

New drug classes

Influenza virus neuraminidase inhibitors

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Neuraminidase promotes influenza virus release from infected cells and facilitates virus spread within the respiratory tract. Several potent and specific inhibitors of this enzyme have been developed, and two (zanamivir and oseltamivir) have been approved for human use. Unlike amantadine and rimantadine that target the M2 protein of influenza A viruses, these drugs inhibit replication of both influenza A and B viruses. Zanamivir is delivered by inhalation because of its low oral bioavailability whereas oseltamivir is administered by mouth. Early treatment with either drug reduces the severity and duration of influenza symptoms and associated complications. Both agents are effective for chemoprophylaxis. Because of a broader antiviral spectrum, better tolerance, and less potential for emergence of resistance than is seen with the M2 inhibitors, the neuraminidase inhibitors represent an important advance in the treatment of influenza.

Following the discovery by G K Hirst in 1942 of an enzyme activity on the influenza virus surface that removed virus receptors from erythrocytes, F M Burnet and colleagues studied this receptor-destroying mechanism extensively and predicted that an inhibitor for the enzyme might be an effective antiviral agent. Then A Gottschalk characterised the chemical structure of neuraminic acid (Neu5Ac), its linkage to glycoconjugates, and the specificity of the enzyme for terminal neuraminic acid residues. The first inhibitors of influenza virus neuraminidase (NA), developed by P Meindl and H Tuppy in 1969, inhibited viral replication but had low potency and specificity. In the 1980s P M Colman and his colleagues reported the crystal structure of influenza virus NA and of its complex with neuraminic acid. Those findings, together with an improved understanding of the mechanism of catalysis, set the stage* for the synthesis of neuraminic acid derivatives with enhanced affinity for influenza NA. In 1993 von Itzstein and co-workers demonstrated that 4-guanidino-Neu5Ac2en (GG167, zanamivir) was a potent and highly specific inhibitor of influenza NA activity that inhibited virus replication *in vitro* and *in vivo*.¹ Thus, a “competitive poison”, for the virus enzyme which had been speculated on back in 1948 by Burnet’s group, was identified. Inhaled zanamivir entered clinical trials in 1994 and is now licensed in Australia, Europe, and North America. The first orally active inhibitor, oseltamivir, was described by Kim and colleagues in 1997.² It has been approved in Switzerland, Canada, and the USA. A second oral agent (RWJ-270201, BCX-1812) entered clinical trials in 1999.

We provide here an overview of influenza virus NA, the antiviral and pharmacological properties of the two licensed inhibitors, and their clinical effectiveness. To

provide up-to-date information we have incorporated data presented only as abstracts so far, and some statements may need modification when the studies are published in peer-reviewed journals. For more details of the mechanisms of action of these drugs, readers are referred to three recent reviews,³⁻⁵ and further references on the data reviewed here can be found on *The Lancet*’s website.*

Influenza virus neuraminidase

The two surface influenza virus glycoproteins, haemagglutinin (HA) and NA (figure 1), interact with receptors which contain terminal neuraminic acid residues. HA attaches to cellular receptors to initiate virus penetration and promotes fusion of viral and

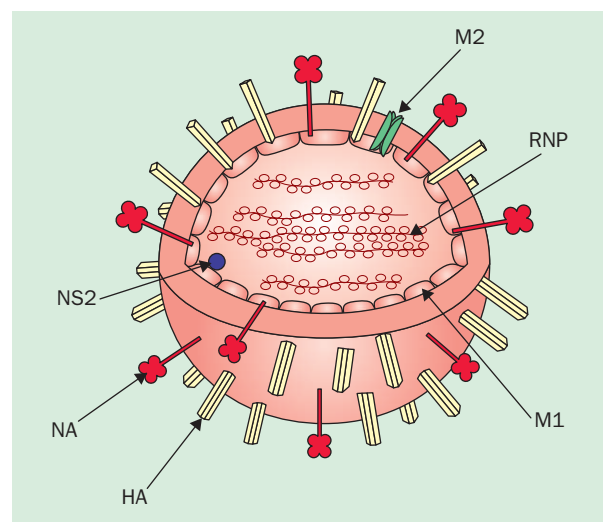


Figure 1: Schematic representation of influenza A virion
Eight ribonucleoprotein segments (RNP) are surrounded by layer of matrix (M1) protein and lipid bilayer taken from host cell at budding. NS2 (NEP) protein is associated with M1. Three viral proteins are incorporated into the lipid bilayer: HA, NA, and M2 protein. HA trimers and NA tetramers form spikes on the surface of the virion. RNP segments contain viral RNA surrounded by nucleoprotein and associated with the polymerase complex.

