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Zanamivir

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Contents

Summary

▲ Zanamivir is the first of a new class of selective influenza virus neuraminidase inhibitors. It inhibits both influenza A and influenza B virus replication *in vitro*.

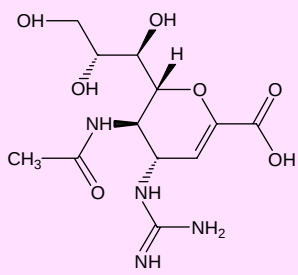
▲ In the ferret model of influenza, zanamivir reduced viral replication and diminished pyrexia associated with the infection.

▲ Repeated passage of influenza virus in the presence of zanamivir could produce resistance *in vitro*. However, there have been no changes in sensitivity to zanamivir in any influenza virus isolates from patients receiving zanamivir in clinical trials.

▲ In experimental infection in humans, in which the virus replicates only in the nasal passages, intranasal zanamivir (3.6 to 16mg) prevented infection with influenza virus. A combination of inhaled (10mg) and intranasal (6.4mg) zanamivir for 14 days was effective in preventing influenza in a nursing home setting during an influenza A virus outbreak.

▲ Inhaled zanamivir (10mg) with or without intranasal zanamivir (6.4mg) reduced the time to alleviation of influenza symptoms compared with placebo in patients with confirmed infection.

Features and properties of zanamivir (GG167)	
Indications	
Influenza A Influenza B	Late phase clinical trials
Mechanism of action	
Antiviral	Neuraminidase inhibitor
Dosage and administration	
Usual dosage in clinical trials	10mg inhaled, 6.4mg intranasal
Route of administration	Inhaled, intranasal
Frequency of administration	2, 4 or 6 times daily
Pharmacokinetic profile	
Time to peak plasma concentration	≤2h
Bioavailability	10% (intranasal), 15% (dry powder inhalation) 20% (nebuliser)
Elimination half-life	3.4h (intranasal), 3.6h (dry powder inhalation)
Adverse events	
No significant effects	



Zanamivir (GG167)

Zanamivir is the first neuraminidase (sialidase) inhibitor to be developed for the prophylaxis and treatment of influenza caused by influenza viruses A and B.

Current prophylaxis and treatment for influenza includes amantadine and rimantadine, but these agents are active against the influenza A virus only, and resistance can develop rapidly.[1] They also have a poor adverse effect profile.[2] Another therapy, inhaled ribavirin, which is indicated for respiratory synctial virus infections, has shown limited efficacy in young children hospitalised with influenza.[22] The oral formulation has been associated with adverse events.[3]

1. Pharmacodynamic Profile

Mechanism of Action

• Zanamivir is a selective inhibitor of both influenza A and B virus neuraminidases. It inhibits the viral cleavage of sialic acid from cell surface glycoconjugates.[4] Consequently, it prevents infection by stopping the release of newly formed virus from the surface of infected cells and preventing viral spread across the mucous lining of the respiratory tract.[3] Because zanamivir is selective, it does not significantly inhibit human lysosomal neuraminidase.[4]

• Zanamivir at nanomolar concentrations has affinity for both influenza A and B virus neuraminidases.[5]

Antiviral Activity

In Vitro *Studies*

• Zanamivir inhibited replication of influenza A and B viruses in Madin-Darby canine kidney (MDCK) cells,[1,4,6,7] and human respiratory epithelial cells.[6]

• Zanamivir produced 50% inhibition of plaque formation at concentrations (IC_{50}) between 4 and 14 nmol/L for laboratory passaged viruses and 2 to 16000 nmol/L against recent clinical isolates of influenza A and B viruses; IC_{50} values for neuraminidase inhibition were 0.64 to 5.6 nmol/L and 0.79 to 7.9 nmol/L, respectively.[4] The antiviral activity was not affected by resistance to amantadine or rimantadine, or by the passage history of the virus.

• Zanamivir also reduced virus yields in human respiratory epithelial cells, with 90% effective inhibitory concentration (EC_{90}) values at 24 and 48 hours of <0.01 mg/L for 2 influenza A strains and 0.54 and 0.25 mg/L for an influenza B strain at each respective time point.[6] Inhibition was comparable to that of ribavirin and superior to that of rimantadine.

• Zanamivir inhibited growth of avian influenza virus in MDCK cells at concentrations previously found effective against human N1 and N2 influenza A and B viruses.[7]

• Combination of zanamivir with rimantadine, ribavirin or deoxyfluoroguanosine had additive effects on viral inhibition.[1]

In Vivo *Studies*

• In mice infected with influenza A virus, intranasal zanamivir 0.01 or 0.4 mg/kg per dose reduced mortality ($p < 0.001$ *vs* placebo), lung consolidation ($p \leq 0.05$) and viral titres in lung homogenates (with 0.4 mg/kg only; $p < 0.001$) over a 10-day period.[8] Virus growth after this period was not observed. In mice infected with influenza B virus, intranasal administration of zanamivir ≥0.4 mg/kg per dose significantly reduced viral titres in lung homogenates ($p < 0.05$ *vs* placebo). Administration of the drug by the intraperitoneal or oral route did not produce *in vivo* antiviral activity.

