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Original Article

Duration of fever and other symptoms after the inhalation of laninamivir octanoate hydrate in the 2016/17 Japanese influenza season; comparison with the 2011/12 to 2015/16 seasons☆

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ABSTRACT

The duration of fever and symptoms after laninamivir octanoate hydrate (laninamivir) inhalation were investigated in the Japanese 2016/17 influenza season and the results were compared with those of the 2011/12 to 2015/16 seasons. A total of 1278 patients were evaluated for the duration of fever and symptoms in the six studied seasons. In the 2016/17 season, the influenza types/subtypes of the patients were 6 A (H1N1)pdm09 (2.9%), 183 A (H3N2) (87.6%), and 20 B (9.6%). The respective median durations of fever for A (H1N1)pdm09, A (H3N2), and B were 38.0, 33.0, and 38.5 h, without significant difference ($p = 0.9201$), and the median durations of symptoms were 86.5, 73.0, and 99.0 h, with significant difference ($p = 0.0342$).

The median durations of fever and symptoms after laninamivir inhalation were quite consistent for the six studied seasons for A (H1N1)pdm09, A (H3N2), and B, without any significant differences. The percentage of patients with unresolved fever patients displayed a similar pattern through the six studied seasons for all these virus types.

There was no significant difference in the duration of fever or symptoms between the Victoria and Yamagata lineages in the 2016/17 season and those of the previous studied seasons. Over the seasons tested, ten adverse drug reactions (ADRs) were reported from 1341 patients. The most frequent ADR was diarrhea and all ADRs were self-resolving and not serious. These results indicate the continuing clinical effectiveness of laninamivir against influenza A (H1N1)pdm09, A (H3N2), and B, with no safety issues.

1. Introduction

The neuraminidase inhibitors (NAIs) oseltamivir phosphate (Tamiflu®, oseltamivir), zanamivir hydrate (Relenza®, zanamivir), peramivir hydrate (Rapiacta®, peramivir), and laninamivir octanoate hydrate (Inavir®, laninamivir) are commonly used for the treatment of influenza in Japan. Viral mutations that emerge in the neuraminidase (NA) gene and other virus gene segments can change the susceptibility to NAIs. We previously reported that the clinical effectiveness of oseltamivir was significantly decreased for the H275Y mutated A (H1N1) virus in the 2008/09 Japanese influenza seasen [1,2]. The 50% inhibitory concentration (IC_{50}) of oseltamivir was increased over 100 fold compared to the reference viruses. Fortunately, the H275Y mutated A (H1N1) virus has not been epidemic since then. However, the presence of A (H1N1) pdm09 that was resistant to oseltamivir and peramivir has been reported by the National Institute of Infectious Diseases of Japan [3]. In our series of studies, an increased IC_{50} for H275Y mutated A (H1N1)pdm09 has been observed [4–6]. Thus, investigations that monitor not only viral susceptibility to NAIs but also the clinical effectiveness of the NAIs on a year by year basis are important.

Laninamivir, which requires only a single inhalation to complete the treatment, was approved in Japan in 2010 for the treatment of influenza A and B [7,8] and is commonly used by doctors in Japan. We previously reported the duration of fever and symptoms after

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the inhalation of laninamivir over five Japanese influenza seasons [9–13]. In this study, we investigate the duration of fever and other influenza symptoms of patients treated with laninamivir in the Japanese 2016/17 influenza season as a part of the post-marketing surveillance program. Comparison of the duration of fever and symptoms was done with the previous five seasons, from 2011/12 to 2015/16.

