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Original article

Continued effectiveness of laninamivir octanate hydrate for influenza treatment in Japan: Comparison between the 2011–2012 and 2012–2013 influenza seasons

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ABSTRACT

The clinical effectiveness of Laninamivir octanoate hydrate (laninamivir) was investigated in the Japanese 2012–2013 influenza season for comparison with that of the Japanese 2011–2012 influenza season. A total of 235 patients were enrolled, of whom 210 were evaluated for the duration of fever and other symptoms. The median durations of fever for A(H3N2) were 32.0 and 38.0 h and the median durations of symptoms for the A(H3N2) were 102.0 and 84.0 h for patients aged under 10 and 10 years or older, respectively. All four influenza B patients were 10 years or older, and their median duration of fever was 43.0 h and the median duration of symptoms was 71.0 h. There was no significant difference in the duration of fever or symptoms between the two seasons. The rates of patients A(H3N2) virus positive at day 5 were 37.2% (16/43) and 12.8% (18/141) for those aged under 10 years and 10 years or older, respectively. The virus positive rate was significantly higher for the patients under 10 years than for the patients aged 10 years or older ($p < 0.0001$). No significant change in IC_{50} value was found between days 1 and 5. Adverse drug reactions were reported by 2 of the 231 patients (0.87%), but neither was serious. These results suggest that laninamivir continued to be effective against influenza A(H3N2) with no safety issues and that it is unlikely that the clinical use of laninamivir will lead to virus resistance.

1. Introduction

The neuraminidase inhibitors (NAIs) oseltamivir, zanamivir, peramivir, and laninamivir octanoate are commonly used for the treatment of influenza in Japan, and treatment is recommended within 48 h from the onset [1–6]. Consequently, the severity and mortality in the pandemic of A(H1N1)pdm09 in 2009 in Japan were kept low compared to other countries [7]. The epidemic strains of influenza have constantly changing antigenicity and susceptibility to antivirals. The A(H1N1) virus with the H275Y mutation had a very high IC_{50} value to oseltamivir in vitro and was epidemic in the Japanese 2008–2009 season. We previously reported that the clinical effectiveness of oseltamivir to the H275Y mutated A(H1N1) virus decreased the clinical effectiveness significantly [8,9]. Thus, it is important to investigate the clinical effectiveness of NAIs and to monitor virus susceptibility on a year by year basis.

Laninamivir octanoate hydrate (laninamivir) is a long-acting NAI approved in Japan in 2010 for the treatment of influenza A and B virus infection, that requires only a single inhalation to complete the treatment [4,5]. It is commonly used by doctors in Japan. We previously reported the duration of fever and other symptoms after the start of treatment with laninamivir in the Japanese 2011–2012 influenza season [10].

In this paper, we investigate the duration of fever and other influenza symptoms among patients treated with laninamivir in the Japanese 2012–2013 influenza season as a part of post-marketing surveillance of laninamivir. The results were compared with those of the 2011–2012 season. We also measured the virus titer of each patient at the initial visit and tested for the 50% inhibitory concentration (IC_{50}) of each NAI for influenza virus isolated at days 1 and 5. Virus positivity at day 5 and a comparison of the IC_{50} values of the isolates at days 1 and 5 are also reported.

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2. Patients and methods

2.1. Patients

Patients with influenza virus infection diagnosed at 23 clinics and 1 hospital in 11 prefectures of Japan from November 2012 to April 2013 were enrolled in this study.

Patients who were positive by a rapid diagnosis test kit and had a temperature ≧37.5 °C were registered after obtaining written informed consent. Patients suspected of having other viral or secondary bacterial infections following influenza virus infection were excluded.

Laninamivir was administered according to the recommended dosage: A single inhalation of 20 mg for patients under 10 years of age and a single inhalation of 40 mg for patients aged 10 years or over.

2.2. Study procedures

Patients were registered by use of a centralized registration procedure as previously described [11]. Participating physicians asked each eligible patient to provide the following information by recording it in a patient diary: 1) Date and time of laninamivir inhalation, 2) Body temperature and the date and time of measurement (measured twice daily in the morning and afternoon for the seven days after inhalation), 3) Seven symptoms (headache, muscle/joint pain, fatigue, chills/sweating, nasal symptoms, sore throat, and cough) were rated on a 4-grade scale (0: free, 1: mild, 2: moderate, 3: severe) and assessed at the time of body temperature measurement (twice daily for seven days). The patient mailed or handed the completed patient diary to his/her physician.