*References available on *The Lancet* website at www.thelancet.co.uk

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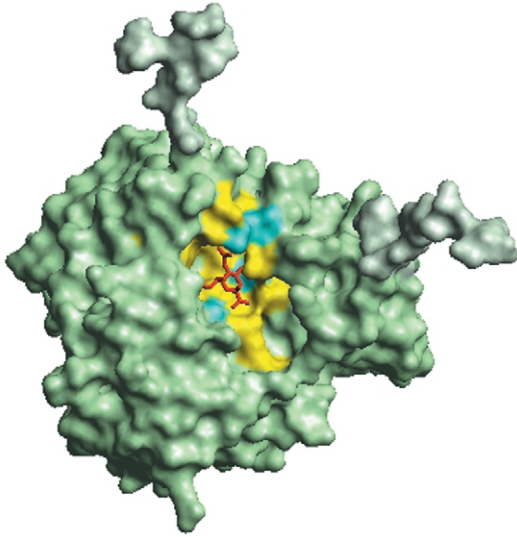


Figure 2: **Complex structure of influenza virus NA A/Tokyo/3/67 (H3N2) (surface representation) and neuraminic acid (stick representation)**

Source: Brookhaven Protein Data Bank. Aminoacid residues in yellow and blue are invariant across all known strains of types A and B influenza viruses.⁷ Stick representation of neuraminic acid is in purple. (Kindly provided by Mikhail Matrosovich, St Jude Children's Research Hospital, USA.)

cellular membranes. NA is a tetramer composed of a cytoplasmic tail, a transmembrane domain, a stalk region, and a globular head. The active site lies in a large depression on the surface of the head (figure 2),⁶ and the residues forming it are highly conserved among all A and B influenza viruses.⁷ Some of them directly contact bound substrate, neuraminic acid, whereas others provide a structural framework for the functional residues.

NA destroys receptors recognised by HA by cleaving the α -ketosidic bond linking a terminal neuraminic acid

residue to the adjacent oligosaccharide moiety. This cleavage facilitates movement of the virus to and from sites of infection in the respiratory tract. Respiratory mucins contain neuraminic acid residues, so the receptor destruction is important for virus penetration through secretions. Progeny virions bud out from the cell surface. Cleavage of HA receptors on the cell membrane is a prerequisite for virus release. Another obstacle on the way of virion liberation is the presence of the neuraminic acid residues on oligosaccharide chains of the newly synthesised HA and NA. The HAs of the neighbouring virions recognise and bind to these neuraminic acid residues and cause self-aggregation of progeny virions. Virion liberation therefore requires the receptor-destroying activity in the NA on both viral surface glycoproteins and cellular membrane. In the presence of the NA inhibitors virions stay attached to the membrane of infected cell and to each other and virus spread is inhibited (figure 3; see also figure 5).

This picture of the role of the NA in influenza virus pathogenicity is not complete—for instance, NA promotes production of proinflammatory cytokines and, for at least one strain, fosters HA cleavage and generalised infection by binding plasminogen.*

Neuraminidase inhibitors

Because of the essential role of NA in influenza virus replication and its highly conserved active site, interest focused on the development of selective inhibitors. Neu5Ac2en, a dehydrated neuraminic acid derivative, mimics the geometry of the transition state during the enzymatic reaction. To increase interaction between Neu5Ac2en and the aminoacid residues forming the enzyme active site, a guanidiny group was substituted for a hydroxyl on carbon atom 4 (panel 1, figure 4). This is zanamivir. Another approach, using a cyclohexene ring and replacement of a polar glycerol with lipophilic side-

