

Inpatient clinical management issues relating to oseltamivir-resistant pandemic (H1N1) 2009 influenza virus



Summary

It is important to:

- Promote pandemic influenza vaccination to healthcare staff, priority groups and household contacts of immunocompromised patients.
- Maintain a high index of suspicion for influenza and start treatment early.
- Avoid breaks in antiviral treatment.
- Consider antiviral resistance in patients with H1N1 who fail to improve after five days of oseltamivir treatment or deteriorate on a reasonable period of treatment and seek antiviral resistance testing.
- Promote the use of good infection control and personal hygiene measures.
- Use zanamivir for the treatment of patients with confirmed or suspected oseltamivir resistance who are still symptomatic, otherwise stop treatment.
- Agree within the local health economy the use of either zanamivir mono-therapy or oseltamivir and zanamivir dual therapy for the treatment of suspected or confirmed pandemic influenza in immunocompromised patients.
- Use zanamivir for prophylaxis for
 - a) Immunocompromised close contacts of cases of pandemic influenza, regardless of whether the virus is susceptible or resistant.
 - b) People with severe underlying health conditions who are close contacts of confirmed cases of oseltamivir-resistant influenza.

Background

This guidance is being developed in response to:

- The emergence of cases of oseltamivir-resistant pandemic (H1N1) 2009 influenza virus with the H275Y mutation – particularly in people who are immunocompromised.
- The identification of a group of immunocompromised patients in whom person-to-person transmission of the resistant virus is considered likely to have occurred.

The H275Y neuraminidase mutation has been shown to cause high-level resistance to oseltamivir in clinical isolates of N1-containing viruses. This mutation has been known about for some time but, prior to 2008, a number of studies found that some influenza viruses with the H275Y mutation seemed to be less fit than seasonal strains in terms of transmission, pathogenicity and viral replication. This, however, changed in 2008/09 with the emergence of a seasonal flu virus with the H275Y mutation, able to replicate and transmit. In a very short period after the virus emerged, it displaced the oseltamivir-susceptible seasonal H1N1 strain.

The impact on the fitness of the current pandemic virus, when it acquires oseltamivir resistance, is not known. If it is not fully transmissible at the current time, there may be an opportunity to reduce the likelihood of such a change happening.

The identification of the resistant virus in a significant number of immunocompromised patients is of concern, as

immunocompromised patients infected with influenza can shed virus for prolonged periods of time, increasing the likelihood of changes occurring within the virus and the virus being transmitted to others.

Guidance exists for the management of patients who have oseltamivir-resistant seasonal H1N1, but there is no published guidance for the current pandemic strain.

General principles

Promote pandemic influenza vaccination

Preventing or reducing the likelihood of infection with the pandemic virus will be important for immunocompromised patients, as the disease may have more severe consequences for this group of patients. Oseltamivir resistance can readily develop during treatment and the resistant virus can be shed for a prolonged period of time. It is therefore important to ensure that vaccination in immunocompromised patients and their household contacts is encouraged. Healthcare staff should also be encouraged to accept the offer of vaccination.

Maintain a high index of suspicion for influenza and start treatment early

The neuraminidase inhibitors work by blocking viral release from infected cells. The earlier that influenza is considered and treatment initiated, the greater the impact on viral load, severity of symptoms and duration of illness.

Avoid breaks in antiviral treatment

Oseltamivir resistance has been identified in patients whose treatment has been stopped before completion of the recommended five days' treatment course, or where therapy has been intermittent. Intermittent or incomplete treatment courses should be avoided.

Consider antiviral resistance in patients with pandemic (H1N1) 2009 influenza who fail to improve after five days of oseltamivir treatment or deteriorate on a reasonable period of treatment

There is no evidence that the natural history of drug-resistant pandemic (H1N1) 2009 influenza is different from wild type virus. In the vast majority of cases, infections with either form of virus will be mild and self-limited. However, in those requiring therapy, a lack of response may be due to the emergence/ transmission of drug resistance, for example in an immunocompromised patient. The emergence of oseltamivir resistance has been detected in patients on treatment, after as few as three days.

