–12] Before amantadine is prescribed, epidemiological and virological evidence of a current influenza outbreak should exist. Prophylaxis of individuals with amantadine and

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rimantadine taken daily reduces influenza illness rates by 50–90%.[7,11–16] There may be an additional protection when either drug is given in combination with influenza vaccine and used for the 4–8 week duration of the outbreak. Chemoprophylaxis should be considered when there is: allergy to vaccine; an inadequate supply of vaccine; substantial antigenic difference between epidemic and vaccine strains; a poor patient immune response; and for 2 weeks after vaccination until antibody levels are protective. The WHO recommends amantadine prophylaxis to augment vaccination protection for elderly patients and those at high risk in institutions.[17] Implementing a programme of prophylaxis requires the identification of high-risk patients, having adequate supplies of drug available, and distributing drug when an outbreak occurs. Alternatively, the drug could be dispensed beforehand and patients informed when to commence their therapy.[18]

Post-exposure prophylaxis of household contacts with rimantadine and amantadine prevents influenza illness by 70–75%, but if the index case is treated simultaneously, both drugs are ineffective. Failure of prophylaxis is apparently due to the emergence of drug-resistant virus in the treated index case. Nucleic acid sequencing of amantadine-resistant strains has identified the genetic basis of resistance to be a single nucleotide change in the gene encoding M_2, resulting in an amino acid substitution at position 26, 27, 30, 31 or 34 in the transmembrane portion of the M_2 ion channel. Uncontrolled studies suggest that the administration of amantadine or rimantadine to elderly residents of nursing homes during outbreaks interrupts transmission of influenza A. However, this approach involves the simultaneous treatment of both cases and contacts and has led to the emergence and possible transmission of drug-resistant virus among residents.[18–20] The attempted control of influenza outbreaks using amantadine or rimantadine is practised widely in the USA, but its timely implementation is logistically difficult and of questionable value. When practised, cases should be treated in isolation to reduce the possible spread of drug-resistant virus.

Both amantadine and rimantadine are effective for the treatment of acute influenza A if commenced early after the onset of illness (<24 h), when duration of fever and symptoms are reduced by 1–2 days. Successfully treated patients can resume normal activities and return to work or school earlier.[7,12,21]

The neuraminidase enzyme of influenza is involved in the spread of virus through the respiratory tract and helps promote the release of viral progeny from infected cells. This enzyme represents a potential target for antiviral therapy as its inhibition prevents the release of newly formed virions. Nonselective inhibitors have been developed but were of no practical value due to inhibition of mammalian neuraminidase. Recently, two selective neuraminidase inhibitors have been developed as a direct result of the determination by X-ray crystallography of the structure of the viral neuraminidase and its interaction with the substrate sialic acid at the virus–cell receptor site.[22,23] The viral neuraminidase cleaves progeny virions from the cell surface, thereby permitting cell-to-cell spread.

Zanamivir is a potent inhibitor of neuraminidase of both influenza A and B,[24] which may cause up to 35% of influenza infections. It has low oral bioavailability and most clinical studies have consequently used topical routes of administration—either intranasal or aerosolized inhalation. Intranasal administration appears to interrupt established infection by preventing viral release and reducing viral penetration of mucus secretions. Initial studies showed intranasal zanamivir to be well tolerated and provide protective efficacy of 87% against experimentally induced influenza.[25] A prophylaxis trial for 4 weeks of the influenza season concluded that orally inhaled zanamivir reduced the number of laboratory confirmed cases by 67% and the number of cases of influenza with fever by 84%.[26] Promising results have been found in treatment studies. Australian double-blind, placebo-controlled trials of patients recruited within 36 h of the onset of symptoms and using inhaled zanamivir found a 25–30% reduction in the median duration of symptoms, and a 70% reduction in complications affecting high-risk patients.[27,28] A multicentre study of aerosolized, with or without intranasal, delivery of zanamivir in 417 patients found a reduction of 1 day in the median length of time to the alleviation of major symptoms ($P \leqslant 0.05$) in those with confirmed influenza.[24] For the subgroups of patients who were febrile at entry or those who started on therapy within 30 h of the onset of symptoms the median time to alleviation of symptoms was reduced by 3 days ($P \leqslant 0.01$). Intravenous zanamivir has been shown to have protective properties in experimentally induced human influenza and to significantly reduce the proinflammatory cytokine and chemokine response associated with influenza infection.[29,30] It has been well tolerated with minimal adverse effects in the studies. Trials in adults have successfully used intranasal sprays and aerosolized inhalation, ensuring delivery of zanamivir to the site of viral replication on the surface of the respiratory tract, but this route may pose practical problems in the elderly or very young.

GS4104 is the orally active prodrug of GS4071, a potent and selective inhibitor of the neuraminidase of influenza A and B viruses. It has good oral bioavailability and for some patient groups may be easier to take than zanamivir given by topical routes. Initial volunteer studies have shown it to be as effective as zanamivir. Two double-blind placebo-controlled trials have shown that treatment with GS4104 within 36 h of onset of influenza symptoms reduced duration of illness by 30%.[31,32] There were also significant reductions in the number of secondary complications such as bronchitis and sinusitis, the duration of fever and the use of paracetamol. Duration of illness was reduced by 40% ($P = 0.015$) in one of the studies if therapy was initiated within 24 h of the onset of symptoms.[31] A seasonal prophylaxis study showed that oral GS4104 reduced the number of

laboratory-confirmed influenza illnesses (with fever and other symptoms) over a 6 week period of local influenza activity with an overall protective efficacy in treatment arms of 74%. Once- or twice-daily dosing produced similar results.[33] GS4104 may produce transient gastrointestinal effects but is generally well tolerated.

Influenza viruses with reduced sensitivity to neuraminidase inhibitors have been isolated following tissue culture passage of virus in the presence of the drug. Two mechanisms of resistance have been identified, one involving mutations in the neuraminidase and the other involving multiple mutations clustered around the binding site of the viral haemagglutinin with its sialic acid receptors. The majority of resistant viruses are haemagglutinin mutants. To date, there has been only one report of resistant virus emerging as a result of clinical use: an influenza B virus recovered from a bone marrow transplant recipient had developed mutations affecting both the viral haemagglutinin and neuraminidase during 14 days of treatment.[34]

Treatment of influenza with antivirals poses several practical difficulties. Therapy should preferably commence within 30 h after the onset of symptoms and studies with zanamivir show that this benefit is limited to those with a temperature of $>37.8°C$.[24] Many patients self-treat with paracetamol or other over-the-counter remedies and do not present within this time, partly as appointments with their general practitioner (GP) may not be available and partly because of the general view that there is no cure for influenza or the common cold. To educate patients otherwise might overwhelm GPs during the winter. Drug therapy is ineffective in infections with other respiratory viral pathogens.[6,24] Although there are no simple rapid diagnostic tests for influenza A and B that can be performed at the bedside, household or surgery, such tests are being developed and would have to be included in the cost implications of treatment. A rapid test may not be needed in all cases: during localized influenza outbreaks, about 50–70% of patients presenting with 'influenzal' symptoms have viral-confirmed influenza infection, although this proportion falls outside the peak time of the outbreak.

Amantadine has been available for several decades but is not widely used. It remains to be seen whether the neuraminidase inhibitors fulfil their promise and are sufficiently better to change clinical practice.

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