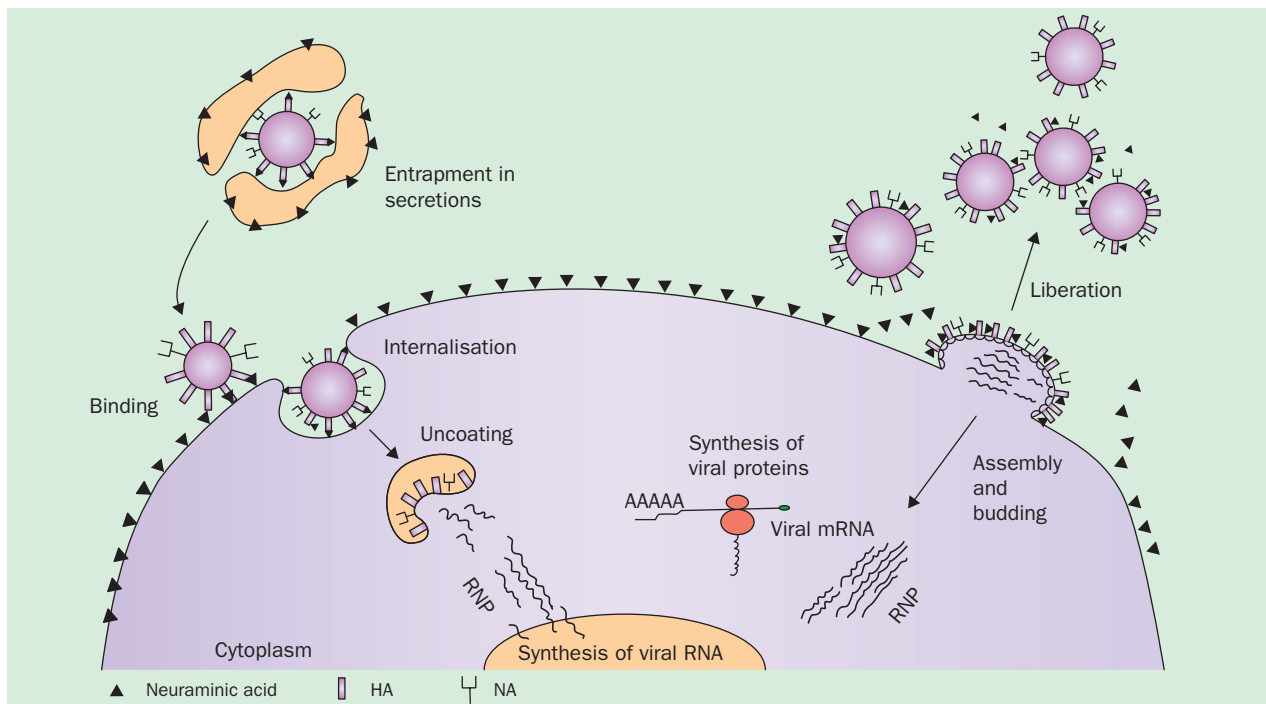


Figure 3: **Influenza virus replication cycle**

Virus attachment through HA to receptors containing terminal neuraminic acid residues and penetration into host cell; transcription of viral RNA and translation of viral proteins; replication of viral RNA and assembly of virion, budding, and subsequent release from host cell.

Panel 1: Influenza neuraminidase inhibitors used in clinical trials			
Name (proprietary name)	Manufacturer	Route	Status
DANA (Neu5Ac2en)	· ·	NA	NA
Zanamivir (GG167, Relenza)	Biota/Glaxo	Inhalation	FDA approved
Oseltamivir (GS4104, Tamiflu)*	Gilead/Hoffmann-La Roche	Oral	FDA approved
RWJ-270201 (BCX-1812)	BioCryst/Johnson & Johnson	Oral	Phase II trials

*Prodrug; active agent is oseltamivir carboxylate (GS4071).
NA=not applicable.

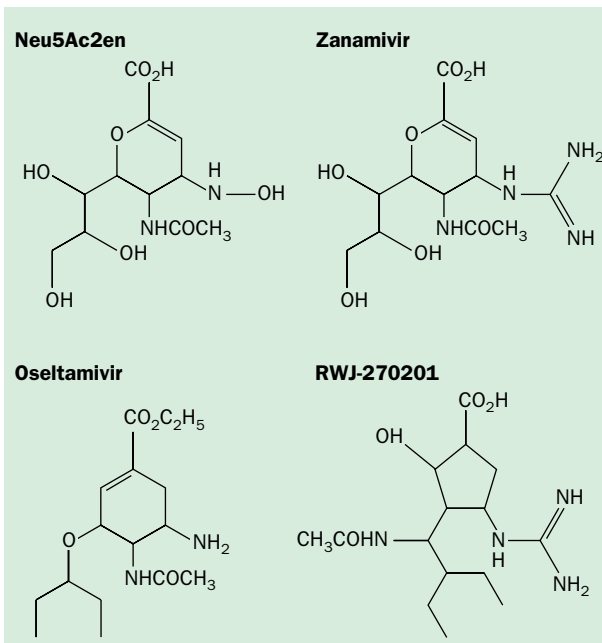


Figure 4: Chemical structures of neuraminidase inhibitors

chains, led to oseltamivir. The bioavailable prodrug oseltamivir is an ethyl ester that is converted into the active carboxylate by hepatic esterases.⁹ RWJ-270201 is a cyclopentane derivative with a guanidinyloxy group and lipophilic chains. These three molecules interact differently within the enzyme active site; the differences may influence antiviral activity and the emergence of resistance but all three are potent and selective influenza NA inhibitors.

These reversible competitive inhibitors of influenza A and B virus NA (panel 2) are active across a wide range of strains,* including clinical isolates and all nine

Inhibitor	Inhibition (IC ₅₀ , nmol/L)		
	A/N1	A/N2	B
Zanamivir	0.5–2.5	0.9–5.6	1.0–7.9
Oseltamivir	0.3–1.0	0.2–0.8	1.7–18.3
RWJ-270201 ^{68,69}	0.2–1.4	0.5–0.9	0.6–11.0

IC₅₀=concentration that reduces enzyme activity by 50%. Range of values based on combined data; observed inhibitory activity depends on assay method and strain.

influenza A NA subtypes in the avian reservoir. Although these agents tend to be less active against influenza B than influenza A enzymes, the clinical importance of this is uncertain. Inhibition of non-influenza-virus sialidases requires concentrations at least a million times higher, and cellular cytotoxicity has not been recognised. Activity against clinical isolates in cell culture varies 1000-fold or more (eg, 2 nmol/L to 16 μmol/L for zanamivir). All three drugs are active against amantadine and rimantadine resistant influenza A viruses but they do not inhibit other respiratory viruses.

These agents show dose-dependent activity in animal models of influenza. The highly polar, zwitterionic nature of zanamivir results in low oral bioavailability. In mice intranasal zanamivir significantly reduced viral titres in lung homogenates whereas intraperitoneal or oral dosing did not. Both zanamivir and oseltamivir protected against the highly virulent H5N1 strain that caused an outbreak of influenza in Hong Kong in 1997.^{10,11} Oral oseltamivir and RWJ-270201 both significantly decreased influenza A mortality in mice, but RWJ-270201 was more effective against influenza B. However, the clinical relevance of relative activities in animal influenza models is uncertain.

