



Oseltamivir Resistance — Disabling Our Influenza Defenses

Anne Moscona, M.D.

Related articles, pages 2636 and 2667

As the potential for an influenza pandemic has galvanized the medical community and the public into action, physicians and patients alike have been heartened by the availability of effective

antiviral drugs. The neuraminidase inhibitors provide valuable defenses against pandemic and seasonal influenza, and physicians have been flooded with requests from patients for personal supplies of oseltamivir (Tamiflu). A benefit of having oseltamivir at home is that the sooner the drug is taken after the onset of symptoms, the better its clinical efficacy.¹ And certainly, enabling ill people to stay home and out of waiting rooms and pharmacies should limit the spread of influenza. So it is not surprising that many believe there should be a supply of oseltamivir in every medicine cabinet. This scenario, however, is potentially dangerous. Misuse of the drug could rob us of the ad-

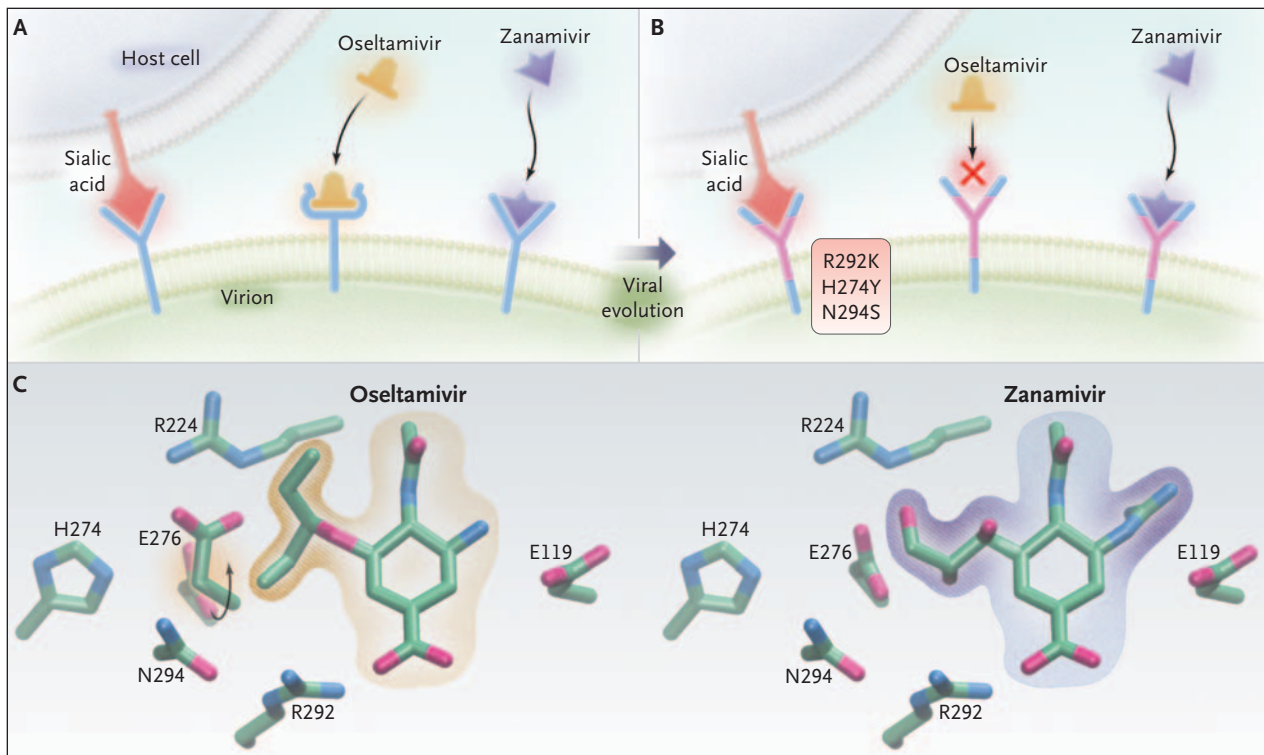
vantages that neuraminidase inhibitors provide, by favoring the emergence of oseltamivir-resistant influenza virus. The potentially serious consequences of oseltamivir resistance in patients with influenza A (H5N1) virus infections is alarmingly underscored by the report by de Jong and colleagues in this issue of the *Journal* (pages 2667–2672).