2. Patients and methods

2.1. Patients

Patient who visited a clinic with a fever 37.5 or over and who were positive by a rapid influenza diagnosis test kit from November 2016 to April 2017 were enrolled in this study 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

A post marketing surveillance program sponsored by Daiichi Sankyo Co., Ltd has been done since the 2011–2012 season. Patients in the 2016/17 season were registered by use of a centralized registration procedure, as previously described [3]. 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 or a parent or guardian mailed or handed the completed patient diaries to their 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 is based on the Japanese Ministry of Health, Labor, and Welfare (MHLW) criteria that existed at the time of clinical trials for the development of anti-influenza drugs in Japan [7,8]. 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. 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), body 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. Influenza virus isolation and typing

Nasal aspirates, nasopharyngeal swabs, or self-blown nasal discharge were obtained for influenza virus isolation, which was done with Madin-Darby canine kidney (MDCK) using a standard procedure. The type and subtype of the isolated virus was determined by RT-PCR using RNA extracted from the clinical specimens and type- and subtype-specific primers for the hemagglutinin gene [14]. The Yamagata and Victoria lineages of influenza B virus were discriminated by real-time RT-PCR using type- and subtype-specific primers and probes for the hemagglutinin gene [15].

2.4. Statistical analysis

For the comparison of baseline characteristics among virus types/subtypes in the 2016/17 season, categorical data were analyzed using Fisher's exact test and continuous data by analysis of variance (ANOVA). Comparisons of the duration of fever or symptoms among virus types/subtypes in the 2016/17 season, between patients under 10 years and 10 years or older by virus types/subtypes in the 2016/17 season, and among seasons by virus types/subtypes were done using the Cox proportional hazards model. The medians for the duration of fever and symptoms were calculated by the Kaplan-Meier method.

The safety analysis set excluded patients without data on the presence or absence of adverse events. The set for the analysis of duration fever and symptoms excluded patients with other infections, body temperature of $\leq$37.4 °C or unknown at first visit, and those whose viral type/subtype was unable to be determined from the safety analysis set.

The level of significance was set at <5% two-sided. Because the study is exploratory, multiplicity adjustments were not performed. All analyses were performed using the SAS system, Release 9.2.

3. Results

3.1. Study population

The study flow chart is shown in Fig. 1. A total of 215 patients were enrolled in the 2016/17 season at the 22 participating institutions listed in acknowledgements. The data of two patients were excluded, leaving the data of 213 patients available for safety analysis. The data of four patients ineligible for the analysis of duration fever and symptoms were excluded, leaving the data of 209 patients available for the seasonal analysis. Available for the comparative analysis among the seasons were 1341 for safety and 1278 for duration of fever and symptoms.

The baseline clinical characteristics of the patients in the 2016/17 season are listed in Table 1. Of them, 6 had A (H1N1)pdm09 (2.9%), 183 A (H3N2) (87.6%), and 20 B (9.6%). Mean ages were 37.0 ± 29.5, 25.8 ± 21.1, and 17.2 ± 15.2 years for A (H1N1)pdm09, A (H3N2), and B, respectively, with no significant differences in age distribution by virus type/subtype ($p = 0.0828$). The percentages of patients under 10 years were 33.3%, 15.3%, and 45.0%, a statistically significant difference among the virus type/subtypes ($p = 0.0037$). The percentages of vaccinated patients were 33.3%, 39.3%, and 30.0%, with no statistical significance among the virus type/subtypes ($p = 0.7316$).

The times from the onset to laninamivir inhalation for A (H1N1) pdm09, A (H3N2), and B were, 28.7, 17.7, and 22.2 h, respectively, with differences among the virus type/subtypes statistically significant ($p = 0.0171$). There was no significant difference in body temperature or mean influenza symptom score at the initial visit by virus type/subtype ($p = 0.2538$ and 0.1568, respectively).

3.2. Duration of fever and symptoms in the 2016/17 season

The median duration of fever and symptoms after laninamivir inhalation for A (H1N1)pdm09, A (H3N2), and B are listed in Table 2. The median duration of fever was shortest for A (H3N2) (33.0 h), followed by A (H1N1)pdm09 (38.0 h) then B (38.5 h), with no significant differences among the virus type/subtypes ($p = 0.9201$).

The duration of fever of the patients under 10 years was significantly shorter than that of patients 10 years or older for A

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