Resistance

Amantadine and rimantadine target the influenza A virus M2 protein,¹² a membrane protein that is essential to virus replication. Rapid emergence of resistance¹³ has been associated with aminoacid substitutions in the transmembrane portion of M2. Influenza viruses cross-resistant to amantadine and rimantadine have been recovered 2–3 days after the start of treatment and rarely (<1% of isolates) among naturally circulating influenza A viruses. A similar concern applies to NA inhibitors. De novo resistance has not been recognised but sequential passage of influenza virus in cell culture in the presence of zanamivir or oseltamivir carboxylate does lead to resistance and resistant variants have now been identified clinically. Two mechanisms of resistance have been recognised.

Panel 3: Influenza virus mutants resistant to NA inhibitors						
Mutation*	Reduction (fold) in NA sensitivity	Reduction (fold) in infectivity for animals	Drug	Source of mutant virus	Virus type and subtype	Ref
119 Glu. Gly	>100	≤4	Zanamivir	In vitro selection	A/H1N9,	14, 17, 21, 24
119 Glu. Ala	>100				A/H4N2,	(and web)
119 Glu. Asp	>1000				B	
119 Glu. Val†	~20	>100 to >1000	Oseltamivir carboxylate	Treated human	A/H3N2	28
292 Arg. Lys	~10 000	>100 to >1000	Oseltamivir carboxylate	In vitro selection	A/H3N2	16, 23, 28
				Treated humans		
292 Arg. Lys	~10–30	~400	Zanamivir	In vitro selection	A/H4N2	19, 21
152 Arg. Lys	>1000	~60	Zanamivir	Treated human	B	27

*N2 numbering of aminoacid residues in NA; substitutions in HA with potential to affect virus susceptibility to NA inhibitors identified in some viruses.³¹⁸ †Reverted to wild type upon replication in ferrets.

Panel 4: Pharmacological properties of zanamivir and oseltamivir

Property	Zanamivir	Oseltamivir
Oral absorption (%)	Very low (<5)	High (~80)
Formulation(s)	Dry powder inhalation	Oral capsule, liquid*
Distribution (%)	Pharynx (~80) >tracheobronchial/lungs (~15)†	Upper and lower respiratory tracts‡
Bioavailability (total) (%)	12–17†	~80‡
T _{max} (h)	0.75–1.5†	2.5–5‡
Peak plasma conc (C _{max}) (ng/mL)	30–50†	~350‡
Volume of distribution (L)	16†	23–26‡
Plasma T _{1/2} elimination (h)	2.5–5†	7–9‡
Metabolism	None	Deesterification
Elimination	Renal	Renal‡
Dose adjustment for renal/hepatic insufficiency	None/none	Yes§/not studied

*Investigational. †After inhalation of dry powder zanamivir 10 mg in lactose vehicle. Investigational formulations include nebulised mist, nasal spray, intravenous. ‡For active metabolite, oseltamivir carboxylate (GS4071), after oral oseltamivir 75 mg. §Reduced from twice to once daily if creatinine clearance <30 mL/min; a single dose appears adequate for haemodialysis patients.

NA-independent resistance*

Reduction of virus susceptibility to the NA inhibitors was observed on early passages of different viruses in the presence of several NA inhibitors. Mutations in or close to the HA receptor-binding site reduced efficiency of virus budding to cellular receptors. This causes decreased dependence on NA function, such that resistant viruses demonstrate broad cross-resistance to NA inhibitors in cell culture. The existence of mechanisms besides substitutions in the HA receptor binding site which could lead to reduced virus dependence on NA function should be investigated. In addition, in vitro-selected mutants may demonstrate drug-dependence in cell culture, although it remains unknown if drug-dependent variants might occur in vivo.

NA-dependent resistance

Resistance also results from aminoacid substitutions at the conserved residues in the NA enzyme active site (panel 3; figure 2).^{14–17} Differences in the degree of cross-resistance result from differences in the geometry of drug interactions with aminoacid residues of NA.¹⁸ For example, an aminoacid substitution at position 292 leads to moderate zanamivir resistance and high level oseltamivir carboxylate resistance,^{16,19} whereas both oseltamivir carboxylate and RWJ-270201 retain activity against the zanamivir-resistant Glu119Gly variant. NA mutations compromise enzyme function and result in reduced enzyme stability,^{20,21} instability of the NA tetramer,²² or a change in the pH optimum.²¹ Resistant variants with NA mutations (panel 3) replicate efficiently in cell culture^{14,21,23} but most show reduced infectivity and virulence in animal models.^{16,21,23,24} Because replication of influenza virus in the respiratory tract imposes higher requirements on HA and NA functions, changes in these surface glycoproteins are likely to decrease influenza virus virulence and transmissibility in vivo, unlike the experience with M2 inhibitors.¹³