One strength of the neuraminidase inhibitors oseltamivir and zanamivir (Relenza) over the older adamantanes is that they are less prone to selecting for resistant influenza viruses.² Indeed, no virus resistant to zanamivir, which is currently available only in an inhaled form, has yet been isolated from immunocompetent

patients after treatment. The recent emergence of oseltamivir-resistant variants is therefore a matter of immediate concern.

Why is resistance developing to oseltamivir? Several years ago, structural analysis³ predicted that aspects of the chemical structure of oseltamivir (not present in zanamivir) could facilitate the development of resistance mutations that would permit neuraminidase to function, allowing drug-resistant virus to survive and propagate. This prediction is now being validated by clinical data.

The mechanism of the development of resistance is illustrated in the diagram. The influenza neuraminidase releases newly formed viruses from infected cells, allowing them to spread from cell to cell. The inhibitor molecules mimic the natural substrate of the influenza neuraminidase (the sialic acid receptors) and bind to the active site, preventing neur-



Mechanism of Resistance to Oseltamivir.

The neuraminidase active site changes shape to create a pocket for oseltamivir, whereas it accommodates zanamivir without such a change (Panel A). Any of several mutations may prevent the binding of oseltamivir by preventing the formation of this pocket (Panel B); the oseltamivir-resistant virus can nonetheless bind to the host-cell sialic acid receptor and to zanamivir. The pocket for oseltamivir, illustrated by key amino acids in Panel C, is created by the rotation of E276 and bonding of the amino acid to R224 — events that are prevented by the mutations R292K, N294S, and H274Y and therefore result in resistance to oseltamivir. An E119V mutation may permit the binding of a water molecule in the space created by the smaller valine, also interfering with oseltamivir binding. None of these mutations prevent the binding of zanamivir or of the natural sialic acid substrate.

aminidase from cleaving host-cell receptors and releasing new virus. All the resistant variants thus far have contained specific mutations in the neuraminidase molecule; but since neuraminidase serves an essential purpose, mutations that allow the virus to survive must not inactivate the enzyme.

To accommodate the bulky side chain of oseltamivir in the active site, the neuraminidase molecule must undergo rearrangement to create a pocket (Panel A). Zanamivir, by contrast, binds to the active site without any rearrangement of the molecule. Several mutations that limit the necessary molecular rearrangement may diminish the binding of oseltamivir (Panel B). Molecular-level analysis (Pan-

el C) shows that the amino acid termed E276 must rotate and bond with R224 to form a pocket for the side chain of oseltamivir. The mutations R292K, N294S, and H274Y inhibit this rotation and prevent the pocket from forming, resulting in resistance to oseltamivir. The mutations nonetheless allow the binding of natural sialic acid substrate, so mutated virus can survive and propagate. In contrast, the binding of zanamivir does not require any reorientation of amino acids, so these mutated viruses remain sensitive to that drug. An E119V mutation also interferes only with oseltamivir binding, possibly because a water molecule can fit between oseltamivir and valine at the active

site but cannot insinuate itself between zanamivir and valine at residue 119.

These mechanisms have clinical implications. The mutations identified in the resistant viruses have thus far all been in the amino acids mentioned above. A 2004 study in Japan found that 9 of 50 children with influenza A (H3N2) virus infection who had been treated with oseltamivir (18 percent) had a virus with a drug-resistance mutation in the neuraminidase gene (R292K, N294S, or E119V).¹ A 2000–2001 Japanese study also revealed resistant influenza A (H1N1) viruses with the H274Y mutation in 7 of 43 oseltamivir-treated children (16 percent).⁴