• In comparison with ribavirin and amantadine, intranasal zanamivir administered before or 24 hours after infection was 100 to 1000 times more active against influenza A and B viruses in reducing nasal viral titre and the incidence of pyrexia in ferrets.[9] Serum antibody response to infection was not affected by zanamivir.

Viral Resistance

• Sequential passage *in vitro* of influenza A[10-12] or B[11] virus in increasing zanamivir concentrations resulted in increased viral resistance to the drug in MDCK cells. Decreased neuraminidase activity and reduced infectivity were noted in resistant strains versus parental virus. However, neuraminidase resistance to zanamivir did not develop during zanamivir therapy in phase II trials in patients with influenza-like illness.[13]

2. Pharmacokinetic Profile

• The kinetics of zanamivir were linear after intravenous, intranasal and inhaled doses in volunteers.[14,23] After an intravenous dose of 1 to 16mg, median elimination half-life was 1.7 hours, volume of distribution at steady state was 16L, and 90% of the dose was excreted unchanged in the urine. After intranasal and inhaled (dry powder) administration, maximum serum concentrations occurred within 2 hours and the terminal phase half-life was 3.4 and 2.9 hours, respectively. Bioavailability was 10 and 25%, respectively, and was 20% after inhalation of zanamivir by nebuliser.[14,23,24]

• Delivery of zanamivir 10mg via a Diskhaler® in volunteers resulted in mean deposition of 13.2% of the dose in the lungs and 77.6% in the oropharynx. Use of a prototype inhalation device resulted in 12.6 and 81.1% deposition, respectively.[15]

• Serum concentrations following twice- or 6-times-daily administration of intranasal zanamivir (3.6 to 16mg) to volunteers inoculated with influenza A virus were similar across gender. In volunteers who received zanamivir 16mg, serum concentrations were also similar across infection type (shed virus or rise in H1 antibody) and presence of upper respiratory illness. A median of 4% of the dose was recovered unchanged in the urine.[16]

• In isolated perfused rat kidneys, cimetidine, ibuprofen, cefuroxime and pseudoephedrine did not alter renal clearance and elimination of zanamivir, which was predominantly cleared as unchanged drug in the urine. Paracetamol (acetaminophen) and its glucuronide reduced zanamivir renal clearance by 16%, but this was not considered clinically significant.[17]

3. Therapeutic Trials

Prophylaxis

• Volunteers in a nursing home were randomised in a nonblind pilot study to receive inhaled zanamivir 10mg plus intranasal zanamivir 6.4mg (n = 65) or rimantadine 100mg (n = 23) for 14 days as chemoprophylaxis during an outbreak of influenza A. Influenza-like illness (respiratory illness with developed fever >100°F) was detected in only 1 volunteer, who had received zanamivir.[18]

• In 4 randomised, double-blind, placebo-controlled trials, a total of 166 volunteers were inoculated intranasally with influenza A (H1N1) virus.[19] Zanamivir 3.6 to 16mg was administered intranasally 2 or 6 times daily for 5 days starting 4 hours before inoculation. Across all dose groups, development of infection (according to laboratory evidence) was prevented in 82%, and development of fever was prevented in 98%, of volunteers ($p < 0.001$ *vs* placebo) [fig. 1]. Significant reductions (50 to 80%) in total symptom scores, nasal mucus weight, incidence of upper respiratory tract illness and cough and paracetamol use were also observed compared with placebo.

Treatment

• In the randomised, double-blind, placebo-controlled trials described above, administration of zanamivir 3.6 to 16mg for 4 days starting on day 1 after inoculation to volunteers who had laboratory evidence of infection reduced peak viral titres by 99% (2.0 $\log_{10}$) [$p < 0.001$ *vs* placebo] and reduced

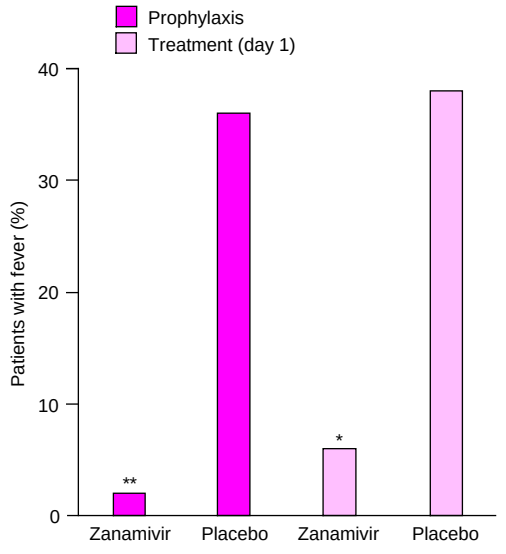


Fig. 1. Effect of prophylactic or therapeutic zanamivir on reducing febrile illness in volunteers. Volunteers were given intranasal zanamivir 3.6 to 16mg 2 or 6 times daily 4 hours before or 1 day after inoculation with influenza A virus.[18] *Symbols*: * $p < 0.05$, ** $p < 0.001$ *vs* placebo.

