

For lay readers as well as physicians

Experts Opinion on Frequently Asked Questions about Oseltamivir Resistance:

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Dr Aoki has participated in clinical trials on oseltamivir for Hoffmann-La Roche and zanamivir for GSK and has served on advisory boards concerning these drugs for their manufacturers.

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Dr. Low has received research funds from Hoffmann-La Roche Limited (Canada) as well as speaker or consultation fees

Dr McGeer had received investigator initiated grants from Hoffmann-La Roche and GlaxoSmithKline, and has been part of speaker's bureau for Gilead Biosciences and GSK.

Dr. Stiver has received honoraria from Hoffmann-La Roche (Canada) for participation on advisory boards, and as a speaker.

General virology questions about resistance

1) What is antiviral resistance (AV-R)?

The term AV-R describes the phenomenon whereby a virus continues to replicate and cause disease in a patient despite the administration of doses of drug that are normally effective for treatment. Antiviral resistance can emerge during treatment if single step mutations are all that are required (drug induced) or can occur because a resistant virus is transmitted from one person to another in the absence of antiviral pressure (constitutive, or naturally occurring).

The presence of a resistant virus does not mean that the clinical outcome will be more severe. Virulence (how likely the virus is to make a person seriously ill if they become infected) is a viral characteristic that does not appear to be linked to antiviral resistance at all.

An example of AV-R of contemporary relevance is the observation of widespread resistance to oseltamivir (Tamiflu®) of one strain (or clade) of the type of influenza A virus called H1N1. The resistant mechanism is due to a mutation in the structure of the N1. Specifically, nucleotide changes in the N1 gene have resulted in a histidine (H) becoming a tyrosine (Y) at amino acid position number 274 in the neuraminidase. This mutation, which results in oseltamivir resistance, is referred to in molecular terms as H274Y (N2 numbering).

2) How can we explain the emergence of oseltamivir resistance? Did it develop because of overuse or inappropriate use of oseltamivir?

In the history of medicine, bacteria and viruses have often acquired resistance to the antibacterial drugs (often called antibiotics, like penicillin) and antiviral drugs, respectively. This usually occurs in direct relation to the frequency of their use to treat patients (so called “drug-pressure”), particularly when suboptimal doses lead to low drug concentrations in tissue (subinhibitory levels).

Oseltamivir resistance does emerge in treated patients, but it does not occur commonly, and, until this year, resistant viruses have never been passed from person to person. This is because oseltamivir resistant strains that have emerged as a result of oseltamivir treatment of patients are not fit; that is, they are less able to infect new human cells. Data from resistance surveillance studies showed a consistently very low prevalence ($\leq 0.5\%$) of oseltamivir resistance in community isolates collected globally between 2001 and 2007.

However, in 2007-2008, we witnessed the very rapid emergence of oseltamivir resistance in influenza A (H1N1) viruses. Within 9 months, almost 100% of the circulating H1N1 influenza A viruses were resistant to oseltamivir. Oseltamivir has not been widely used, and resistance appeared equally quickly in countries using very little oseltamivir (for instance, Norway), and those using much more (for instance, Japan), so “drug-pressure” does not appear to be an explanation for this phenomenon or its dissemination. The cause remains to be determined; however, it is thought to be the result of mutations in other sites of the N1 protein or elsewhere in the genome that occurred as the influenza virus evolves to evade the human immune system. Influenza viruses must continuously evolve, so that they can continue to infect people – this

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ongoing change is why we must update the influenza vaccine every year. In this case, those initial mutations in the N1 protein could have made the virus less fit and able to infect new cells. A further mutation was able to restore the viruses this fitness; unfortunately this mutation was an H274Y mutation, thus, by happenstance, was able to confer resistance to oseltamivir. Therefore, as immunity develops in the population worldwide, it is possible that the specific viral strain containing the resistance mutation could disappear as suddenly as it emerged.