The surprisingly high rate of

emerging resistance in the Japanese studies may have been due to the use of insufficient doses of the drug and resultant failure to eradicate the virus. In both studies, the children were given 2 mg of oseltamivir per kilogram of body weight, and many were very young (75 percent were one to three years of age in the 2004 study, as were 43 percent of those in the 2000–2001 study). Of 147 children in a U.S. trial (including 26 younger than five years) who received the age- and weight-tailored (and therefore sometimes substantially higher) doses that have been approved outside of Japan, none shed resistant virus.¹

It is therefore worrisome that personal stockpiling of oseltamivir is likely to lead to the use of insufficient doses or inadequate courses of therapy. Shortages during a pandemic would inspire sharing of personal supplies, resulting in inadequate treatment. Such undertreatment is of particular concern in children — the main source for the dissemination of influenza within the community, since they usually have higher viral loads than adults and excrete infectious virus for longer periods. The habit of stopping treatment prematurely when symptoms resolve (a well-established tendency with antibiotic therapy) could also lead to suboptimal treatment of influenza and promote the development of drug resistance.

Could drug-resistant viruses then spread? Although many oseltamivir-resistant (non-H5N1) viruses that have been studied in animals have compromised biologic fitness, some resistant variants have been transmitted among ferrets, arousing concern about transmissibility among humans.⁵ In fact, according to recent data collected in Japan by the Neur-

aminidase Inhibitor Susceptibility Network, 3 of 1200 isolates from ill patients without known exposure to neuraminidase inhibitors contained resistance mutations, suggesting that these resistant viruses are transmitted at least at a low level in humans and are not severely biologically compromised.

There have now been several reports that oseltamivir-resistant influenza A (H5N1) viruses with the H274Y mutation have been isolated from humans with avian influenza infection who were treated with oseltamivir.⁴ The cases described by de Jong et al. raise the worrisome prospect that even with therapeutic doses, oseltamivir resistance may develop during the course of illness and may affect clinical outcomes. Nothing is yet known about the transmissibility of oseltamivir-resistant influenza A (H5N1) viruses in humans, and it will be important to study these isolates in animals to determine how the H274Y mutation affects virulence, pathogenicity, and transmissibility.

There is much to be learned about the clinical and virologic course of H5N1 infection in humans, as well as the response to therapy and the development of resistance. We know that the virus may have a longer incubation period than other influenza viruses, potentially increasing the period of transmissibility before symptoms appear, and that the virus frequently leads to fulminant lower respiratory tract infection.⁴ Interventions of any kind have failed when initiated late in the course of illness, but early therapy with neuraminidase inhibitors is probably beneficial; the cases reported by de Jong et al. suggest that even therapy initiated later in the illness may limit ongoing viral replication. H5N1 virus infec-

tions may require higher doses of oseltamivir for longer periods than do other types of influenza.⁵ Indeed, it is becoming clear that more medication than the currently recommended doses may be required for adequate treatment. If so, treatment with the current doses could not only fail but also select for resistant influenza A (H5N1) viruses.

Like any successful infectious agent, influenza virus will most likely evolve to evade any single drug. By targeting several points in the viral life cycle simultaneously with different drugs, we are more likely to discourage the emergence of viruses that can resist all drugs at once. But we currently rely solely on the neuraminidase inhibitors — and solely on oseltamivir in many situations, such as in patients who cannot use inhaled medication or in patients infected with H5N1 virus, in whom systemic drug levels may be important. We must not abrogate the usefulness of these drugs by exposing circulating influenza to them in such a way as to facilitate the selection of resistant viruses. The study by de Jong et al. confirms that oseltamivir-resistant H5N1 virus is now a reality. The need to learn more about how and when resistance to the neuraminidase inhibitors develops, while we focus on the development of new antiviral drugs, is pressing. This frightening report should inspire us to devise pandemic strategies that do not favor the development of oseltamivir-resistant strains. Improper use of personal stockpiles of oseltamivir may promote resistance, thereby lessening the usefulness of our frontline defense against influenza, and should be strongly discouraged.

An interview with Dr. Moscona can be heard at www.nejm.org.

Dr. Moscona is a professor in the Departments of Pediatrics and Microbiology and Immunology at Weill Medical College of Cornell University, New York.