Infection control and personal hygiene measures are important

The possibility of oseltamivir resistance highlights the need for good infection control as a non-pharmaceutical way of preventing transmission and spread of viruses.

Issues

The likely issues that may be encountered are set out below and the proposed management options are outlined

Note that in this document the words 'viral isolate' are

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used to describe either cell culture-grown virus, or viral nucleic acid. While recognising that genotypic resistance may not necessarily be associated with phenotypic resistance, initial actions in practice will be based on rapid genotypic sequence-based or PCR-based results. It is also implicit in the document that rapid (one day turnaround) resistance detection will be available. Where this is not available, some modification to the suggested approaches will be required.

Treatment: Immunocompetent patients

1. Oseltamivir-resistant virus detected in a patient already on oseltamivir treatment.

1.1 Patient who is recovering, or well

In this situation it is recommended that:

- The patient should adopt a high standard of personal hygiene and infection control procedures should be put in place, including isolation in a single room.
- There would appear to be no benefit in continuing treatment with oseltamivir. Therefore, in line with recent WHO recommendations¹, the oseltamivir should be stopped; a switch to zanamivir is not required if the patient continues to improve. If the patient deteriorates, see 1.2 below.
- Surveillance of household contacts should be undertaken; any household contacts with symptoms should be investigated and consideration given to treatment and testing for influenza.
- Healthcare staff, carers and household contacts of immunocompromised patients should be vaccinated against pandemic influenza, if this has not already been done.
- The patient's condition should be monitored and testing for influenza undertaken at 10 days after the start of treatment.
- If influenza H1N1 still detected:
 - Undertake repeat resistance testing.
 - Continue with infection control measures and surveillance measures.
- Any further testing should be carried out in consultation with the local microbiologist/virologist.

1.2 Hospitalised patient who is still symptomatic or deteriorating

In this situation is recommended that:

- Infection control and personal hygiene are maintained as above.
- In line with WHO recommendations, oseltamivir should be stopped and replaced with zanamivir, on the basis that:
 - Oseltamivir is no longer likely to be effective.
 - Zanamivir would affect both susceptible and resistant viruses.
 - Reduced zanamivir susceptibility has been detected only very rarely in H1N1 influenza subtypes.

- Zanamivir treatment should be continued for ten days, unless the clinical condition of the patient warrants continuation of treatment for a longer period
- Zanamivir should be administered by inhaler, unless the patient is unable to use this method of delivery. Nebulisation of the contents of the rotadisks should NOT be undertaken if the patient is being ventilated. If the patient's condition is deteriorating, IV zanamivir should be considered. IV zanamivir is available on a named-patient basis (off licence) on a compassionate basis and is currently being used for very ill patients not responding to first-line therapy.
- Surveillance of household contacts should be undertaken.
- Healthcare staff, carers and family contacts of patients should be vaccinated against pandemic influenza, if this has not already been done.
- The patient's condition should be monitored and testing for H1N1 influenza should be considered after five days.
- If influenza H1N1 is detected:
 - Undertake repeat resistance testing.
 - Continue with infection control and surveillance measures.
 - If the patient is likely to remain in hospital then, in consultation with the local microbiologist/virologist, consider retesting every five days until there is a negative swab. A second swab should be taken 48 hours after the negative swab and, if this is negative, infection control measures can be stopped. In a patient with lower respiratory tract symptoms, a tracheal or lower respiratory tract specimen is preferable to a nose/throat swab.
- Household contacts should remain under surveillance until the patient is considered negative.

2. Hospitalised patient with flu-like symptoms who has an epidemiological link (a close contact) to a confirmed case of oseltamivir resistance

It is recommended that:

- A high level of suspicion should be assumed that the condition will be influenza.
- Zanamivir should be offered on the basis that:
 - Infectious material from a patient with oseltamivir resistant virus is likely to have a high percentage of resistant virus, against which oseltamivir will have little effect.
 - Zanamivir would affect both susceptible and resistant viruses.
- Zanamivir treatment should be continued for ten days, unless the clinical condition of the patient warrants continuation of treatment for a longer period.
- Zanamivir should be administered by inhaler unless the patient is unable to use this method of delivery. Nebulisation of the contents of the rotadisks should NOT be undertaken if the patient is being ventilated. If the patient's condition is deteriorating, IV zanamivir should

1 www.who.int/csr/disease/swineflu/notes/briefing_20091202/en/index.html 9 WHO Guidelines for pharmacological management of pandemic (H1N1) 2009 influenza and other Influenza viruses - 20 August 2000

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be considered. IV zanamivir is available on a named-patient basis (off licence), on a compassionate basis, and is currently being used for very ill patients not responding to first-line therapy.