The duration of fever was defined as the time from the inhalation of laninamivir to afebrile. The definition of afebrile used in this study was based on the Japanese Ministry of Health, Labour, and Welfare (MHLW) criteria that existed at the time of clinical trials for the development of anti-influenza drugs in Japan. In these criteria, an afebrile adult is defined as having a temperature of 36.9 °C or lower, while an afebrile child has a temperature of 37.4 °C or lower, because children generally have a higher body temperature than adults [4,5]. The duration of symptoms was defined as the time from inhalation until the patient noted improvement of all symptoms to a mild grade.

The parameters investigated were sex, presence/absence of pregnancy for women, age, subtype/type of influenza virus, date and time of onset of influenza (defined as when fever or chills first occurred), temperature, severity of symptoms at the hospital visit, history of influenza vaccination, history of allergies and other diseases, date and time of inhalation and laninamivir dosage, concomitant medications, and adverse events.

2.3. Virological tests

A specimen from a nasal swab, posterior pharyngeal throat swab, and/or self-blown nasal discharge was obtained at the visits on days 1 and 5 (allowable range: days 4–6). The clinical samples were placed in viral transport medium and frozen at −80 °C ± 10 °C until use. Influenza was confirmed by virus isolation using MDCK cells according to the standard methods [12]. For virus titration, the serially diluted, thawed swab samples were infected with MDCK cells and cultured for seven days. The virus titer was calculated as the $\log_{10}$ $TCID_{50}$ (50% tissue culture infective dose per ml of the viral transport medium), according to the Behrens–Karber equation. A specimen with a $TCID_{50}$ of 1.5 or more was defined as being influenza virus positive.

The type/subtype of influenza virus was determined by RT-PCR with type- and subtype-specific primers for the hemagglutinin sequences of A(H1N1), A(H1N1)pdm09, A(H3N2), and B. The IC_{50} was determined by a fluorescence-based neuraminidase inhibition assay as previously reported [13]. To verify the IC_{50} results, the A/Yamagata/32/89 strain was included as the assay control regardless of the assay year, to allow comparison of the IC_{50} values.

2.4. Statistical analysis

Median values for the duration of fever and symptoms were calculated by the Kaplan–Meier method. The positivity rates of influenza virus at day 5 were compared by Fisher's exact test. The log-transformed IC_{50} value of the virus isolated from the specimen on day 1 was compared with that on day 5 by the paired *t*-test. All analyses were performed using the SAS system, Release 9.2.

3. Results

3.1. Study population

A total of 235 patients were enrolled at the 24 participating institutions listed in Acknowledgements. The data of 4 patients ineligible for safety analysis and 21 ineligible for the analysis of the duration of fever and other symptoms were excluded, (Fig. 1), leaving the data of 210 patients available for the evaluation of the duration of fever and other symptoms after the laninamivir inhalation.

The baseline clinical characteristics of the patients are summarized in Table 1. The studied population consisted of 106 males (50.5%) and 104 females (49.5%), 43 (20.5%) under 10 years and 167

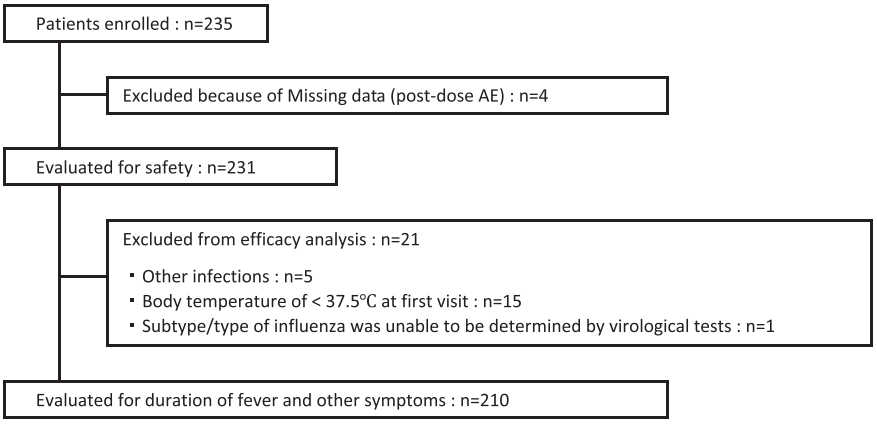

Fig. 1. Patient flow chart.