

Invited Article

Oseltamivir resistance in swine influenza: a brief discussion

Viroj Wiwanitkit

Wiwanitkit House, Bangkhae, Bangkok Thailand.

Swine flu, an atypical H1N1 influenza virus infection, is a new emerging infectious disease starting from Mexico in 2009, and is presently pandemic around the world. For treatment of this infection, oseltamivir is recommended as drug of choice. Generally, a big problem for using oseltamivir in treatment of classical H1N1 influenza virus infection is drug resistance. In this brief paper, the author discusses on the situation of oseltamivir resistance in swine influenza. Briefly, the oseltamivir resistance of swine flu is expected to be possible due to many underlying factors. It is needed to perform surveillance on oseltamivir resistance in swine flu. Planning for management of case of emerging oseltamivir drug resistance is needed. (Wiwanitkit V. Oseltamivir resistance in swine influenza: a brief discussion. *North Am J Med Sci* 2009; 1: 96-98).

Keywords: H1N1; Swine flu; oseltamivir; influenza; virus infection; resistance

Correspondence to: Professor Viroj Wiwanitkit, Wiwanitkit House, Bangkhae, Bangkok Thailand 10160. Tel.: 6624132436. Email: wviroj@yahoo.com

Introduction

Influenza virus infection is classified as a common respiratory tract infection. Recently, atypical influenza virus infection became the global threaten. In early 2009, swine, atypical H1N1 influenza virus infection, originated in Mexico and spread to many countries around the world. This new atypical virus is the product of natural genetic reassortment of influenza virus from human beings, swine and bird [1]. At present, World Health Organization already documents for level VI, the highest level, and precaution for this new disease indicating for its worldwide pandemic situation. The present focus of medical scientists is how to control this new emerging disease. Also, for the infected cases, searching for the best treatment protocol is the focus

of physicians around the world. Generally, there are some specific drugs indicating for treatment of classical influenza. Oseltamivir and zanamivir are the two drugs that are confirmed for its present usefulness in treatment of classical H1N1 influenza virus infection. Oseltamivir, an oral antiviral drug, is presently recommended for treatment of swine flu. Here, the author discusses on the problem of usage of oseltamivir in the new pandemic influenza infection, drug resistance.

Table 1 Recommended dosage of oseltamivir and zanamivir in treatment and prevention for swine flu (according to the WHO recommendation)

Drugs	Treatment	Prevention
Oseltamivir	(> 10 years) 75 mg bid x 5 days	(> 10 years) 75 mg od x 10 days*
	(6 - 9 years) 60 mg bid x 5 days	(6 - 9 years) 60 mg od x 10 days*
	(3 - 5 years) 45 mg bid x 5 days	(3 - 5 years) 45 mg od x 10 days*
	(1 -2 years) 30 mg bid x 5 days	(1 -2 years) 30 mg od x 10 days*
	(6 - 11 months) 25 mg bid x 5 days	(6 - 11 months) 25 mg od x 10 days*
	(3 - 5 months) 20 mg bid x 5 days	(3 - 5 months) 20 mg od x 10 days*
Zanamivir	(< 3 months) 12 mg bid x 5 days	(< 3 months) 12 mg od x 10 days*
	(> 7 years) 10 mg bid x 15 days	(> 7 years) 10 mg od x 10 days**
		(> 7 years) 10 mg od x 28 days***

* Either in cases with closed contact to the patients or in pandemic period; ** in cases with closed contact to the patients; *** in pandemic period.

Efficacy of oseltamivir in swine influenza

Since the starting of the pandemic situation of swine flu, oseltamivir has been recommended and used as the first line

antiviral drug. No doubt that oseltamivir has a good efficacy in treatment. According to the recent publication in New England Journal of Medicine, the clinical usefulness of

oseltamivir in treatment of swine flu can be confirmed [1]. Several publications also confirm the effectiveness of oseltamivir in treating swine flu [2–5]. The main question is why oseltamivir, which is primarily designed for classical influenza treatment, is still effective for treatment of swine flu. There are some reports explaining this query in view of molecular phenomenon. First, swine flu and classical influenza are still within the group of H1N1 influenza virus infection. The two pathogens have no significant difference in oseltamivir receptor. The similarity of the drug receptors between the two influenza infections are already confirmed in some recent publications [6–8]. The preserved drug receptor area is the main reason for retained susceptibility to oseltamivir in swine influenza [6–8]. However, the mutation in swine influenza still makes the change in required drug-viral interaction energy that will bring decreased efficacy in treatment [5].

Oseltamivir resistance in swine influenza

It is the present focus for clinical observation on oseltamivir resistance in swine influenza. In USA, oseltamivir is still confirmed for no drug resistance in the report from disease surveillances [9]. However, this does not mean that there will be no drug resistance. This observation is also similar in other countries [9 - 10]. If there is a significant mutation or genetic drift, the present oseltamivir will be useless. For classical influenza, the oseltamivir is already documented for drug resistance [11 – 13]. The problem is usually due to inappropriate use of antiviral drug, in cases without indication. This can also be expected in case of swine influenza. In addition, in case of pandemic situation, the new variant that is highly resistant to oseltamivir can be expected.