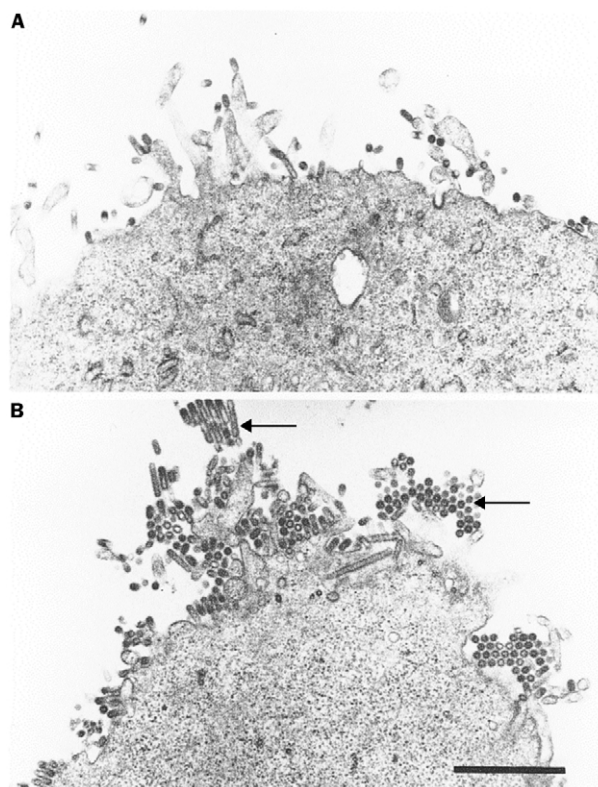


Figure 5: Electron micrographs of MDCK cells infected with influenza A virus

(A) Normal assembly and budding of virus in absence of NA inhibitor. (B) Lateral aggregation and formation of large bundles by virus in presence of NA inhibitor. Bar=1 μm. (Kindly provided by K Gopal Murti, St Jude Children's Research Hospital, Memphis, USA.)

Resistance in man

In the absence of a reliable cell-culture method for resistance surveillance, screening is based on NA inhibition phenotype and NA and HA sequence analyses. During clinical trials of zanamivir, no loss of NA susceptibility and no changes in the receptor-binding site of the HA were observed.^{25,26} Immunosuppression provides a higher risk environment for the development of drug resistance. A 2-week long treatment of a bone-marrow transplant recipient with influenza B infection led to the emergence of a zanamivir-resistant virus (panel 3).²⁷ Oseltamivir-resistant variants have been recovered in only 1% or so of isolates from immunocompetent adult patients in the active site of the NA that are associated with greatly impaired replication in animals (panel 3). No drug-induced HA variants have been recognised to date. Clinical resistance requires further study, especially in children and immunocompromised hosts, but data available so far suggest that resistance is infrequent and unlikely to limit the clinical usefulness of these drugs in most settings.

Pharmacokinetics

Both drugs have long durations of antiviral activity so dosing can be only twice daily for treatment and once daily for prophylaxis.

Zanamivir

In most studies zanamivir has been administered topically as nasal sprays or drops, a nebulised mist, or

the currently approved dry-powder aerosol. The powder is mixed with lactose (5 mg zanamivir per 20 mg lactose). The lactose particles are large (>40 µm) and deposit in the oropharynx in uninfected healthy adults; 13–15% of inhaled zanamivir is deposited in the tracheobronchial tree and lungs and 78% in the oropharynx^{29,30} but deposition studies have not been reported in patients with influenza or underlying chronic airway diseases. Inhaled zanamivir is projected to provide local respiratory mucosal concentrations well above those inhibitory for influenza A and B virus neuraminidases.^{29,30} Median zanamivir concentrations are above 1000 ng/mL in sputum 6 h post-inhalation and remain detectable at 24 h.³¹ After intranasal dosing, zanamivir remains detectable in nasal washings for 2–7 days.²⁹ Plasma concentrations are low and overall systemic exposure, based on urinary recovery, is estimated to be 15% of dose (panel 4). The volume of distribution approximates that of extracellular water. The plasma elimination half-life after inhalation averages about 3–5 h.³² Intravenous zanamivir is rapidly cleared by the kidney without significant metabolism (plasma $T_{1/2}$ elimination about 1.8 h).

Oseltamivir

The oseltamivir ethyl ester is well absorbed and rapidly metabolised to active oseltamivir carboxylate. The bioavailability of the oseltamivir carboxylate is about 80% after oral administration of the prodrug, and systemic exposure to oseltamivir is only 3–5% of that of oseltamivir carboxylate; plasma concentrations peak at about 1 h and decline rapidly with a half-life of 1–3 h.^{33,34} Oseltamivir carboxylate concentrations peak at 3–4 h and the half-life is 6–10 h. Systemic exposure to oseltamivir carboxylate at steady state is about 25% higher in elderly people, but tolerance is good and dose adjustments are not necessary.³⁴ Animal studies indicate excellent distribution throughout the respiratory tract,³⁵ but comparable human studies have not been reported. Administration of oseltamivir with food does not significantly affect peak plasma levels or bioavailability but does seem to diminish the risk of gastrointestinal upset. Oseltamivir carboxylate is eliminated through the kidney by filtration and tubular secretion without metabolism. Probenicid coadministration doubles the half-life, which indicates secretion by the anionic pathway. Dose adjustments are indicated for advanced renal insufficiency (panel 4).