1. Moscona A. Neuraminidase inhibitors for influenza. *N Engl J Med* 2005;353:1363-73.
2. Bright RA, Medina MJ, Xu X, et al. Incidence of adamantane resistance among in-

fluenza A (H3N2) viruses isolated worldwide from 1994 to 2005: a cause for concern. *Lancet* 2005;366:1175-81.

3. Varghese JN, Smith PW, Sollis SL, et al. Drug design against a shifting target: a structural basis for resistance to inhibitors in a variant of influenza virus neuraminidase. *Structure* 1998;6:735-46.
4. The Writing Committee of the World Health

Organization (WHO) Consultation on Human Influenza A/H5. Avian influenza A (H5N1) infection in humans. *N Engl J Med* 2005;353:1374-85.

5. McKimm-Breschkin JL. Management of influenza virus infections with neuraminidase inhibitors: detection, incidence, and implications of drug resistance. *Treat Respir Med* 2005;4:107-16.

The Run on Tamiflu — Should Physicians Prescribe on Demand?

Allan S. Brett, M.D., and Abigail Zuger, M.D.

Related articles, pages 2633 and 2667

“Doctor, I need a prescription for that bird flu drug.” If recent newspaper headlines are any indication,¹ this request has been repeated tens of thousands of times around the country this fall. So much oseltamivir (Tamiflu) has been prescribed — presumably for personal stockpiling in case of an avian influenza pandemic, given that the human influenza season has not yet begun — that at the end of October, the drug’s manufacturer stopped shipping it to the United States.

A busy outpatient office is no place to think through complicated ethical dilemmas. But a request for oseltamivir is just that, and it must be examined from both the perspective of individual patient–physician encounters and that of public health. From the first perspective, such requests raise a more general question: What is the physician’s obligation to grant patients’ requests for specific interventions? As an outgrowth of the patient-autonomy movement, patients’ preferences have come to play an important role in clinical decision making. It is widely accepted that, in nearly all clinical circumstances, patients may refuse unwanted interventions proposed by physicians. Less straightforward, however, are clinical encounters in which patients insist on inter-

ventions that are deemed inappropriate by physicians. These encounters have been discussed both in the context of common problems in primary care (e.g., when patients demand antibiotics for viral infections) and in the context of life-sustaining treatment near the end of life (in cases in which physicians have deemed further treatment to be futile). The literature on ethics in the clinical setting and professional guidelines generally support the conclusion that physicians are not obligated to honor requests for nonbeneficial tests and treatments — although what should count as nonbeneficial or inappropriate may remain problematic.

Physicians are trained and licensed to practice medicine according to scientific evidence and professional standards. When there is at least a modicum of benefit from the perspective of conventional medicine, physicians should generally defer to patients’ requests, and a patient’s weighing of benefits and harms should drive the decision. But if a patient requests an intervention that falls outside the boundaries established by scientific evidence, a physician is not obligated to provide it.

In the case of avian influenza, a human outbreak in any given geographic area is currently a purely hypothetical concern; physicians

are not required to dispense medications for hypothetical scenarios when it is not yet possible to determine who is at risk. If a human outbreak occurred, it is unclear whether the virus would be generally susceptible to oseltamivir and whether this drug would still be the treatment of choice. Moreover, in an epidemic, any indicated drug could be used in several different ways — for preexposure prophylaxis, postexposure prophylaxis, or treatment after symptoms have appeared. If oseltamivir were dispensed well in advance of an outbreak, patients would probably use their stockpiles in a chaotic fashion, rather than optimally for any of these indications. Indeed, some or most of it would no doubt be wasted on viral illnesses other than influenza.

From the perspective of the individual patient–physician encounter, these factors suggest that physicians have no obligation to prescribe oseltamivir to patients who request it for a hypothetical outbreak of avian influenza: the threshold for a modicum of benefit has not been reached. The relative lack of side effects does not constitute a sufficient reason for prescribing oseltamivir.

From a public health perspective, preventive or therapeutic interventions should be optimally