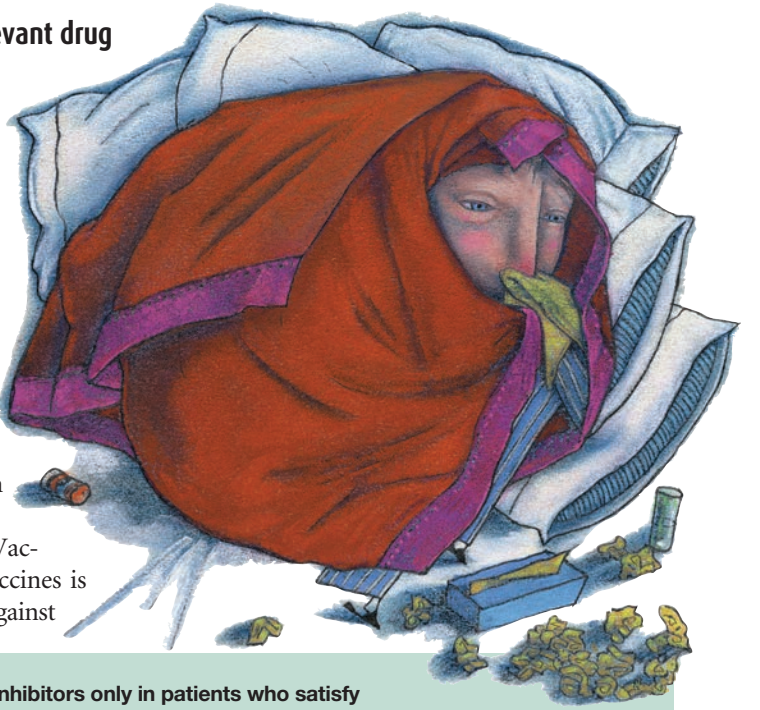
Using neuraminidase inhibitors against influenza

Two drugs specific for the treatment of influenza virus infection have recently become available in Australia. They are effective against all known epidemic strains and there is no indication of clinically relevant drug resistance. However, the therapeutic benefits are dependent on accurate diagnosis and early treatment.



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Influenza is a major source of morbidity within the population at large and causes significant mortality, principally in the older adult population, in people with underlying risk conditions and, to a lesser extent, in the very young. Vaccination with inactivated virus vaccines is still the best means of protection against

IN SUMMARY

- **Use the neuraminidase inhibitors only in patients who satisfy all of the following criteria: have a compatible clinical illness; present within 48 hours of onset of illness; and are in an area where there is local influenza activity or have returned from an area of influenza activity within the previous few days**
- **Treatment should be started as early as possible. The earlier patients are treated and the sicker they are, the greater the benefit they will get.**
- **Treatment should be considered for all patients suspected of having influenza, but especially those at high risk of serious influenza infection (by the NHMRC definition). These patients have the greatest potential benefit from treatment, with a likely reduction of the acute illness and prevention of complications.**
- **Other patients may also elect to use neuraminidase inhibitors depending on how ill they are, how early they are being treated, and their social or financial need to reduce the severity of influenza infection.**
- **Treatment may also be considered when there is a significant risk of spread to susceptible high risk contacts, such as nursing home residents.**

continued

Table. Patients at high risk of serious or complicated influenza*

- All persons aged 65 years or older
- All Aboriginal and Torres Strait Islander persons aged 50 years or older
- Adults and children (≥6 months of age) with chronic disorders of the pulmonary or circulatory system, including severe asthma
- Adults and children (≥6 months of age) with chronic illnesses requiring regular medical follow up or hospitalisation in the preceding year (includes diabetes mellitus and renal dysfunction)
- Patients receiving immunosuppressive therapy or suffering from immunosuppressive illnesses

* NHMRC definition.

Figure 1. Molecular model showing neuraminidase tetramers and haemagglutinin trimers on the surface of the influenza virus.

the illness and its complications, particularly in those at high risk of serious disease (Table).

