News

China's efforts at avian influenza treatment and prevention

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Keywords: Avian influenza virus, H5N1, Treatment and prevention, China

In recent years, an unprecedented epizootic avian influenza virus, known as A (H5N1), that is highly pathogenic has crossed the species barrier in Asia to cause many human fatalities and an increasing pandemic threat from Southeast Asian to other countries, with occasional transmission to humans (*Enserink M. Science. 2009; 323:324*). According to the latest statistics from the *Hongkong Government Information Center*, as of January 19, 2009, 393 human cases of positivity for H5N1 involving 248 deaths have been reported from 2003 to 2009 (*http://www.info.gov.hk/info/flu/eng/global.htm*).

H5N1 virus, an influenza A virus subtype that occurs mainly in birds, is highly contagious among birds and can be fatal to them. At present, despite the detected cases of infection with the influenza A virus, human-to-human transmission is rare (*Beigel JH, Farrar J, Han AM, et al. N Engl J Med. 2005; 353:1374-1385*). However, given the extreme variability of this kind of virus, together with the fact that humans have no natural immunity to it, there is great concern about the possibility of a new mutational virus subtype or reassortment of the current avian influenza virus with a pandemic potential.

To date, the pathogenesis of human transmission is still not clear; as a consequence, despite considerable knowledge about viral infectivity current antiviral treatment and therapeutic measures cannot control this disease. All in all, the apparent lethality of H5N1, combined with its inexorable spread, are what have led scientists worldwide to take it seriously.

China is one country where these issues are a major concern. According to Xinhua News, as of January 19, 2009, there have been 4 cases in which 3 people died of the H5N1 virus, and the latest involves a woman from Ji'nan who died on January 19th (*http://news.china.com/zh_cn/domestic/945/20090121/15292507.html, available as of January 21, 2009*).

From a geographical point of view, China is located along the main migratory routes of birds, and migratory birds have become essential carriers and disseminators of avian flu. Additionally, China has large numbers of poultry and a large population, providing more chances for transmission, including bird-to-bird, bird-to-human, and even potentially human-to-human transmission. As a result, since the first case of human infection was detected in Hong Kong, the public has welcomed a series of measures that have been taken by Chinese authorities to provide effective avian influenza treatment and prevention, which are summarized in the following.

First, extensive dissemination of knowledge related to H5N1 has taken place to eliminate public stress and to raise awareness of hygiene and safety and encourage self-vaccination. Moreover, a medical monitoring system and network laboratories have been established to improve and standardize infection detection, reporting, quarantine, and treatment and to facilitate communication with the WHO Global Influenza Surveillance Network.

Second, institutions handling epidemics and animal disposal should be provided in order to decisively handle and promptly announce any epidemics. For instance, in areas where a pathogen is suspected or that have been affected by disease, primary measures have concentrated on inoculation, compulsory vaccination, and proper disposal of carcasses and animal waste, and especially contaminated manure, with the exception of eradicating all natural reservoirs within 3 kilometers of the area. In other areas and especially those with poultry farms or processing plants, vaccination or disinfection is performed using ultraviolet radiation or chemical disinfectants.

Third, import and export inspection and quarantine have been enhanced to prevent incoming and outgoing epidemics. At the same time, the government has implemented stricter trafficking laws and regulations and imposed severer and harsher penalties on the smuggling of poultry products.

Fourth, but not last, the government has increased funding of scientific research to develop effective vaccination or anti-influenza agents as soon as possible. The PRC is currently forming noted scientific teams from both clinical and research institutes to study the mechanisms for H5N1 infection in terms of aspects such as virus mutations, circulation, and cross-infection

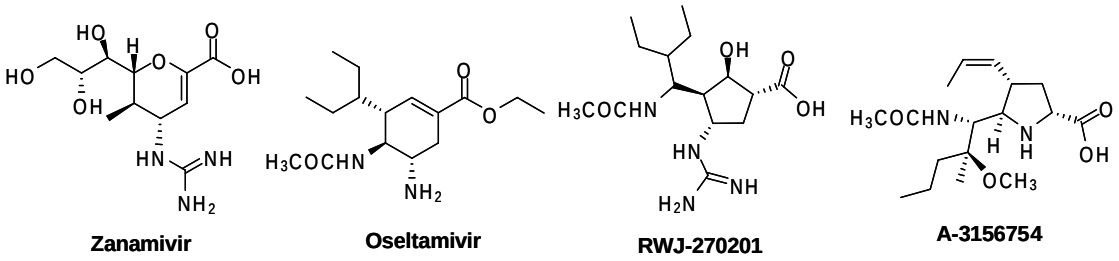

Figure 1. Four NA-based antiviral agents.

between animals and humans.

Given these efforts, however, vaccination provides limited control because of the tendency of the virus to mutate, allowing it to evade the immune system. Thus, vaccines must be reformulated each year due to high antigenic drift (*Sun S, Cui Z, Wang J, et al. Avian Pathol. 2009; 38:31-34*). Thus, effective naturally available or chemically synthesized anti-influenza therapeutics represent an urgent need at present.

Early options for the therapeutic treatment of influenza are Amantadine and Rimantadine, which act by interfering with the M2 protein ion channel that is found only in influenza virus A. However, the clinical use of these agents is limited both because of their insensitivity to influenza virus B as well as to the rapid emergence of resistance (*Heins JR, Plamp J. S D J Med. 2004; 57:529-531*).

Recently, neuraminidase (NA) inhibitors have quickly developed as anti-influenza agents because NA is crucial to the release of virion progeny by infected cells as well as its important role in the replication and movement of the virus through the mucus of the respiratory tract and because these inhibitors can reduce the propensity of the virus particles to aggregate (*Liu C, Eichelberger MC, Compans RW, Air GM. J Virol. 1995; 69:1099-1106*).

The most famous NA-based inhibitors of influenza, Relenza (Zanamivir-ZMV by Glaxo Wellcome/Biota) and Tamiflu (Oseltamivir-OMV by Hoffman-La Roche/Gilead), have been confirmed as effective and safe for the treatment of influenza and both have been approved by the US FDA. Additionally, two other NA inhibitors, RWJ-270201 (BCX-1812) and A-315675, are undergoing phase III trails in North America and Europe (*Young D, Fowler C, Bush K. Philos Trans R Soc Lond B Biol Sci. 2001; 356:1905-1913*), respectively; the two are shown in Figure 1.

In China, a series of measures have been taken by authorities to support the development of effective anti-influenza agents. As early as 2005, for instance, after the outbreak of highly pathogenic avian influenza an "Emergency research project regarding anti-influenza agents" was undertaken by the Shanghai Institute of Materia Medica (SIMM) (*http://www.simm.ac.cn/news/200812179035.htm, available as of December 17, 2008*). Led by professors Jiang Hualiang and Shen Jingkang from SIMM, the scientific research group consists of three units, the SIMM, Nanjing Simcere Dongyuan Pharmaceutical Co., Ltd., and Nanjing EffactPharm Drug Development Corp.

Thanks to their efforts, conditions for the synthesis and corresponding capsule preparation of Zanamivir were accomplished, and imitation and "me-too" drugs were developed at the same time. Zanamivir was approved by the Chinese State Food & Drug Administration (SFDA) for clinical testing on November 7, 2008 (Permit No 2008L09511).

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