3) Is oseltamivir resistance a new phenomenon?

Oseltamivir resistance was not demonstrated in influenza viruses before oseltamivir was administered to patients. It did begin to appear at low levels (generally in less than 4% of viruses) worldwide following the advent of oseltamivir treatment. However, in young children or patients with severe immune deficiency (eg. post stem cell transplant) oseltamivir treatment has been associated more commonly with the emergence of drug-resistant viruses. The widespread appearance of resistance in A(H1N1) viruses in 2008, in patients who had not been treated with oseltamivir is both new and concerning.

4) Is there a difference between antibiotic resistance and antiviral resistance?

Generally, resistance to antibacterials and antivirals are the same: they both usually arise because of use of the drugs to treat microorganisms; they do not alter virulence of microorganisms, but they mean that treated patients do not respond to treatment as they would if their microorganism was susceptible.

There is, however, one noteworthy difference. Antiviral agents are generally specific to one or a small group of viruses, while most antibacterials are active against many different kinds of bacteria. Antivirals active against influenza are only effective against influenza viruses. Thus, treatment of a patient with suspected influenza with an anti-influenza drug who in fact has a different infection will not apply any drug pressure, because no influenza viruses are exposed to the drug. That is very different from the situation with antibacterial drugs. Whenever an antibacterial drug is used, the antibacterial will produce drug pressure not only on the bacterium causing the infection (whatever it is), but also on all of the other bacteria colonizing the person. In addition, when susceptible colonizing bacteria are killed, resistant bacteria to which the patient is exposed may take their place.

Surveillance and detection of antiviral resistance

5) How is antiviral resistance measured/detected in laboratories?

AV-R is detected in different ways. One method involves growing the virus from specimens (usually nasal, nasopharyngeal or throat swabs) taken from infected patients and then determining whether the virus grows in cell cultures in the presence of the usual drug concentrations attained in patients. Viruses that can replicate in such a test are 'resistant'. Another method which is used to detect oseltamivir resistance depends upon analysis of the gene sequences of the virus. Oseltamivir resistance is associated with a specific unique genetic mutation (called H274Y) in the neuraminidase gene. Identification of this mutation then identifies that virus as having oseltamivir resistance.

6) What is being done to monitor antiviral resistance in Canada and elsewhere?

In Canada, as in many other countries, formal plans are in place to monitor the susceptibility of influenza virions in a timely manner. In Canada, the National Microbiology Laboratory (NML), some provincial public health laboratories, and some viral research laboratories are able to test influenza isolates for antiviral resistance. Collation of Canadian data is performed by the Centre for Immunization & Respiratory Infectious Diseases at the Public Health Agency of Canada (PHAC). Data about resistance testing at the NML are published weekly on the Fluwatch website (<http://www.phac-aspc.gc.ca/fluwatch/index.html>)

7) Has resistance to oseltamivir been reported in Canada this flu season? Is the situation different in other countries?

As of May 2, 2009 the overall seasonal influenza activity in Canada is declining. The season appears to be have been dominated by influenza B viruses, which represent 58% of the influenza viruses that have been antigenically characterized by the National Microbiology Laboratory (NML). A /H1N1 and A /H3N2 viruses represent 25% and 17% of the circulating strains, respectively. Since the start of the season all the A/H3N2 and B isolates tested have been sensitive to oseltamivir, whereas all of the A/H1N1 isolates tested have been resistant to oseltamivir due to the H274Y mutation. All of the H1N1 isolates were susceptible, but all of the A/H3N2 isolates were resistant to amantadine (note that influenza B isolates are always amantadine resistant). All of the influenza isolates (A/H1N1, A/H3N2 & B) tested to date are sensitive to zanamivir.