High risk individuals would also benefit from access to specific antiviral treatment that could be used if they did develop influenza. That may occur because they are unvaccinated, because they become infected despite vaccination, or because there are known to be strains circulating that are not adequately covered by the vaccine in use. In addition, many of the general population, most of whom are unvaccinated, would like the option of a treatment that reduces the morbidity and inconvenience caused by influenza.

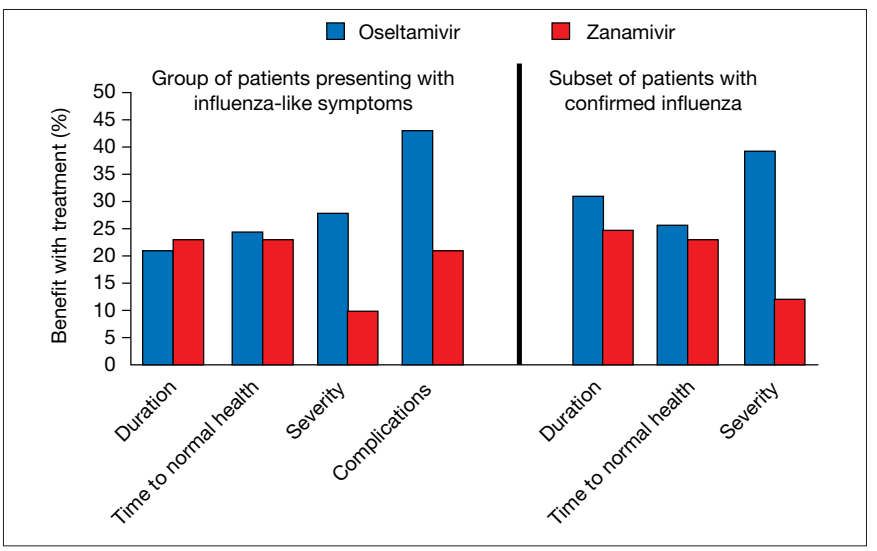

Figure 2. Summary of the benefits from treatment of influenza with neuraminidase inhibitors for patients treated within 48 hours of onset.[1-4] As these agents will only work in patients with influenza, the effectiveness in the group of patients with influenza-like illness will depend on the proportion who actually have influenza. (Complications data were not available for the subset.)

Amantadine has been available for many years as a specific anti-influenza drug, but it has had little use because of neurological side effects, activity against only influenza A, and the rapid emergence of virulent drug-resistant viruses.

Recently, two drugs in a new group called the neuraminidase inhibitors have become available. They act by blocking the active site of the influenza neuraminidase enzyme (Figure 1). The neuraminidase is required to assist the release of viral particles from infected cells, so the inhibition reduces the spread and growth of the virus within the body. Zanamivir (Relenza) is delivered as an inhaled powder and oseltamivir (Tamiflu) is delivered as a capsule. They are specific for influenza, active against all circulating strains and well tolerated; however, therapeutic benefits are confined to patients with true influenza treated within 48 hours or less of symptom onset.

The following summarises available data on drug safety and effectiveness, evidence of benefit in various patient groups and considerations regarding the accuracy of clinical diagnosis of influenza, to assist physicians in deciding when these agents should be prescribed. (The separate studies are not referenced in

this article, but the 'Further reading' section lists recommended reviews of these studies.)

Treatment of clinical influenza

Controlled trials have been conducted in patients presenting with influenza-like illness. As only a proportion (60 to 80%) of these patients are shown to have influenza and as these agents act only on influenza, the data are usually analysed both for all patients presenting with influenza-like illness (the 'intention-to-treat' or ITT group) and the subset of those who have confirmed influenza. Variations in the proportion of patients with influenza do influence the outcomes for the ITT group in different trials. (Data are presented for the ITT group to give an idea of what can be expected if you treat all patients presenting with an influenza-like illness without knowing whether they have influenza.)