"How to manage" in case of emerging oseltamivir resistance swine influenza

"How to manage" in case of emerging oseltamivir resistance swine flu is a big interesting problem. If the generalized oseltamivir resistance occurs, it is no doubt that another preserved antiviral drug, zanamivir has to be used. This is based on the similar rationale to the case of H5N1 influenza, bird flu [14]. However, the expectation of a rapid resistance to zanamivir can be imagined since zanamivir is the drug in the same group as oseltamivir. This is the reason for the urgent need on new drug searching.

Conclusions

The situation of oseltamivir resistance in swine flu is the present concern of medical society. The oseltamivir resistance of swine flu is expected to be possible due to etiologies. Surveillance on oseltamivir resistance in swine flu is useful. In management of possible case of emerging oseltamivir drug resistance, a good planning is required at present.

References

- 1 Shinde V, Bridges CB, Uyeki TM, Shu B, Balish A, Xu X, Lindstrom S, Gubareva LV, Deyde V, Garten RJ, Harris M, Gerber S, Vagasky S, Smith F, Pascoe N, Martin K, Dufficy D, Ritger K, Conover C, Quinlisk P, Klimov A, Bresee JS, Finelli L. Triple-reassortant swine influenza A (H1) in humans in the United States, 2005-2009. *N Engl J Med.* 2009 Jun 18; 360(25):2616-2625.
- 2 Temte JL. Basic rules of influenza: how to combat the H1N1 influenza (swine flu) virus. *Am Fam Physician.* 2009 Jun 1; 79(11):938-939.
- 3 Couzin-Frankel J. Swine flu outbreak. What role for antiviral drugs? *Science.* 2009 May 8; 324(5928):705.
- 4 Perez-Padilla R, de la Rosa-Zamboni D, Ponce de Leon S, Hernandez M, Quiñones-Falconi F, Bautista E, Ramirez-Venegas A, Rojas-Serrano J, Ormsby CE, Corrales A, Higuera A, Mondragon E, Cordova-Villalobos JA; the INER Working Group on Influenza. Pneumonia and Respiratory Failure from Swine-Origin Influenza A (H1N1) in Mexico. *N Engl J Med.* 2009 Jun 29. [Epub ahead of print]
- 5 Wiwanitkit V. Antiviral drug treatment for emerging swine flu. *Clin Ter* 2009; 160(3):243-245.
- 6 Wang SQ, Du QS, Huang RB, Zhang DW, Chou KC. Insights from investigating the interaction of oseltamivir (Tamiflu) with neuraminidase of the 2009 H1N1 swine flu virus. *Biochem Biophys Res Commun.* 2009 Jun 10.
- 7 Maurer-Stroh S, Ma J, Lee RT, Sirota FL, Eisenhaber F. Mapping the sequence mutations of the 2009 H1N1 influenza A virus neuraminidase relative to drug and antibody binding sites. *Biol Direct.* 2009 May 20; 4:18.
- 8 Rungrotmongkol T, Intharathep P, Malaisree M, Nunthaboot N, Kaiyawet N, Sompornpisut P, Payungporn S, Poovorawan Y, Hannongbua S. Susceptibility of antiviral drugs against 2009 influenza A (H1N1) virus. *Biochem Biophys Res Commun.* 2009 Jul 31; 385(3):390-394.
- 9 Centers for Disease Control and Prevention (CDC). Update: infections with a swine-origin influenza A (H1N1) virus--United States and other countries, April 28, 2009. *MMWR Morb Mortal Wkly Rep.* 2009 May 1; 58(16):431-433.
- 10 Centers for Disease Control and Prevention (CDC). Update: drug susceptibility of swine-origin influenza A (H1N1) viruses, April 2009. *MMWR Morb Mortal Wkly Rep.* 2009 May 1; 58(16):433-435.
- 11 Heng PK, Leung TW, Ho EC, Leung PC, Ng AY, Lai MY, Lim WW. Oseltamivir- and amantadine-resistant influenza viruses A (H1N1). *Emerg Infect Dis.* 2009 Jun; 15(6):966-8.
- 12 Urt AC, Ernest J, Deng YM, Iannello P, Besselaar TG, Birch C, Buchy P, Chittaganpitch M, Chiu SC, Dwyer D, Guigon A, Harrower B, Kei IP, Kok T, Lin C, McPhie K, Mohd A, Olveda R, Panayotou T, Rawlinson W, Scott L, Smith D, D'Souza H, Komadina N, Shaw R, Kelso A, Barr IG. Emergence and spread of oseltamivir-resistant A (H1N1) influenza viruses in Oceania, South East Asia and South Africa. *Antiviral Res.* 2009 Jul; 83(1):90-93.
- 13 Arcía J, Sovero M, Torres AL, Gomez J, Douce R, Barrantes M, Sanchez F, Jimenez M, Comach G, de

- Rivera I, Agudo R, Kochel T. Antiviral resistance in influenza viruses circulating in Central and South America based on the detection of established genetic markers. *Influenza Other Respi Viruses*. 2009 Mar; 3(2):69-74.
- 14 Hite NJ, Webster RG, Govorkova EA, Uyeki TM. What is the optimal therapy for patients with H5N1 influenza? *PLoS Med*. 2009 Jun 23; 6(6):e1000091.