- Infection control and personal hygiene should be maintained, as already described.
- Nose and throat swabs should be taken for testing.
- Healthcare staff, carers and household contacts of immunocompromised patients should be vaccinated against pandemic influenza, if this has not already been done.
- If influenza H1N1 is detected, oseltamivir resistance testing should be undertaken.
- If resistance is detected:
 - The patient's condition should be monitored and, in consultation with the local microbiologist/virologist, consideration given to testing for H1N1 influenza every five days until there is a negative swab; a second swab should then be taken 48 hours later. In a patient with lower respiratory tract symptoms, a tracheal or lower respiratory tract specimen is preferable to a nose/throat swab. If this is negative, infection control measures can be stopped.
 - Surveillance of household contacts should be undertaken
 - Infection control and surveillance measures should remain in place until the patient is considered negative.

Treatment: Immunocompromised patients

There is increasing evidence that oseltamivir resistance to pandemic (H1N1) 2009 influenza is most likely to emerge in people who are immunocompromised. The only two clusters of oseltamivir-resistant pandemic influenza infection, where probable person-to-person transmission has occurred, have been in immunocompromised patients. It is therefore considered prudent to offer either zanamivir as monotherapy, or oseltamivir combined with zanamivir, to all immunocompromised patients who develop an influenza-like illness over the forthcoming winter season. Treatment should be continued for ten days, unless the clinical condition of the patient warrants a longer period of treatment. For the purposes of this paper, the description of immunocompromised patients contained in the 'Green Book' is used. Every effort should be made to ensure that immunocompromised individuals and their household contacts are vaccinated with the pandemic influenza vaccine.

Immunocompromised patients with an influenza-like illness

There have been attempts to treat this group with oseltamivir in higher doses and for longer (150mg bd for ten days). This has the theoretical advantage of greater experience with oseltamivir treatment in the immunocompromised and in more severe cases than treatment with zanamivir; also oseltamivir can be given to all age groups (zanamivir is currently restricted to those patients capable of effectively using the disk inhaler, and is not licensed for use in children under the age of five years).

However, resistance is known to emerge even with higher

doses of oseltamivir in immunocompromised patients. Also, the influenza virus, including oseltamivir-resistant virus, can be shed for long periods of time in immunocompromised patients, creating significant infection control problems in the hospital and community setting.

If one of the primary aims of treatment is to minimise the possible emergence of oseltamivir resistance and the problems associated with this, then, on balance, the use of oseltamivir is **not** recommended, even to initiate treatment while waiting for confirmation of influenza.

There are therefore two possible options:

1. Use zanamivir in combination with oseltamivir.
2. Use zanamivir as monotherapy.

1. Use of zanamivir in combination with the usual dosage of oseltamivir for ten days:

- It is suggested that there may be a potential additive effect of oseltamivir on susceptible virus that is present, even in infections where the oseltamivir-resistant virus predominates. However, there is no data on the effectiveness of the combination of oseltamivir and zanamivir and there is some data, as yet unpublished, suggesting possible adverse interactions between the two drugs leading to lack of drug efficacy compared to monotherapy.
- There is the possibility that zanamivir-resistant virus might emerge in immunocompromised patients treated with only one drug, while treatment with two antivirals would immediately suppress zanamivir-resistant virus by the action of oseltamivir already present and neither mutation would emerge. However, this is largely theoretical and is modelled on the way that resistance can emerge in the treatment of HIV; reduced zanamivir susceptibility has been detected only very rarely in H1N1 influenza subtypes.