Drug interactions

Neither drug has recognised drug interactions of clinical relevance. In vitro neither zanamivir nor oseltamivir (or its carboxylate) inhibit or induce cytochrome P450 isoenzymes.^{36,37} Zanamivir does not affect expression of liver microsomal isoenzymes in animals. Plasma protein binding is below 10% for both compounds. No formal interaction studies have been conducted with antiretroviral agents.

An NA inhibitor would not be expected to affect the antibody response to injected, inactivated influenza vaccine and this has been confirmed with zanamivir.³⁸ These agents could therefore be used for immediate protection in conjunction with late-season immunisation. However, oral oseltamivir and, possibly, inhaled zanamivir might reduce the replication and immunogenicity of intranasal, live-attenuated vaccine.

Safety and tolerability

Preclinical toxicology showed that zanamivir and oseltamivir have low acute toxicity, and no specific end-organ toxicity was recognised at doses relevant to human exposure. Long-term carcinogenicity studies are negative with zanamivir and in progress with oseltamivir, but neither agent shows genotoxic or mutagenic effects. Most participants in clinical studies have been healthy adults or people with stable underlying medical conditions of mild-moderate severity so pharmacovigilance will be important as the drugs become more widely used.

Zanamivir

Intravenous zanamivir (600 mg twice daily for 5 days) or inhaled zanamivir (up to 96 mg daily) have been generally well tolerated.³² When used for treatment or prophylaxis, the frequency and types of adverse events are no different in zanamivir and placebo (lactose) recipients.³⁶ No untreated controls have been included in these studies, but the lactose excipient has been used in asthma medications. This lactose dose (80 mg per dose) is insufficient to cause symptoms in lactase-deficient individuals. In treatment studies the most-reported adverse effects appear to relate to the underlying influenza (nasal symptoms, diarrhoea, nausea, headache, cough, throat discomfort, dizziness, nosebleeds), and none has occurred at a frequency of more than 3%.

No acute bronchospasm or respiratory tract irritation was found with inhaled zanamivir in previously healthy people during clinical trials, but rare reports of transient wheezing have been reported post-marketing. One of 13 uninfected asthmatic patients experienced transiently decreased spirometric values after inhaled zanamivir, but no overall changes in methacholine-induced airway reactivity were found during 14 days of zanamivir exposure.³⁹ From a treatment study of patients with asthmatic or chronic obstructive pulmonary disease (COPD) plus influenza, preliminary results indicate that both increases and decreases by more than 20% in FEV₁ occurred in higher proportions of zanamivir recipients (35% and 15%, respectively) than placebo recipients (25% and 6%, respectively) at day 6 (data on file, GlaxoWellcome). Only one of 78 zanamivir-treated patients stopped therapy for a non-respiratory complaint, and no differences in clinical asthma exacerbations were noted during treatment (14% for both placebo and zanamivir). In general, inhaled zanamivir appears to be tolerated in mild-to-moderate asthma but its tolerability remains to be established in those with serious bronchopulmonary disease and those requiring ventilatory support. According to the US FDA, some patients with underlying asthma or COPD have experienced serious deteriorations in respiratory function following zanamivir inhalation.⁴⁰ Although influenza itself causes such deteriorations, zanamivir treatment in patients with underlying airway disease requires careful monitoring and the availability of fast-acting bronchodilators. Patients who develop bronchospasm or a decline in lung function should stop the drug.

Oseltamivir

Oseltamivir has been generally well tolerated and not associated with clinical laboratory abnormalities to date.

Panel 5: Neuraminidase inhibitors in treatment of influenza acquired in community; trials in adults							
Ref	Season	Treatment	Patients (% with proven influenza)	Age range (mean)	Duration of illness	Reduction in days to alleviation of symptoms in patients with influenza (median)	Comments
41	1994–95	Inhaled zanamivir, 10 mg bid for 5 days	417 (63%)	≥13 yr (32 yr)	≤48 h	1 (5 vs 4) 3 (7 vs 4 in febrile)	3 days reduction in patients treated ≤30 h
51	1997	Inhaled zanamivir 10 mg bid for 5 days	455 (71%)	≥12 yr (37 yr)	≤36 h	1·5 (6·5 vs 5·0) 2·0 (6·5 vs 4·5 in febrile)	Reduced complications and antibiotics (15% vs 38%) in patients with underlying conditions
53	1997–98	Inhaled zanamivir 10 mg bid for 5 days	777 (73%)	≥12 yr	≤48 h	1 (6 vs 5)	Reduced complications
52	1997–98	Inhaled zanamivir 10 mg bid for 5 days	356 (78%)	≥12 yr	≤48 h	2·5 (7·5 vs 5·0)	Reduced complications and antibiotics (11% vs 5%). No differences between doses
56	1997–98	Oseltamivir 75 mg or 150 mg bid for 5 days	629 (60%)	18–65 yr	≤36 h	1·4 (4·3 vs 2·9 vs 2·9)	Reduced complications
57	1997–98	Oseltamivir 75 mg or 150 mg bid for 5 days	719 (66%)	18–65 yr	≤36 h	1·2–1·5 days (4·9 vs 3·6 vs 3·4)	No difference between doses

