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Original article

The duration of fever and other symptoms after the initiation of laninamivir octanoate hydrate in the Japanese 2011–2012 influenza season

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ABSTRACT

Laninamivir octanoate hydrate (laninamivir) is a long-acting, single inhalation neuraminidase inhibitor that was approved in Japan in 2010 for the treatment of influenza A and B virus infection. We investigated the duration of fever and other symptoms after the initiation of laninamivir in the Japanese 2011–2012 influenza season. Virus isolation was done and the 50% inhibitory concentration (IC_{50}) was measured for the virus isolates at days 1 and 5. For 211 patients (A(H3N2): 190, B: 21), the median durations of fever of A(H3N2) and B patients were 33.0 and 50.0 h, respectively ($p = 0.0989$). Fever was resolved within 72 h after inhalation by 89.7% of the A(H3N2) patients and by 81.0% of the patients with B. The median durations of symptoms for A(H3N2) and B patients were 89.0 and 94.0 h, respectively ($p = 0.5809$). On day 5, the influenza virus-positive rates for A(H3N2) and B patients were significantly different: 25.8% (40/155) and 70.6% (12/17), respectively ($p < 0.0001$). No significant change in IC_{50} value was found between day 1 and day 5 for any of the four tested neuraminidase inhibitors, and no IC_{50} value exceeded 50 nM. The incidence of adverse drug reactions was 1.3% (3/234), with no serious reactions reported. These results show that laninamivir was effective for the treatment of both influenza A(H3N2) and B in this study, with no safety issues. The clinical effectiveness of laninamivir for A(H3N2) was superior to that for B.

1. Introduction

The epidemic strains of influenza are constantly changing. In the Japanese 2008–2009 influenza season, almost 100% of the A(H1N1) viruses were H275Y mutants with oseltamivir resistance, and the clinical usefulness of oseltamivir was decreased [1,2]. In the 2009–2010 season, oseltamivir resistant A(H1N1) disappeared and strain was the pandemic A(H1N1)pdm09 for which oseltamivir was effective. In the 2010–2011 season, although the predominant epidemic strain was A(H1N1)pdm09, A(H3N2) and influenza B also became epidemic. In the 2011–2012 season, A(H3N2) became the predominant virus replacing A(H1N1)pdm09 [3]. Thus epidemic influenza viruses can change markedly in a short time, making it important to constantly monitor the efficacy of neuraminidase inhibitors (NAIs) for each viral type/subtype.

Laninamivir octanoate hydrate (laninamivir) is a long-acting NAI, approved in Japan in 2010 for influenza A and B, that requires only a single inhalation to complete the treatment [4]. In this paper, we investigate the duration of fever and other symptoms after treatment with laninamivir in the Japanese 2011–2012 influenza season. We also isolated influenza viruses from clinical specimens and measured the IC_{50} of isolated viruses for four NAIs at days 1 and 5. The difference between influenza A(H3N2) and B and the relation between the duration of fever and other symptoms after the initiation of laninamivir and IC_{50} values are also discussed.

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 2011 to April 2012 were enrolled in this study.

Patients positive by a rapid diagnosis test kit and who had a temperature ≥37.5 °C were registered after providing informed

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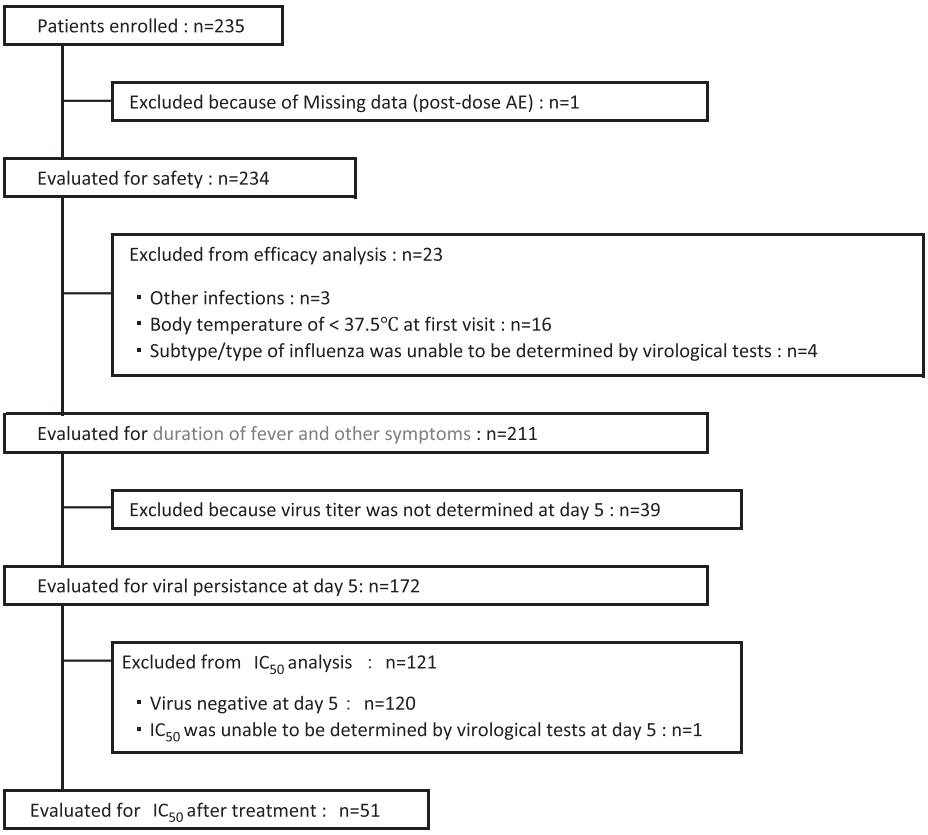

Fig. 1. Flow chart.

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 [5]. Participating physicians asked each eligible patient to provide the following information and record 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 7 days after inhalation), 3) A total of 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 7 days). The patients mailed in their completed patient diary or handed it 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 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 have higher body temperatures than adults [6,7]. 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 [8]. A specimen with a $TCID_{50}$ (the 50% tissue culture infective dose) of 1.5/ml 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} of four neuraminidase inhibitors (laninamivir, oseltamivir carboxylate, zanamivir, and peramivir) was determined according to previously reported methods [9].

2.4. Statistical analysis

Median values for the duration of fever and symptoms were calculated by the Kaplan–Meier method. For comparisons between A(H3N2) and B patients and to determine the exploratory variables that influence the duration of fever and other symptoms after initiation of laninamivir, Cox proportional hazards model was adapted. The rate of influenza A(H3N2) and B virus positivity on day 5 was compared by Fisher's exact test. The log-transformed IC_{50} values of