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Original Article

Neuraminidase inhibitor susceptibility profile of human influenza viruses during the 2016–2017 influenza season in Mainland China☆

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ABSTRACT

To understand the current situation of antiviral-resistance of influenza viruses to neuraminidase inhibitors (NAIs) in Mainland China, The antiviral-resistant surveillance data of the circulating influenza viruses in Mainland China during the 2016–2017 influenza season were analyzed.

The total 3215 influenza viruses were studied to determine 50% inhibitory concentration (IC_{50}) for oseltamivir and zanamivir using a fluorescence-based assay.

Approximately 0.3% (n = 10) of viruses showed either highly reduced inhibition (HRI) or reduced inhibition (RI) against at least one NAI. The most common neuraminidase (NA) amino acid substitution was H275Y in A (H1N1)pdm09 virus, which confers HRI by oseltamivir. Two A (H1N1)pdm09 viruses contained a new NA amino acid substitution respectively, S110F and D151E, which confers RI by oseltamivir or/and zanamivir. Two B/Victoria-lineage viruses harbored a new NA amino acid substitution respectively, H134Q and S246P, which confers RI by zanamivir. One B/Victoria-lineage virus contained dual amino acid substitution NA P124T and V422I, which confers HRI by zanamivir. One B/Yamagata-lineage virus was a reassortant virus that haemagglutinin (HA) from B/Yamagata-lineage virus and NA from B/Victoria-lineage virus, defined as B/Yamagata-lineage virus confers RI by oseltamivir, but as B/Victoria-lineage virus confers normal inhibition by oseltamivir. All new substitutions that have not been reported before, the correlation of these substitutions and observed changes in IC_{50} should be further assessed.

During the 2016–2017 influenza season in Mainland China the majority tested viruses were susceptible to oseltamivir and zanamivir. Hence, NAIs remain the recommended antiviral for treatment and prophylaxis of influenza virus infections.

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1. Introduction

Neuraminidase inhibitors, which include oral oseltamivir, inhaled zanamivir, intravenous peramivir and inhaled long-acting laninamivir, are currently used for the prophylaxis and treatment of influenza virus infection. In the majority of countries, only oseltamivir and inhaled zanamivir are approved [1]. The four NAIs are approved and used only in Japan, and the peramivir is approved in China, the Republic of Korea as well the USA [2–4]. The NAIs tightly bind to the NA glycoprotein on the surface of the influenza virus, interfering with the function of viruses' efficient replication and their mobility within infected host cells [5]. The effectiveness of NAIs can be diminished by the NA mutations that generate during patient treatment or due to natural variation.

Emergence of viruses with reduced NAIs susceptibility is not unprecedented, but occasionally has been observed both on a local and global scale over the last decade.

The most extreme example was in 2007–2008, when the former seasonal A (H1N1) viruses acquired a H275Y substitution at NA residue which conferred oseltamivir resistance and spread globally in approximately 1 year [6–11]. In subsequent seasons, A (H1N1) pdm09 viruses containing NA H275Y substitution have been

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detected, with large clusters reported in Japan, USA, Australia, China [12–16]. The A (H1N1)pdm09 viruses carrying NA H275Y substitution became the concern for public health because the viruses were able to replicate and transmit as efficiently as normal wild-type viruses. Hence, In order to better understand the status of influenza virus's antiviral susceptibility and provide the scientific evidence for appropriate treatment and clinical management guidelines, it is important to monitor the antiviral resistance of different types of influenza virus.

In this study, we investigated the neuraminidase inhibitor susceptibility of human influenza viruses in Mainland China during the 2016–2017 influenza season.

2. Materials and methods

2.1. Neuraminidase inhibitors

The NA inhibitors oseltamivir carboxylate (Hoffman-La Roche), zanamivir (Relenza®) were prepared in sterile distilled water and stored in aliquots at −20 °C until use.

2.2. Viruses

Viruses isolated from specimens collected between week 14/2016 (April 4th, 2016) and week 13/2017 (April 2nd, 2017) were obtained from the Chinese National Influenza Surveillance Network. The viruses were submitted to Chinese National Influenza Center and propagated in either Madin-Darby canine kidney (MDCK) cells or embryonated chicken eggs prior for testing. The Chinese National Influenza Surveillance Network including 408 network laboratories and 554 sentinel hospitals, covers 32 provinces in Mainland China (including the autonomous regions/municipalities directly under the Central Government).