Doses up to 500 mg twice daily for 7 days have been tested in uninfected adults.³³ The most frequent adverse effect is nausea of mild-to-moderate intensity; vomiting is less common. These symptoms usually are transient, occurring most often after first dose, and resolve in 1–2 days despite continued drug administration in most people. In adults with influenza illness, the frequencies of nausea alone and of emesis are both 8–10% greater than the frequencies seen with placebo. Gastrointestinal adverse effects are no greater problem in treating elderly and high-risk patients, and much lower when the drug is used for prophylaxis.⁴¹ The gastrointestinal upset is probably due to local irritation; drug ingestion with food appears to reduce the risk.⁴² Although a slight increase in headache frequency was observed in one prophylaxis study in older people, oseltamivir appears to avoid the CNS intolerance associated with M2 inhibitors.

Clinical efficacy

Experimental influenza

Zanamivir and oseltamivir are effective for prevention and early treatment of experimental influenza A in volunteers^{42,43} and both have significant antiviral effects in experimental influenza B.^{44,45} RWJ-270201 (BCX-1812), shows significant dose-related antiviral activity after oral administration in experimental influenza A (F Hayden, unpublished). Intravenously administered zanamivir is distributed into respiratory secretions and is also highly protective against experimental influenza A⁴⁶ and the associated elaboration of nasal cytokines and chemokines.⁴⁷ Early treatment with zanamivir or oseltamivir significantly reduces the otological manifestations, including middle-ear pressure abnormalities, of experimental influenza.^{42,48} Early treatment with oseltamivir also reduces proinflammatory cytokine concentrations in the upper respiratory tract.⁴²

Natural influenza

Treatment studies are summarised in panel 5. An early trial found that twice-daily inhaled zanamivir reduced

the time to alleviation of influenza illness by 1 day (20%) and by 3 days (40%) in those with febrile illness or those treated within 30 h of symptom onset.⁴⁹ Addition of intranasal zanamivir appears to reduce nasal symptoms but not affect overall recovery, and increasing the dose frequency for the combination of intranasal and inhaled to four times daily provides no additional benefit.⁵⁰ Non-febrile patients or those treated 30 h after symptom onset get little or no symptom benefit. Three pivotal placebo-controlled trials found that inhaled zanamivir 10 mg twice daily for 5 days provides 1–2·5 day reductions in time to alleviation of illness in adults and in teenagers aged 12 or more.^{51–53} A pooled analysis found a 1·5 day reduction in febrile patients with a 3 day reduction in those aged ≥50 years or rated as having some symptoms by the investigator.⁵⁷ These studies found similar clinical benefits in influenza A and B⁵⁴ and confirmed more rapid return to usual activities. In an aggregated analysis of 2499 influenza patients, inhaled zanamivir reduced the frequency of antibiotic prescriptions for lower respiratory complications by 40% but did not reduce prescriptions for presumed upper-respiratory-tract complications.⁵⁵ Intranasal zanamivir reduces nasal virus recovery; inhaled zanamivir may reduce pharyngeal virus recovery,²⁶ but sputum or lower respiratory samples have not been assessed for effects on viral replication.

Therapeutic benefits have been found with oseltamivir in previously healthy adults with febrile influenza treated within 1½ days of illness onset. Two pivotal studies found that oral oseltamivir 75 mg twice daily for 5 days reduces the time to illness alleviation by 1·2–1·4 days (30%), illness severity (30% reduction in scores), and time to resumption of usual activities.^{56,57} No greater clinical effects were seen when the dose was doubled. Reductions in fever duration, cough, ancillary medication use, and viral titres⁵⁸ have been found. The frequency of physician-diagnosed secondary complications leading to antibiotic prescriptions was halved.⁵⁹ Data on influenza B illness are limited.

As with M2 inhibitors, neither of these drugs interferes with the antibody response to acute influenza.

Prevention

Both drugs prevent influenza. One 4-week seasonal prophylaxis study in adults, mostly non-immunised and young, found that inhaled zanamivir 10 mg once daily reduced the likelihood of laboratory confirmed influenza infection (with or without symptoms) by 31%, of influenza illness by 67%, and of influenza illness with fever by 84%.⁶⁰ A post-contact prevention study, with once-daily prophylaxis for 10 days in healthy family members, found that inhaled zanamivir reduced the likelihood of influenza illness by 79%.⁶¹ This strategy had failed with oral rimantadine, in part due to the rapid emergence of drug resistance. Short-term prophylaxis with intranasal zanamivir alone is ineffective.⁶²

A 6-week prophylaxis trial found that oral oseltamivir 75 mg once daily reduced the risk of influenza infection by 50%, of influenza illness by 76%, of influenza illness with fever by 90%, and of culture proven influenza illness by 100%.⁴¹ No greater protection was seen with twice-daily administration. In elderly, largely immunised nursing-home residents, 6 weeks of oral oseltamivir 75 mg once daily reduced the risk of influenza illness by 92% in homes experiencing outbreaks.⁶³ Once-daily oseltamivir reduced the risk of illness by 89% in household contacts.⁶⁴

