Influenza virus resistance to oseltamivir: what are the implications?

Douglas M. Fleming1, Alex J. Elliot1, Adam Meijer2, W. John Paget3

Influenza caused by an oseltamivir-resistant influenza A(H1N1) virus was widespread across Europe during the 2007–08 winter.1 About 25% of A(H1N1) viruses tested in the European Influenza Surveillance Scheme (EISS) were resistant with an H274Y mutation in the neuraminidase glycoprotein.1 Early indications during the 2008–09 season are that a large proportion of circulating A(H1N1) viruses have retained oseltamivir resistance, and that the resistant virus will likely become dominant in the United States but not in Europe.2,3 Further analyses have indicated that these oseltamivir-resistant A(H1N1) viruses retain sensitivity to zanamivir and the M2 ion channel inhibitors (M2Is).2

Resistance to anti-influenza drugs

Two classes of drugs are used in the treatment and prevention of influenza: the M2Is (amantadine and rimantadine) targeting influenza A viruses, and the neuraminidase inhibitors (NIls; oseltamivir and zanamivir), which target the neuraminidase of influenza A and B viruses. Widespread resistance to NIls has not been previously observed outside the context of treated persons; a low frequency of oseltamivir resistance was detected in influenza viruses (<0.5%) during 1999–2007.4,5 The natural development of antimicrobial drug resistance under the pressure of exposure is biological and to be expected, however, development of antimicrobial drug resistance under the pressure of exposure is biological and to be expected, however, the mutated A(H1N1) virus has circulated widely in Europe and elsewhere, but seemingly not as a result of treatment in the mutated A(H1N1) virus has circulated widely in Europe and elsewhere, but seemingly not as a result of treatment in the United States but not in Europe.2,3 The natural development of antimicrobial drug resistance under the pressure of exposure is biological and to be expected, however, the mutated A(H1N1) virus has circulated widely in Europe and elsewhere, but seemingly not as a result of treatment in the United States but not in Europe.2,3 Further analyses have indicated that these oseltamivir-resistant A(H1N1) viruses retain sensitivity to zanamivir and the M2 ion channel inhibitors (M2Is).2,5

Implications for treatment

Influenza-like illnesses can be caused by several viruses; management however is based on influenza A and B viruses. Historically, it has been necessary to distinguish between these because the M2Is are not effective against influenza B. It is now necessary to distinguish between the A virus subtypes. Transmissible oseltamivir-resistant virus has only been observed in the A(H1N1) subtype to date, however, phenotypic and genotypic studies have determined molecular markers of resistance to NIls in influenza A (H1N1 and H3N2) and influenza B viruses and therefore the possibility of the emergence of transmissible resistance in other types or subtypes cannot be ignored and perhaps should be assumed.6–8 High-quality virological surveillance of respiratory infections (including antiviral susceptibility monitoring) remains a high priority in guiding management decisions.

The severity of illness associated with A(H1N1) viruses has been less than that associated with A(H3N2) viruses in recent years. Preliminary reports do not suggest unusual disease syndromes associated with resistant A(H1N1) viruses;1,8 two recent fatal oseltamivir-resistant cases occurred in the Netherlands, however, the immunocompromised nature of the patients makes it difficult to interpret the role of the resistance genotype in these fatal episodes.9

Patient management issues

Public health management of influenza is primarily based on an influenza vaccination programme which has been gradually extended in Europe to include more people. Antivirals are essential when circulating and vaccine virus strains are poorly matched. The circulation of transmissible oseltamivir-resistant viruses may well preclude the use of oseltamivir for prophylaxis.

Antiviral drugs must be given early in the treatment of influenza and before any prospect of knowing the sensitivity of the virus. In the absence of resistance, oseltamivir is the most attractive of the three main options (M2Is, zanamivir and oseltamivir) because of its efficacy against influenza A and B, the preferred oral administration, good safety record and minimal side effects. Zanamivir has similar wide efficacy but its presentation as an inhaled powder has limitations.