2.3. Neuraminidase inhibition assay

A fluorescence-based NA inhibition assay, based the NA-Fluor™ kit (Applied Biosystems, Foster City, CA, USA), was used to determine virus sensitivity to NAIs as described previously [16–18]. The IC_{50} values were determined with the GraphPad Prism 5 software (GraphPad Software, La Jolla, CA, USA). Interpretation of IC_{50} was performed using the World Health Organization Expert Working Group on Surveillance of Influenza Antiviral Susceptibility (WHO-AVWG) criteria: compared to a reference IC_{50} (e.g a median IC_{50} of viruses of the same type/subtype/lineage), influenza A viruses are classified as normal inhibition (NI) with <10-fold increase in IC_{50}, classified as reduced inhibition (RI) if they have a 10- to 100-fold increase in IC_{50} and highly reduced inhibition (HRI) if > 100-fold increase in IC_{50}, influenza B viruses the corresponding fold increases are <5, 5–10 and > 50 respectively [19].

2.4. RNA extraction and NA gene sequencing

Viruses showing RI or HRI were subjected to do the sequence analysis and find out amino acid substitution of NA residue, it aimed to indentify the molecular markers relative to the antiviral resistance phenotype. The viral RNA was extracted by An RNeasy Kit (Qiagen, Chartsworth, CA, USA). RT-PCR was performed using SuperScripthIII One-Step RT-PCR System (Invitrogen, USA), the reaction conditions and primers of the RT-PCR and products were purified as described previously [20]. The Qubit dsDNA BR Assay System (Covaris, Woburn, MA, USA) was used to determine the concentration of PCR products. The deep sequencing was done using MiSeq sequencer (Illumina, San Diego, CA, USA) and the sequences were obtained from the FASTQ file using the CLC Genomics Workbench software (CLC bio, Cambridge, MA, USA). The NA sequences were submitted to Global Initiative on Sharing All Influenza Data (GISAID). The accession numbers are presented in the Supplemental Table 1. Amino acids position numbering is listed A subtype and B type specific.

2.5. Sequence analysis

Sequence alignment was constructed with MEGA version 7.0 software (the Biodesign Institute, USA).

3. Results

3.1. Overall analysis of phenotypic antiviral susceptibility data from Mainland China

During the 2016–2017 influenza season, A (H1N1)pdm09 virus, A (H3N2) virus and B/Victoria-lineage virus were co-circulating in Mainland China, but A (H3N2) virus was predominant virus. According to different sampling date and place the test viruses were randomly selected, a total of 3215 influenza viruses (13.87%), including 1063 A (H1N1) pdm09, 1068 A (H3N2), 807 B/Victoria-lineage and 277 B/Yamagata-lineage viruses, were phenotypically tested for susceptibility to oseltamivir and zanamivir (Fig. 1). Of the 3215 viruses tested, 10 (0.3%) exhibited RI or HRI by at least one NAI.

3.2. NAIs susceptibility of A (H1N1)pdm09 viruses

Seven A (H1N1)pdm09 viruses among of 1063 tested (0.7%) viruses showed RI or HRI by oseltamivir and zanamivir (Table 1), which was lower than in the 2013–2014 season in Mainland China [16]. Of these, five viruses were NA H275Y variants, showing HRI by oseltamivir (199.53- to 2115.79-fold greater than the median), while retaining NI by zanamivir. These 5 viruses were distributed in different provinces of the Mainland China: Fujian (n = 2), Guangdong (n = 1), Hebei (n = 1), Zhejiang (n = 1). All five patients had unknown antiviral treatment histories prior to specimen collection. All samples were collected from the outpatients with mild symptom and there was no severe case involved. The patients were 2 females and 3 males. The median age was 6 years, the maximum age was 49 years, and the minimum age was 1 year, including 3 children (Table 2).

One virus with a NA S110F amino acid substitution, which has not been described before, showed RI by oseltamivir (10.47-fold greater than the median) and zanamivir (18.45-fold greater than the median) (Table 2). Another virus, A/Guangdong -Chancheng/SWL1263/2017 exhibited borderline RI (10-fold) by zanamivir and carried D151E (Table 2), which was previously reported in A (H3N2) virus with RI to oseltamivir [21].

3.3. NAIs susceptibility of A (H3N2) viruses

One thousand and sixty-eight A (H3N2) viruses were tested. All viruses showed NI by oseltamivir and zanamivir. The median IC_{50} of oseltamivir for tested viruses was 0.32 nM and ranged from 0.10 nM to 2.03 nM, while the median IC_{50} of zanamivir for these viruses was 0.39 nM, ranging from 0.15 nM to 2.01 nM (Table 1). It was matched with the data reported by WHO-AVWG, The frequency of A (H3N2) viruses displaying RI/HRI remained very low in the world in previous seasons [15,22–24].

3.4. NAIs susceptibility of B/Victoria-lineage viruses

Three (0.4%) of the 807 B/Victoria-lineage viruses showed RI or HRI by zanamivir (Table 1). One virus, B/Anhui-Jiujiang/325/2016

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