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Original Article

Duration of fever and other symptoms after the inhalation of laninamivir octanoate hydrate; comparison of the 2011/12 to 2015/16 Japanese influenza seasons

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ABSTRACT

The duration of fever and symptoms after laninamivir octanoate hydrate (laninamivir) inhalation were investigated in the Japanese 2015/16 influenza season, and the results were compared with those of the 2011/12 to 2014/15 seasons. A total of 1068 patients were evaluated for the duration of fever and symptoms in the five studied seasons. The influenza types/subtypes were 125 A(H1N1)pdm09 (62.2%), 17 A(H3N2) (8.5%), and 59 B (29.4%) in the 2015/16 season. The median durations of fever were 40.0, 41.0, and 47.0 h, and the median durations of symptoms were 87.0, 76.0, and 93.0 h for A(H1N1)pdm09, A(H3N2), and B, respectively, with no significant difference. The median durations of fever were 52.0 and 46.0 h and the median durations of symptoms 93.0 and 88.0 h for the Victoria and Yamagata B lineages, respectively, with no significant difference. Fever resolution after laninamivir inhalation by the A(H1N1)pdm09 patients was similar in the 2013/14 and 2015/16 seasons. Fever resolution after laninamivir inhalation was similar in all comparisons of the 2011/12 to 2015/16 seasons for both A(H3N2) and B, with no significant difference among the five seasons. Over the seasons tested, eight adverse drug reactions (ADRs) were reported for 1128 patients. The most frequent ADR was diarrhea, and all ADRs were resolved 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. Through influenza epidemics, viral mutations that emerge in the neuraminidase (NA) gene 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 [1,2], which has not been epidemic since the 2008–2009 season. However, A(H1N1)pdm09 that carries the H275Y mutation in NA has been found in our series of studies and an increase of the IC50 has been confirmed [3,4] Thus, investigations that monitor and evaluate clinical effectiveness and viral susceptibility to NAIs on a year by year basis are important.

Laninamivir, which requires only a single inhalation to complete the treatment, is a long-acting NAI approved in Japan in 2010 for the treatment of influenza A and B [5,6]. It is commonly used by doctors in Japan. We have reported the duration of fever and symptoms after the inhalation of laninamivir over four Japanese influenza seasons [7–10].

In this paper, we investigate the duration of fever and other influenza symptoms of patients treated with laninamivir in the Japanese 2015/16 influenza season as a part of the post-marketing surveillance program. Comparison of duration of fever and symptoms was done with the 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 °C or over and who were positive by a Japanese Health Ministry approved rapid

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influenza diagnosis test kit from November 2015 to April 2016 were enrolled in this study after obtaining written informed consent. Rapid influenza diagnosis test kit used was chosen by each physician. 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. has been done since the 2011–2012 season. Patients in the 2015/16 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 [5,6]. 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. A patient who received at least one dose of vaccine was considered vaccinated.

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 hemagglutinine gene [11]. 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 hemagglutinine gene [12].

2.4. Statistical analysis

For the comparison of baseline characteristics among virus types/subtypes in the 2015/16 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 2015/16 season, between patients under 10 years and 10 years or older by virus types/subtypes in the 2015/16 season, among seasons by virus types/subtypes were done using the Cox proportional hazards model. The median for the duration of fever and symptoms were calculated by the Kaplan-Meier method. The safety analysis set excluded the patients without data on the presence or absence of adverse events or without laninamivir inhalation from the patients enrolled. The analysis of duration fever and symptoms excluded patients with other infections, body temperature ≤37.4 °C or unknown at first visit, and 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

A total of 209 patients were enrolled in the 2015/16 season at the 22 participating institutions listed in acknowledgements. The data of two patients ineligible for safety analysis and that of six ineligible for the analysis of duration fever and symptoms were excluded, leaving the data of 201 patients in the 2015/16 season available for the seasonal analysis and that of 1068 patients available for the comparative analysis (Fig. 1).

The baseline clinical characteristics of the patients in the 2015/16 season are listed in Table 1. Of them, 125 had A(H1N1)pdm09 (62.2%), 17 A(H3N2) (8.5%), and 59 B (29.4%). Mean ages were 26.1 ± 19.7, 21.8 ± 16.3, and 16.6 ± 10.6 years for A(H1N1)pdm09, A(H3N2), and B, respectively, with significant differences in age distribution by virus type/subtype ($p = 0.0026$). The percentage of vaccinated patients was 38.4%, 23.5%, and 33.9%, with no statistically significance ($p = 0.4784$). The time from the onset to laninamivir inhalation was similar, 20.0, 22.0, and 20.7 h respectively ($p = 0.8081$). There was no significant difference in body temperature at initial visit by virus type/subtype. The mean influenza symptom score at the initial visit was 10.6 ± 3.8, 11.1 ± 3.6, and 9.9 ± 3.7, with no significant difference ($p = 0.3449$).

3.2. Duration of fever and symptoms in the 2015/16 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(H1N1)pdm09 (40.0 h), followed by A(H3N2) (41.0 h) then B (47.0 h). The median duration of symptoms was shortest for A(H3N2) (76.0 h), followed by A(H1N1)pdm09 (87.0 h) then B (93.0 h). The differences in the duration of fever and symptoms were not significant ($p = 0.7039$ and $p = 0.8676$, respectively).

The duration of fever of the patients under 10 years was shorter than that of patients 10 years or older for A(H1N1)pdm09 and B, but longer for A(H3N2). The duration of symptoms of the patients under 10 years was also shorter than that of patients 10 years or older for A(H1N1)pdm09 and B, but longer for A(H3N2). However, these differences were not statistically significant except for the difference in the duration of fever to A(H1N1)pdm09. There was no significant difference between the vaccinated and unvaccinated patients in the durations of fever and symptoms for the three virus type/subtype groups (data not shown).

3.3. Duration of fever and symptoms over five influenza seasons

The median durations of fever and symptoms of the five seasons by virus type/subtype are listed in Table 3. The median durations of

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