Special risk groups

The NA inhibitors have received only limited study in patients at increased risk for influenza complications, and no controlled treatment data are available for frail elderly people, infants, immunocompromised hosts, or pregnant women. The breath-activated device for delivering zanamivir requires a cooperative patient who can inspire effectively. Compliance has been excellent but children under 5 years, patients with dementia, and very frail old people cannot use the device. However, 74% of elderly residents in one nursing home had no difficulty.⁶⁵

Preliminary results from small unpublished studies show that in people aged 65 or more, including those developing influenza despite immunisation,⁶⁶ inhaled zanamivir has therapeutic effect and tolerance levels similar to those in younger adults. Another open trial found that inhaled zanamivir (10 mg daily for 14 days) terminated an outbreak of influenza that had persisted despite amantadine use.⁶⁵ Preliminary analysis of oseltamivir treatment in elderly ambulatory adults indicates that illness reduction and tolerance are similar to those observed in younger adults with acute influenza (data on file, Hoffmann-La Roche). Long-term oseltamivir prophylaxis reduced the risk of influenza illness by 92% in a cohort of elderly nursing-home residents, and did so without excess adverse events.⁶³

In higher-risk adults, mostly mild asthma patients, one placebo-controlled zanamivir trial found symptom benefit and reduced complications leading to antibiotics (panel 5).⁵¹ A pooled analysis of studies with inhaled zanamivir indicated non-significant 2.5 day reductions in the time to alleviation of major symptoms and 37% lower rates of influenza complications leading to antibiotic use.⁶⁷ Clinical trials in influenza patients with asthma or chronic obstructive airway disease are in progress with both zanamivir and oseltamivir.

The therapeutic value of these agents in treating pneumonia or other lower-respiratory-tract disease due to influenza is uncertain. One infant with a bone-marrow

transplantation complicated by influenza B virus pneumonia did not clear virus despite 1 week of aerosolised ribavirin followed by 2 weeks of nebulised zanamivir.²⁷

When used for treatment of influenza in children aged 5–12 years, inhaled zanamivir reduced time to alleviation of illness by 1.25 days and return to usual activities, illness severity, and ancillary medicine use (data on file, GlaxoWellcome). An alternative delivery system, such as nebulisation, is needed for younger children and infants. A liquid formulation of oseltamivir is effective in children aged 1–10 years with acute influenza, reducing illness duration by 1.5 days and significantly reducing the frequency of complications leading to antibiotic prescriptions (data on file, Hoffmann-La Roche).

The efficacy and safety of these drugs have not been established in pregnancy. However, in contrast to the M2 inhibitors, no teratogenicity or reproductive toxicity has been found in laboratory animals. Both zanamivir and oseltamivir carboxylate distribute across the placenta and into breast milk in animals.³⁶ Given the potential teratogenicity of the M2 inhibitors, the NA inhibitors would be preferred, especially during the second and third trimesters, when the risk of serious complications increases. The lower systemic exposure from inhaled zanamivir is a consideration in this decision.

Conclusion

The NA inhibitors represent a significant advance over the M2 inhibitors amantadine and rimantadine in influenza therapy. They have a broader spectrum of antiviral activity, less potential for emergence of clinically important resistance, better tolerability, and proven efficacy in reducing respiratory events leading to antibiotic use after influenza.

Inhaled zanamivir and oral oseltamivir are effective for both prevention and treatment of acute influenza. Early treatment reduces illness severity and duration and speeds functional recovery. Efficacy has been established in febrile illness of short duration in adults and in children. However, this treatment is not indicated for minor, non-febrile illness or when influenza symptoms have been present for more than 2 days in immunocompetent persons. Appropriate use of these drugs requires prompt and accurate diagnosis of influenza. A clinical diagnosis is reasonably accurate in adults during confirmed community outbreaks (panel 5), so information from influenza surveillance is important. The increasing availability of point-of-care, rapid diagnostic tests may prove useful in surveillance and, if sufficiently sensitive and specific, in guiding individual treatment decisions.

Although not currently approved for prevention in most countries, the NA inhibitors do seem to be effective for chemoprophylaxis and could be used for long-term protection of those unable to receive vaccine or not responding to it, or when the vaccine is unavailable or ineffective due to antigenically novel viruses. Short-term prevention (10–14 days) could be considered for outbreak control in institutions, for immediate protection in conjunction with late-season immunisation, post-exposure prevention in households, and in travellers likely to be exposed out of season.

Zanamivir and oseltamivir approval status varies with country and indication, and important questions about clinical efficacy remain unanswered. No direct

comparisons between zanamivir and oseltamivir have been done. Nor do we know if combinations of agents might be able to exert more potent antiviral effects and greater clinical benefit. Whether treatment of sick people with these drugs reduces the risk of spreading infection to close contacts remains unstudied. Once there is broader use of these agents, large databases comparing outcomes in treated and untreated patients should prove useful in determining whether early treatment does reduce hospital admissions and mortality, especially in elderly or high-risk patients. More information is also needed on efficacy and tolerability in people with severe influenza, underlying airways disease, immunocompromise, and/or unstable underlying conditions.

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