The current picture of influenza activity in Europe contrasts with the Canadian situation since influenza A/H3N2 has been the dominant virus in Europe, accounting for an estimated 69% of total virus detections this season. (Source : European Influenza Surveillance Scheme, http://www.eiss.org/cgi-files/bulletin_v2.cgi). In the US, the majority of the seasonal influenza viruses antigenically characterized are of the seasonal strain A/H1N1 (Source: <http://www.cdc.gov/flu/weekly/>).

In both Europe and in the US, the resistance pattern of antivirals observed reflects closely the situation in Canada. That is, all A/H3N2 and B isolates tested are sensitive to oseltamivir, whereas almost 100% of the A/H1N1 isolates tested are resistant to oseltamivir. The majority of

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This pattern of resistance is what is being reported from most of the world. However, A(H1N1) isolates from China this year (2008/9) appear to be different, with only 3/23 (14%) being resistant to oseltamivir

(http://www.who.int/csr/disease/influenza/H1N1webupdate20090318%20ed_ns.pdf).

Impact of antiviral resistance on the prevention and treatment of seasonal influenza

8) Can oseltamivir still be used to treat or prevent seasonal influenza? What about other antivirals? Are they still effective against the influenza virus resistant to oseltamivir?

Oseltamivir, zanamivir and amantadine are the three anti-influenza drugs available in Canada. To date, all isolates of influenza are susceptible to at least one of these medications. As resistance is evolving, recommendations on the use of antivirals for seasonal influenza require frequent updating.

AMMI Canada has published general guidelines for the use of antivirals to prevent and treat influenza (AMMI Canada Position Paper, Can J Infect Dis 2006; 17 (5): 273-284; available at <http://www.cps.ca/english/statements/ID/ID06-04.pdf>). The Infectious Disease Society of America (IDSA) is expected to publish guidelines for the diagnosis, treatment and prevention of influenza in the second quarter of 2009.

For seasonal influenza management, health care practitioners considering using antivirals in the treatment of patients should also regularly review public health updates to determine the likelihood of type (A or B) or subtype-specific (A/H1N1, A/H3N2) influenza illness in their area. Clinicians should be alert for changes relevant to antiviral options throughout the season and consult public health as needed.

The CDC in the US has recently issued updated interim guidance for the use of antiviral medications during the 2008-09 influenza season

(<http://www.cdc.gov/flu/professionals/antivirals/index.htm>)

It includes different options for antiviral treatment of seasonal influenza depending on whether influenza A/H1N1 virus infection suspected. This guidance may change as more information becomes available.

In Canada, British Columbia (BC) and Saskatchewan have published similar guidelines (BC interim guidelines available at

http://www.bccdc.org/downloads/pdf/epid/reports/BC_Interim_Antiviral_Treatment_Guidelines_Influenza.pdf and Saskatchewan guidelines available at:

<http://www.health.gov.sk.ca/Default.aspx?DN=a46930ae-5e6f-452a-b8e5-f98ddd540ab6>)

The choice of antiviral depends on how likely it is that the influenza infection is due to A(H1N1) vs. A(H3N2) or B, and whether or not zanamivir (an inhaled powder) can effectively be administered. For seriously ill patients in whom influenza A(H1N1) is suspected based on local influenza activity and the age of the patient, either zanamivir, or combination amantadine and oseltamivir are recommended.

9) Does oseltamivir resistance change the effectiveness of the seasonal flu vaccine?

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No - Influenza AV-R does not impair the ability of the vaccine containing that strain to confer protection on the recipient. The A(H1N1) strain that is oseltamivir resistant is well-matched to this year's vaccine...another good reason to be immunized.

10) Is the illness caused by the influenza virus resistant to oseltamivir (H1N1) worse than the flu caused by any other sensitive strain?