the frequency of febrile illness in all but 2 patients ($p < 0.01$ *vs* placebo) [fig. 1]. There was also a 40 to 65% reduction in total symptom scores, nasal mucus weights, frequency of cough and paracetamol use in zanamivir recipients. Administration on day 2 after inoculation to volunteers who were already ill resulted in rapid decline in viral titres and a decrease in viral titre area under the plasma concentration–time curve of 75% ($p < 0.05$). Zanamivir had similar effects at both the twice- and 6-times-daily doses.[19]

- In 2 parallel, randomised, double-blind multicentre trials, a total of 262 patients with confirmed influenza A or B infection of ≤48 hours' duration were assigned to 3 treatment groups: inhaled zanamivir 10mg plus intranasal placebo, inhaled zanamivir 10mg plus intranasal zanamivir 6.4mg, or placebo by both routes, twice daily for 5 days.[20] The median time to alleviation of influenza symptoms was 4 days in patients receiving inhaled zanamivir alone ($p = 0.05$) and those receiving inhaled plus intranasal zanamivir ($p = 0.02$) versus 5 days in patients given placebo (fig. 2). In patients who were febrile at study entry (n = 111) or were given treatment within 30 hours after symptom onset (n = 130), symptoms were alleviated in both zanamivir groups in a median of 4 days, compared with 7 days in the placebo group ($p \leq 0.01$).

- In a randomised, blinded, placebo-controlled study, treatment with zanamivir (inhaled and intranasal) twice or 4 times daily for 5 days, with a 21-day follow-up, resulted in improved health status and patient functioning, reduced healthcare requirements in patients with influenza, and an earlier return to the workplace (patients receiving the 4-times-daily regimen only).[21]

4. Tolerability

- In patients with confirmed influenza infection, the most commonly reported adverse events during zanamivir treatment were related to the upper respiratory and gastrointestinal tract, but these were difficult to distinguish from influenza symptoms.[20]

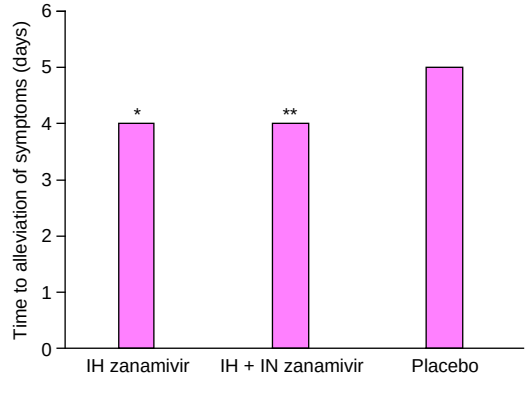


Fig. 2. Effect of zanamivir on time to alleviation of major symptoms of influenza. Patients with influenza A or B infection of ≤48 hours' duration were treated with inhaled zanamivir (10mg) plus intranasal placebo (n = 85), inhaled zanamivir (10mg) plus intranasal zanamivir (6.4mg) [n = 88], or placebo (n = 89), twice daily for 5 days. Alleviation of symptoms was defined as the absence of feverishness, and no, or only mild, symptoms of headache, muscle aches, sore throat and cough for ≥24 hours.[19] *Abbreviations and symbols:* IH = inhaled; IN = intranasal, * $p = 0.05$, ** $p = 0.02$ *vs* placebo.

• After intranasal administration of zanamivir 3.6 to 16mg twice or 6 times daily in volunteers inoculated with influenza A virus, important adverse events or effects on spirometry, ECG or laboratory values were not observed.[19]

• Zanamivir and placebo produced similar frequencies of local nasal irritation.[19,20]

• No cytotoxicity was observed when zanamivir was tested against influenza A in MDCK and human cells *in vitro* in concentrations up to 10 mmol/L, whereas cytotoxicity could be measured for ribavirin [50% cytotoxic concentration (CC_{50}) of 0.005 to 4.5 mmol/L], amantadine (CC_{50} of 0.04 to 1.0 mmol/L) and rimantadine (CC_{50} of 0.01 to 4.0 mmol/L).[4]

5. Zanamivir: Current Status

Zanamivir is a neuraminidase inhibitor that is in late phase clinical trials. It has shown clinical efficacy in the prophylaxis and treatment of influenza A and B.

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