In all cases, treatment was commenced a maximum of 48 hours after onset of illness because treatment beyond this time has no effect.

A summary of the benefits of treating all patients presenting with influenza-like illness and just those with confirmed influenza is shown in Figure 2.

Effect on the duration of illness

In trials for both drugs, treatment shortened the duration of illness by an average of one to two days for all treated patients, and by a further half a day in the subset of patients with confirmed influenza. This is accompanied by an earlier return to normal health of about two days. The zanamivir data indicated that patients with febrile influenza and/or those at high risk of serious influenza infection get a reduction of up to three days. Oseltamivir is also at least as effective in high risk patients, including those with underlying respiratory or cardiac disease.

In the oseltamivir trials it was clear that the earlier patients are treated, the greater the benefit. Those treated within 24 hours of onset were a half to one day better off than the whole group. Indeed, there appears to be a progressive benefit the earlier treatment is begun, with those treated within six hours of onset having a 50% better reduction of duration than those treated at 48 hours. Patients receiving treatment within 12 hours of onset recovered three days faster than the placebo group. As might be expected, the benefit to those commenced on treatment towards the end of the 48-hour period will be very limited.

Both drugs seem to be equally effective in vaccinated and unvaccinated individuals, although the data are limited at the moment.

Effect on the severity of illness

Neuraminidase inhibitor therapy significantly reduces the total symptom score, particularly in the first four to five days of illness. Zanamivir treatment produced a reduction of about 10%, but it was slightly greater in the influenza-confirmed group. The oseltamivir trial in low risk patients showed an 18 to 23% reduction in severity in all treated patients, and a 28 to 38% reduction in those with confirmed influenza. For both drugs, the main effects are on the symptoms that patients find most troublesome, including cough, headache, fever, myalgia, weakness and loss of appetite.

As might be expected, there was also a reduction in the complications of influenza in treated patients. In low risk patients, oseltamivir reduced complications by nearly 50%, and zanamivir reduced them by about 20%, although the latter did not reach statistical significance. These reductions were mainly in sinusitis and bronchitis. An experimental study in adults with influenza A showed that zanamivir reduced changes in middle ear pressure.

In high risk individuals, zanamivir showed a much greater effect than it had in low risk patients, with a 70% decrease in complications, particularly bronchitis and pneumonia. At the moment there are no data for oseltamivir in high risk patients, but it is likely to be effective in reducing complications.

Antibiotic use has been reported to

MedicineToday PATIENT HANDOUT

Are you considering taking a neuraminidase inhibitor for possible flu?

- If you have influenza, treatment with this medication will make you better quicker. If you start the medication within 2 days of falling ill, you will recover 1 to 2 days earlier. If you start on the first day, you will get better up to 3 days earlier.
- Treatment will reduce your chance of getting complications such as sinus, ear or chest infections by up to 50%.
- The treatment has very few side effects. If you are having the tablets, you should take the first dose with food. You may feel sick with the first couple of doses, but it will pass. If you are having the inhaled drug, you must follow the instructions on the use of the inhaler device carefully.
- If you have asthma or other chest disease you may not be able to have the inhaled medication.
- Many people who think they have influenza actually have another virus. If that is the case for you, this treatment will not alter the course of your illness, but it will not be harmful to you. Tests that can show immediately whether you have influenza are not usually available, so the decision about whether to use this medicine must be made based on your illness.
- If you have private health insurance, your fund may assist you with the purchase of this medication.

be reduced by 80% in low risk individuals treated with oseltamivir and by 65% in high risk patients given zanamivir. There is also a more modest reduction in use of over-the-counter (OTC) medications.