Although no controlled studies are available, the illness caused by AV-R viruses does not appear to be either more or less severe than that caused by AV-susceptible strains of the same virus. A recent retrospective study has shown no differences in severity between resistant and susceptible strains in Norway during the 2008 season (Hauge and al., Emerg Infect Dis, Feb 2009). In this study, it was noted that 2/69 (2.9%) patients with susceptible H1N1 infection in Norway, developed pneumonia, compared to 14/153 (9.2%) with oseltamivir resistant H1N1 infections. However, the number of total cases was small and the confidence intervals overlapped 1.0. In addition, patients with resistant isolates were significantly older and more likely to have underlying chronic disease than those with susceptible isolates, which may explain why they were more likely to have complicated disease.

11) Is the resistant virus more easily transmitted?

As noted above, oseltamivir-resistant strains that have emerged as a result of drug pressure have been found to be less transmissible (less fit) and therefore have not disseminated. However, the new clade (strain) of A(H1N1) that is oseltamivir resistant appears to spread just as well as other successful influenza viruses. It does not appear to be more likely to cause outbreaks or transmission to people in close contact, although data are still limited.

12) Is the oseltamivir resistant strain likely to disappear or to continue to predominate in the future?

As it is unclear what the determinants are for the appearance and persistence of AV-R strains, we cannot predict the future. Usually, new clades of A(H1N1) circulate for a few years, so that we can expect this resistant clade to be around for another 2-3 years. Also, the AV-R H1N1 virus may disappear as suddenly and completely as it appeared in 2008 since all of the oseltamivir resistant strains with the H274Y mutation belong to one clone (clade 2b). It is, however, impossible to predict whether the next successful clade of A(H1N1) will be resistant or susceptible to oseltamivir. Only time will tell.

Impact of antiviral resistance on pandemic preparedness

13) Does the emergence of resistance in current H1N1 strains mean that the virus causing the next pandemic is more likely to be oseltamivir resistant?

Inasmuch as we have an incomplete understanding of how oseltamivir resistance originated and became widespread, we are not able to predict whether this resistance will arise again in a similar fashion, or be passed to other influenza viruses.

There are several reasons to think that this is unlikely. A pandemic strain could in theory “recombine” with an H1N1 strain and acquire the N1 gene. However, in this case, there would be a high level of community immunity to the N1 protein, and the resulting pandemic would likely be mild. However, we don’t know that the current N1 with the H274Y mutation would be compatible with the pandemic strain’s genetic background. Similarly, we don’t know what kind of evolutionary pressure resulted in oseltamivir resistance in the N1 protein so we cannot predict its appearance in other neuraminidase proteins. There is some reason to believe that N1 proteins acquire the H274Y change more easily than other types of neuraminidase, giving hope that oseltamivir resistance will be less likely in other types of influenza.

14) Could H1N1 become a pandemic strain?

No. Influenza A(H1N1) strains have been causing illness globally for many years. As a result, many individuals have been infected with one or more strains of A(H1N1) and are either immune or partially immune to newly evolved strains. Accordingly, worldwide susceptibility to A(H1N1) doesn’t exist, precluding H1N1 becoming a pandemic virus.

15) What are the implications for the antivirals stockpiled as part as Canada’s pandemic plan?

Antiviral drugs, including oseltamivir, are one component of a multi-faceted approach to pandemic preparedness planning and response. The effectiveness of any drug during a pandemic is difficult to predict, as it is not possible to know which virus will cause the next pandemic. Since A(H1N1) will not be the cause of the next pandemic, there is no direct implication. Obviously, resistance to any antiviral may develop over time; however, resistance in current seasonal strains does not predict what resistance will occur during the next pandemic. Most countries with antiviral stockpiles have stockpiled both oseltamivir and zanamivir, another antiviral with a different resistance pattern.

16) Have any recommendations on the use of antivirals for human avian or pandemic influenza changed as a result of this unexpected resistance?

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At this time, oseltamivir remains the drug recommended by the World Health Organization as the first-line influenza antiviral drug for the treatment of patients infected with the avian influenza A/H5N1. A/H5N1 strains remain susceptible to oseltamivir.

17) Will widespread use of oseltamivir increase resistance?

