

Points to Consider: Antiviral Drug Resistance

Introduction

Development of resistance to antimicrobial agents (including antivirals) is considered to be a natural consequence of rapid replication of microorganisms in the presence of a selective pressure. I.e. it is a natural evolutionary event and should be an expected outcome of the use of antimicrobial agents. The speed with which such resistant organisms develop, and their ability to persist in the population, will be influenced by several factors including the extent to which the antimicrobial agent is used, and the viability of the new (mutated) resistant organism.

Microorganisms may also differ naturally in their sensitivity to antimicrobial agents, and the existence of such insensitivity can have an impact on emergence of resistance in two ways. (i) It provides evidence that drug resistant organisms are viable, and could therefore emerge and persist in the population in response to drug use. (ii) Use of antimicrobial agents may create an environment in which pre-existing insensitive strains may have a selective advantage and spread.

Background to drug resistant influenza viruses

1 Adamantanes (amantadine, rimantidine)

The existence of viruses resistant or insensitive to this class of antiviral agent is well documented. Many of the currently circulating strains of virus (both human and animal) lack sensitivity to these agents, and clinical use of amantadine or rimantadine has been shown to select for resistant viruses in a high proportion of cases, and within 2-3 days of starting treatmentⁱ. Such rapid emergence of resistance during treatment may explain the reduced efficacy of rimantidine or amantadine prophylaxis when the index cases were also treatedⁱⁱ.

2 Neuraminidase inhibitors (oseltamivir, zanamivir)

Early laboratory (*in vitro*) studies with neuraminidase inhibitors failed to demonstrate natural insensitivity to these drugs as all strains of influenza A and B tested were sensitive to inhibition of the viral neuraminidase. This included examples of all known influenza A neuraminidase subtypes (N1-9) and viruses of both animal and human origin and over 1000 clinical isolatesⁱⁱⁱ. Drug resistant viruses were selected by laboratory passage (*in vitro*) but these viruses were considered either to be less viable or to show resistance only *in vitro*.

Until recently emergence of resistance to neuraminidase inhibitors following clinical use has occurred only infrequently, though a higher incidence was reported for oseltamivir compared to zanamivir^{iv}. However, more recently a variant of the seasonal H1N1 with a mutation in the neuraminidase gene (H274Y) that confers a high level of resistance to oseltamivir (but not zanamivir) *in vitro* has been detected with increasing frequency and may now form a significant proportion of the currently circulating seasonal H1N1. The spread of this oseltamivir resistant virus appears not to correlate with use of oseltamivir^{vii}.

Considerations for the new Influenza A H1N1

The new influenza A H1N1 of swine origin has been shown in laboratory tests to be sensitive to both oseltamivir and zanamivir and to lack the H274Y neuraminidase mutation, but insensitive to the adamantanes^{vii}. However, two factors need to be taken into account when assessing the risk of emergence of new oseltamivir resistant viruses:

- 1 The prevalence of the H274Y mutation in currently circulating seasonal H1N1 viruses provides evidence that such viruses can be viable
- 2 The high prevalence of seasonal H1N1 viruses containing the mutated NA gene increases the probability that new reassortants could emerge comprising the HA gene from the new virus and the mutated NA gene from current (seasonal) viruses.

Thus, while there is no proof that variants of the new H1N1 virus with either an H274Y mutation, or the NA gene from currently circulating seasonal H1N1 would be viable, it should at this time be recognised as a real possibility.

This does not exclude the possibility that oseltamivir and/or zanamivir resistance could also arise through other mechanisms.

Implications for clinical management and public health measures

To maintain the long term utility of oseltamivir and zanamivir in management of a pandemic, the medicines should be used in a manner which minimises the risk of selection of resistant viruses, where this is possible within national pandemic plans and clinical and public health needs.

Situations which can increase the risk of selection of resistant virus include (but are not limited to):

- Widespread community use of antiviral medicines without substantial clinical benefit (e.g. self limiting mild influenza)
- Therapeutic or prophylactic use of medicines without other infection control measures to limit spread of any virus from treated individuals
- Treatment of individuals with a persistent influenza infection (usually due to some other underlying cause)

Implications for surveillance and research

It is evident from the foregoing that extensive surveillance and monitoring for the emergence of antiviral resistance should be maintained. Systems are already in place, including specific methodology to monitor for the H274Y mutation^{viii}. However, methodologies need to be capable of detecting:

- Mutations on neuraminidase other than the H274Y that could confer resistance to neuraminidase inhibitors
- Reassortants between the current seasonal H1N1 and the new H1N1
- Other mechanisms for changes in drug sensitivity

Formal proof that changes in virus gene sequences or susceptibility *in vitro* lead to a reduction in clinical efficacy will take some time to establish, and appears not yet have been done for the currently circulating H1N1 viruses. However, laboratory data that show presence of known resistance mutations, combined with loss of sensitivity *in vitro*, will almost certainly be widely accepted as an indication that the drug is unlikely to be effective in clinical use.

Laboratories worldwide can be expected to explore the likelihood of emergence of new H1N1 viruses resistance to neuraminidase inhibitors. Such studies may include deliberate creation of reassortants between the current seasonal viruses and the new virus, and the genetic modification of the new virus to insert known mutations such as the H274Y.

ⁱ Hayden and Hay 1992. Emergence and transmission of influenza A viruses resistant to amantadine and rimantidine. *Curr Top Microbiol and Immunol* 176: 119-130

ⁱⁱ Hayden 1994. Amantadine and rimantidine resistance in influenza A viruses. *Curr Opin in Inf Dis* 7:674-677

ⁱⁱⁱ McKimm-Breschkin et al 2003. Neuraminidase sequence analysis and susceptibilities of influenza virus clinical isolates to zanamivir and oseltamivir. *Antimicrobial Agents and Chemotherapy* 47: 2264-2272

^{iv} Moscana 2005. Neuraminidase inhibitors for influenza. *N Eng J Med* 353: 1363-1373

^v Dharan et al 2009. Infections with oseltamivir-resistant influenza A(H1N1) virus in the United States

^{vi} Kramarz et al 2009. Use of oseltamivir in 12 European countries between 2002-2007 – lack of association with the appearance of oseltamivir-resistant influenza H1N1 viruses. *Eurosurveillance* 14: 1-5

^{vii} MMWR April 28 2009: Update, Drug susceptibility of Swine-Origin Influenza A H1N1 Viruses

^{viii} http://www.who.int/csr/resources/publications/swineflu/pyrosequencing_protocol/en/index.html