While the number of patients with complications in the trials is still small, it does appear that the neuraminidase inhibitors can reduce complications. The size of the benefit, particularly for more serious complications such as pneumonia and death, will be more accurately determined as further data become available. The reductions in complications and use of antibiotics and OTC medications are important benefits in improving health, reducing costs from influenza and offsetting the cost of these new agents.

Treatment of complicated influenza

There are no data in the literature on the value of treating established complicated influenza, particularly bronchitis, pneumonia and rarer cases of encephalitis, myositis or other complications. If patients are severely ill, there are no intravenous formulations for either drug and no nebulised formulation of zanamivir. It is likely that attempts would be made to deliver either oseltamivir via a nasogastric tube or zanamivir via an endotracheal tube, but the efficacy in these circumstances is unknown.

Treatment of influenza in children

Currently, there are limited data available on the use of these drugs in children. A placebo-controlled trial of zanamivir in children aged 5 to 12 years showed a 0.5 day reduction in duration of illness in all treated patients, and a 1.25 day reduction in those with confirmed influenza. A placebo-controlled trial of a liquid formulation of oseltamivir, in children aged 1 to 12 years, showed a reduction in illness duration by 1.5 days, time to return to normal health by two days, severity by 29%, otitis media by 44% (not statistically significant) and antibiotic use by 40%.

Therefore, both agents are likely to be effective in treatment of children with influenza, with efficacy similar to that in low-risk adults. Currently, only zanamivir is licensed for use in children in Australia. Selection of patients for treatment based on clinical presentation is more difficult in children than in adults because of the wider range of presenting symptoms and greater likelihood of other causes of illness. Small children are unlikely to be able to use the inhaler device for delivery of zanamivir. A liquid formulation of oseltamivir would be an advantage for these children, but it is not yet available in Australia.

Treatment in patients who are immunocompromised

Regarding treatment in immunocompromised patients, there are no data available from clinical trials. However, anecdotal reports suggest that these drugs will effectively suppress viral replication, but they probably do not eliminate infection while immune function remains suppressed. The duration of treatment is likely to be longer than for immunocompetent individuals, depending on the course of the illness, and in some patients long term treatment may be needed. The obvious concern is that drug resistant viruses may emerge in these patients (see the section near the end of this article); therefore, it is essential that the diagnosis is confirmed by laboratory tests and that viruses are isolated and monitored for drug sensitivity.

Prevention of influenza

Trials indicate that these drugs are 70 to 75% effective in preventing infection and 85 to 90% protective against febrile influenza. They have been used successfully to prevent spread within households, and to control outbreaks in high risk institutionalised patients, such as in nursing homes. In these situations, the drug is used for around two to four weeks until the outbreak is controlled or vaccine-induced protection is achieved. Longer term prophylaxis may also be used in immunosuppressed individuals who will not respond to vaccination, as has been advocated for amantadine. Necessarily, there will be considerable expense in maintaining treatment for the eight to 12 weeks of the influenza season, although prophylactic doses are only half the treatment dose.

Currently, only zanamivir is licensed in Australia for prophylactic use, and only in circumstances where prophylaxis of healthy young adults can be justified, such as the appearance of new strains not covered by the vaccine.

Side effects

The side effects of zanamivir seem to be minimal and no serious adverse reactions have been reported in the trials that have been published. However, during post-marketing surveillance there have been reports of deterioration in respiratory function in patients with underlying airways disease (asthma and chronic obstructive pulmonary disease), and rare reports of bronchospasm in patients without airways disease. Patients who develop wheezing or breathlessness when using zanamivir should discontinue its use,

and it should be avoided in patients with underlying respiratory disease. If it is used in the latter group, then a fast-acting bronchodilator should be available for use, or a bronchodilator should be used before the administration of zanamivir if the timing is appropriate.

Nausea and vomiting were reported in 10 to 15% of patients in the oseltamivir trials, but were largely confined to the first dose. Food taken with the first dose will reduce these, and they rarely led to discontinuation of the treatment.