It seems unlikely that widespread use of oseltamivir will contribute to a large increase in the prevalence of oseltamivir resistance in influenza viruses other than H1N1. To date, oseltamivir resistant strains that have emerged as a result of drug pressure are not fit and have not disseminated. Use of oseltamivir may increase the risk of resistance in the future; however, it will also prevent deaths and morbidity in those treated now. As with all antibacterials and antivirals, it is important to use oseltamivir appropriately.

18) Has antiviral resistance been observed in H5N1 viruses?

A total of 188 patients infected with H5N1 virus have been treated with oseltamivir. Oseltamivir treatment provided a significant survival benefit as compared to no treatment despite delayed treatment in many cases. Early treatment was associated with highest treatment benefit. To date, the selection of oseltamivir resistant H5N1 variants in patients treated with oseltamivir has been reported in three cases. In one case, the prophylactic dose (75 mg QD) rather than the treatment dose (75 mg BID) was given to a patient already exhibiting clinical symptoms, thus underdosing the patient and increasing the risk of resistance selection. In the other two cases the recommended dosing regimen was administered. However, whereas 1 patient received treatment on day 2 of illness, the other patient started treatment on day 6. Sequence analysis revealed the presence of the H274Y mutation in the N1 neuraminidase in all three cases.

Additional questions about the novel H1N1 influenza ('flu') virus

19) Is the newly emerged H1N1 flu virus (human swine flu) virus sensitive to antivirals?

Both the United States centers for Disease Control (CDC) and the World Health Organization (WHO) have confirmed that the H1N1 flu virus (human swine flu) is susceptible to the neuraminidase inhibitor antivirals (oseltamivir and zanamivir); the virus is resistant to the other class of antivirals, the M2 Inhibitors (or 'adamantanes') which includes amantadine and rimantadine.

20) How can we explain the difference in resistance profile between the seasonal A/H1N1 virus strain circulating during the regular influenza season (oseltamivir-resistant) and the newly emerged swine-origin A/H1N1 virus (oseltamivir-sensitive)?

The new swine-origin A/H1N1/California/04/2009-like influenza virus strain currently causing outbreaks around the world represents an entirely new group of A/H1N1 viruses with different antigenic and virologic characteristics as compared to the seasonal A/H1N1 virus currently circulating and causing seasonal flu (A/H1N1/Brisbane/59/2007).

In particular, the new swine-origin flu virus does not carry the H274Y resistance mutation in neuraminidase, and is therefore sensitive to oseltamivir. In contrast, it does possess the mutation in the M2 gene that confer resistance to amantadine and rimantadine.

21) What are the implications for treatment decisions?

Both zanamivir and oseltamivir are now recommended by the Public Health Agency of Canada (http://www.phac-aspc.gc.ca/alert-alerte/swine_200904-eng.php) and the US CDC (<http://www.cdc.gov/h1n1flu/>) for management of patients infected with the new swine-origin A/H1N1 influenza virus.

Treatment guidelines may change as more information on antiviral susceptibilities become available.

Can we expect that an increase use of oseltamivir could trigger the development of resistance to oseltamivir in the new virus?

The World Health Organization operates an extensive surveillance system monitoring influenza outbreaks for the emergence of new strains and possible antiviral resistance. So far no resistance to oseltamivir has been found in the new A/H1N1 influenza virus from clinical cases.

The risk of drug-induced resistance selection depends on a number of factors that may be different between subgroups of H1N1 influenza viruses, including virus replication capacity and viral load, neuraminidase activity, replication capacity of the drug induced resistant virus variant and duration of virus shedding. When data related to these factors become available for the new H1N1 flu virus, they will allow an improved estimate of resistance selection risk during antiviral treatment of infections due to this virus.

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No resistance selection has been observed in prophylaxis studies with oseltamivir to date. Oseltamivir only shows activity against the influenza virus and, therefore, there is no pressure to drive resistance if it is given to someone who has not been infected or someone with a different type of infection.