2. Use zanamivir as monotherapy for ten days.

- Probable transmission of oseltamivir-resistant pandemic H1N1 virus to immunocompromised patients has been recorded – possibly because they are more susceptible to infection as a result of their condition.
- Zanamivir would affect both susceptible and resistant viruses.
- There is no information on the effectiveness of the combination of oseltamivir and zanamivir.
- Zanamivir is available for IV use on a named-patient basis (off licence), on a compassionate use basis, and is currently being administered to very ill patients not responding to first line therapy.

The infection control personal/hygiene measures, monitoring of cases and the investigation of cases and contacts described in the section on treatment of immunocompetent patients subheaded 1.1 and 1.2 should be followed.

Note – in immunocompromised patients, virus can be shed for much longer than in immunocompetent patients and therefore control measures and surveillance will need to be in place for longer.

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At the current time, there is no clear evidence to support one option or the other and this is an area where evidence from clinical trials is needed. Until more evidence is available it is recommended that clinicians, in consultation with their local microbiologist/virologist, agree a local policy.

Prophylaxis

If prophylaxis is to be offered to close contacts of confirmed cases of oseltamivir resistance, there is a need to be clear about the policy objective. Is this to implement a form of containment, that is, trying to arrest transmission by offering prophylaxis to a large number of individuals, or is it to mitigate the infection in a high-risk individual by targeting those contacts considered most at risk, for example, immunocompromised individuals?

At the current time we have no evidence that transmission of oseltamivir-resistant virus has occurred outside the two described clusters involving immunocompromised patients; the current emphasis is therefore on mitigating the potential impact on a group of high-risk individuals.

1. Prophylaxis of immunocompetent patients

1.1 Patients with a serious underlying medical condition who are close contacts of a patient with suspected or confirmed pandemic influenza virus

It is recommended that:

- Oseltamivir prophylaxis is used according to current Department of Health guidance².

1.2 Patients with a serious underlying medical condition who are close contacts of a patient with a laboratory proven oseltamivir resistant virus

It is recommended that zanamivir should be used on the basis that:

- Infectious material from a patient with an oseltamivir-resistant virus is likely to have a high percentage of resistant virus against which oseltamivir will have little effect.
- Zanamivir would affect both susceptible and resistant viruses.
- The prophylactic dose of oseltamivir is half that of the treatment dose and oseltamivir resistance is therefore likely to emerge more easily.
- There are documented reports of people on oseltamivir prophylaxis developing resistant virus.

2. Prophylaxis of immunocompromised patients who are close contacts of a patient with suspected or confirmed pandemic influenza virus, regardless of whether the virus is susceptible or resistant

It is recommended that zanamivir should be used on the basis that:

- Oseltamivir resistance is more likely to develop in immunocompromised patients.
- The prophylactic dose of oseltamivir is half that of the

Appendix 1 Adapted from the *WHO Guidelines for pharmacological management of pandemic (H1N1) 2009 influenza and other Influenza viruses* – 20 August 2009

	Pandemic (H1N1) 2009 influenza virus^b	Multiple co-circulating influenza A subtypes or viruses with different antiviral susceptibilities^c	Sporadic zoonotic influenza A viruses, including H5N1
Mild to moderate uncomplicated clinical presentation			
At-risk population	Oseltamivir or zanamivir	Zanamivir, or oseltamivir plus M2 inhibitor (amantadine in the UK)	Oseltamivir or zanamivir
Otherwise healthy ^a	Need not treat	Need not treat	Oseltamivir
Severe or progressive clinical presentation			
At-risk population	Oseltamivir (zanamivir if resistant)	Oseltamivir plus M2 inhibitor (amantadine in the UK), or zanamivir	Oseltamivir plus M2 inhibitor (amantadine in the UK)
Otherwise healthy			

Notes

^a The current UK guidance differs from the WHO guideline, in that oseltamivir is offered to otherwise healthy individuals.

^b The current pandemic H1N1 virus is resistant to amantadine and therefore this drug is not recommended for use.

^c The oseltamivir resistant H1N1 observed in the 2008/09 influenza season was sensitive to amantadine.

² www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/documents/digitalasset/dh_107132.pdf