M2Is by themselves are unlikely to be used in the treatment and prophylaxis of seasonal influenza because of the likelihood of developing resistance and an adverse side effect profile though they may be used in combination with oseltamivir.10 Combination therapy both as treatment and prophylaxis increases problems for compliance especially where side effects are prominent.

The use of drugs in individual patients is determined by physicians: public health management strategies are determined in a wider context where cost effectiveness is an important criterion and where the use of vaccination and drug treatment must be considered as an integrated strategy. In the United Kingdom, the National Institute for Clinical Excellence (NICE) is currently reviewing the use of NI drugs. Previous NICE guidance advising treatment of persons in risk groups and limited prophylaxis in particular target areas has not been widely adopted (www.nice.org.uk). Indeed, over the eight winters 1999–2000 to 2006–07 there were only 5000 treatment courses of NI antivirals dispensed to the population of England (400 million person-years) at a cost to the National Health Service of £108 000 (Prescription Pricing Division, personal communication). The added benefit of NI antivirals seen in persons over 50 years presenting with more severe symptoms might also prompt further consideration of the appropriate use of these drugs.11 Guidance given with a strong emphasis on limiting the use of NI antivirals may have perversely discouraged their use in circumstances where they

1 Birmingham Research Unit of the Royal College of General Practitioners, Birmingham, UK
2 National Institute for Public Health and the Environment, Bilthoven, the Netherlands
3 NIVEL – the Netherlands Institute for Health Services Research, Utrecht, the Netherlands

Correspondence: Douglas M. Fleming, Birmingham Research Unit of the Royal College of General Practitioners, Lordswood House, 54 Lordswood Road, Harborne, Birmingham, B17 9DB, UK, tel: +44 121 426 1125, fax: +44 121 428 2084, e-mail: dfleming@rcgpbhamresunit.nhs.uk

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are specifically recommended. These recent developments highlight the requirement for patient management to be dynamic; patient management guidelines need to be continuously updated and based on the best available information at any particular time.

Implications for global pandemic planning

Oseltamivir has been used extensively in sporadic outbreaks of influenza strains with pandemic potential as an effective control measure. There have been, however, cases of resistance documented during human outbreaks of the H5N1 avian influenza virus, specifically in SE Asia. Global plans for pandemic management have relied heavily on stockpiles of oseltamivir, preferred to zanamivir because of simpler arrangements for product storage and secondary manufacture of a dispensed formulation, and with greater potential for use in children. Certain countries have also acquired stockpiles of M2Is, which is particularly relevant in light of emerging resistance to NIs. Additional antiviral reserve capacity is needed and this is likely to come primarily from zanamivir with the necessary additional costs. In the clinical trials of zanamivir, recruited subjects received training in the use of the inhaler device and this would have repercussions for effective patient management in a pandemic.

These recent developments highlight the requirement for pandemic planning to be dynamic. Plans need to be continuously updated and based on the best available information at any particular time. It is important that (as in many but not in all countries) national pandemic planning committees are established with an ongoing responsibility to update national plans.

New NI drugs (e.g. peramivir) are being evaluated: will the resistance patterns seen in the experimental situation be sufficiently different to the current circulating mutations to give us a real choice in selecting an effective treatment? Drug-resistant viruses are likely to increase our dependence on vaccines for pandemic management. Rapid advances in vaccine development need to be factored into pandemic plans.

Monitoring infrastructure

The emergence of transmissible oseltamivir-resistant viruses in Europe during the 2007–08 season and the recently reported spread of these viruses in the United States emphasizes the importance of global surveillance. The work of the Neuraminidase Inhibitor Susceptibility Network, the European Community Network of Reference Laboratories for Human Influenza (CNRL) project and the work of the general practitioners who collect clinical samples and National Influenza Centres for virological analysis are all necessary and integral parts of surveillance activity. It is vital that this work continues and is further strengthened.

Conflicts of interests: D.M.F. has served on advisory boards to vaccine and antiviral drug manufacturers and received lecture fees and financial support from the pharmaceutical industry to attend conferences related to influenza prevention and treatment. All other authors declare no conflict of interest.

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