

Press Release

22 January 2007

Tamiflu resistance found in Egypt patients

Headline: Genetic mutation reducing the effectiveness of oseltamivir has been discovered in two H5N1 patients in Egypt.

Summary: Genetic analyses of viruses isolated from two patients who died from H5N1 last month in Egypt have found a mutation which suggests the effectiveness of the antiviral, oseltamivir, also known as Tamiflu, may be reduced. This genetic change is not well characterized in terms of how much it may reduce the clinical effectiveness of oseltamivir. However, the current understanding suggests the reduction is less than for some other, better known genetic changes associated with antiviral resistance. It is unclear if the oseltamivir resistance developed after the patients were treated with the drug or if they were infected with a naturally occurring strain which carried the mutation. Investigations are ongoing and assessment is incomplete at this point.

Background:

- The two patients -- a 16-yo female and a 26-yo male -- were uncle and niece.
- The 16 years old (yo) was admitted Zefta H5N1 referral hospital on 19 December 2006, preceded by her uncle (26 yo) on the 17th of December along with another relative -- 35 yo female, the sister of the 26 yo male. (This person has not been laboratory confirmed but is viewed by MOHP as positive based on exposure history and clinical course.)
- All three patients had lived together in the same house.
- The family had a duck die off on the 11th and 12th of December and the rest were slaughtered on the 13th and 14th. All three patients participated in the slaughtering.
- All were started on Tamiflu on 21 December
- All were placed on mechanical ventilation on 23 December
- Also on 23 December, samples were taken from the three
- All three patients died -- 35 yo on 24 December; 16 yo on 25 December; and 26 yo on 28 December.
- Genetic analysis was conducted both in Egypt and at the US CDC
- A mutation, known as N294S mutation has been confirmed in both patients by both NAMRU III and US CDC.
- This is not a new mutation. It has been found, and the data published, in a patient given oseltamivir in Vietnam (Le at al., Nature 437, 1108, 2005)
- It has been determined that samples from the two Egyptian patients are sensitive to the antiviral zanamivir
- CDC received samples on January 8, afternoon. On January 10, two of three were positive for influenza A (H5N1) in the real-time PCR typing-subtyping test. The NA and M gene sequencing of two positive isolates was conducted on January 12. The neuraminidase-inhibition assay was performed on January 16.

Current key messages:

- Assessment of the information is still ongoing, and incomplete at this time.
- H5N1 constantly mutates
- It is through sensitive surveillance that this mutation was discovered.
- The mutation has NOT produced a human pandemic strain. There is no indication of increased transmissibility with this virus.
- The WHO Pandemic Alert Level remains at 3, and there is no suggestion that it will be changed.
- Tamiflu effectiveness may have been diminished in these two patients.
- Mutation in the viruses of these two patients cannot be extrapolated to mean that Tamiflu has lost its effectiveness in other patients in Egypt or elsewhere. It has not.
- This is the first time two related patients have shown this resistant virus
- Even the Egyptian viruses tested are still vulnerable to other antivirals.
- The question is as yet unanswered as to whether the mutation arose in response to treatment or the mutation existed in an animal prior to the human infections.

Additional messages:

- The N294S mutation has been determined in experiments in vitro and in animals to moderately reduce the effectiveness of oseltamivir in laboratory testing less than some other genetic mutations but the clinical reduction in people is not certain.
- Even the virus with the mutation is vulnerable to the antiviral zanamivir amantadine and rimantadine..
- N294S mutation has been shown to have no effect on transmission of viruses in one reverse genetics study at St. Jude.
- N294S mutation has been seen previously and published in Vietnam patient (need reference: Le et al., Nature 437, 1108, 2005).
- The mutation has been seen in animals before. There are two H5N1 sequences available from GenBank from Asian ducks in 2001 and 2002 that have shown this N294S mutation.
- NA sequences done by NAMRU 3 are to be published on GenBank on Jan 23rd.
- In vitro neuraminidase inhibition studies indicate roughly 10 fold difference in sensitivity of isolates from 26 y.o. and 16 y.o. patients when compared with a sensitive control isolate A/Egret//Egypt/06. The latter virus was used because it has the closest NA sequence to those from humans. Experts consider the isolates as moderately resistant to Oseltamivir.

Long term messages:

- WHO does not have any reason to alter its recommendations about the value of oseltamivir, based on two patients, both under treatment with the drug.
- WHO encourages that samples be taken from animals in the area around the patients' home and examined for the mutation.
- WHO urges treating physicians to consider combination therapy for patients in this area.