In-use patient surveys

Follow up surveys of patients who have been prescribed zanamivir have been conducted in Australia and France. However, the very low return rates for the questionnaires and the absence of tests to determine which patients were infected with influenza mean that little weight can be attached to the results.

The surveys did provide a chance to determine the ease of use of the Diskhaler device. Both surveys reported that the device was easy to use in all ages, with 90% finding the device 'easy' or 'very easy' to use. This finding contrasts with that of a controlled trial carried out in hospitalised elderly patients comparing the Diskhaler with another device, the Turbohaler. In this trial, even after individual tuition 50% of the elderly patients were still unable to use the Diskhaler, compared with only 6% for the Turbohaler.

The differences may be due to the low return rates in the surveys, which may overestimate the ease of use, and the fact that the controlled trial was confined to a group that may have had particular difficulties. If zanamivir is prescribed, careful instruction in the use of the Diskhaler is necessary and, even with that, many elderly patients may still not be able to use the device properly.

Deciding when to use a neuraminidase inhibitor

Zanamivir is approved in Australia for treatment of influenza in patients 5 years or older, and oseltamivir in patients 12 years or older, within 48 hours of onset of illness. Zanamivir also has a limited prophylactic indication.

Currently, neither drug attracts a subsidy under the PBS scheme. Private health insurance funds may offer some support. Both drugs are relatively expensive at around $49 per course, making accurate diagnosis important to maximise the potential benefit to the patient.

Unfortunately, clinical diagnosis of influenza is notoriously unreliable and, even at the peak of the influenza season, only around 50% of patients with an influenza-like illness seen in general practice will return a positive laboratory test result. The likelihood of influenza will increase if the patient has a rapid

onset of high fevers with constitutional and respiratory symptoms. Current laboratory-based diagnostic tests will not routinely provide results quickly enough to help make a decision about treatment within 48 hours of onset of illness. As treatment should commence as early as possible, any delay in the decision will reduce the efficacy.

A number of rapid near-patient tests for diagnosis of influenza are appearing, but availability is limited and their reliability is not well established. It is clear that they will miss many people with influenza, possibly over 25%, and that a small proportion of patients who are positive on the tests do not have influenza. At the moment, their role in individual patient diagnosis remains uncertain, but their value will become clearer as more data appear and better tests become available. They also have a role in complementing routine surveillance activities to rapidly establish the presence of influenza in a community and in this way to improve the accuracy of clinical diagnosis.

At the moment, decisions about use of neuraminidase inhibitors must be based primarily on:

- clinical presentation
- confirmation of the presence of influenza in the community
- the risk of serious disease
- the patient's desire to avoid the discomfort and inconvenience of influenza.

While a variety of definitions of 'influenza-like illness' have been used, the one currently recommended in Australia is 'an acute upper respiratory tract infection characterised by cough, history of fever and fatigue'. If a near-patient test is used, it may assist the decision, but you should be aware of its limitations. Where possible, patients who are treated should still be tested by routine methods, to aid in assessing the clinical diagnosis, defining risks to susceptible contacts and determining the reasons for response, or lack of response, to treatment.

Resistance of influenza to neuraminidase inhibitors

Whenever new anti-infectives become available there is always a concern about the emergence of resistance. Studies to date indicate that, although resistance to neuraminidase inhibitors can be induced in the laboratory, resistance is uncommon in clinical use of oseltamivir and rare for zanamivir. Also, the resistant isolates that have been detected in patients do not seem to be virulent, transmissible or clinically important.

A global network program for actively monitoring resistance has recently been established. It will focus particularly on immunosuppressed patients, who are most likely to develop resistant virus strains.

Conclusion

The neuraminidase inhibitors have provided us with an additional intervention in the efforts to reduce influenza and its impact. They should not replace vaccination as the primary prevention tool, but should be considered for treatment use in patients who have suspected influenza. If used properly, they will reduce the impact of this infection on the community. MT

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Further reading

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