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Original Article

Clinical effectiveness of four neuraminidase inhibitors (oseltamivir, zanamivir, laninamivir, and peramivir) for children with influenza A and B in the 2014–2015 to 2016–2017 influenza seasons in Japan

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ABSTRACT

The clinical effectiveness of four neuraminidase inhibitors (NAIs) (oseltamivir, zanamivir, laninamivir, and peramivir) for children aged 0 months to 18 years with influenza A and B were investigated in the 2014–2015 to 2016–2017 influenza seasons in Japan. A total of 1207 patients (747 with influenza A and 460 with influenza B) were enrolled. The Cox proportional-hazards model using all of the patients showed that the duration of fever after administration of the first dose of the NAI was shorter in older patients (hazard ratio = 1.06 per 1 year of age, $p < 0.001$) and that the duration of fever after administration of the first dose of the NAI was shorter in patients with influenza A infection than in patients with influenza B infection (hazard ratio = 2.21, $p < 0.001$). A logistic regression model showed that the number of biphasic fever episodes was 2.99-times greater for influenza B-infected patients than for influenza A-infected patients ($p < 0.001$). The number of biphasic fever episodes in influenza A- or B-infected patients aged 0–4 years was 2.89-times greater than that in patients aged 10–18 years ($p = 0.010$), and the number of episodes in influenza A- or B-infected patients aged 5–9 years was 2.13-times greater than that in patients aged 10–18 years ($p = 0.012$).

1. Introduction

It has been shown that neuraminidase inhibitors (NAIs) can alleviate the major symptoms of uncomplicated influenza A and B and reduce the duration by approximately 1–1.5 days when administered within 48 h of onset of illness compared with the effect of a placebo [1–4]. NAIs reduce the incidence of acute otitis media in children aged one to five years who are suffering from seasonal influenza [5] and contribute to survival benefit in patients infected with influenza A(H1N1)pdm09 virus [6]. In Japan, almost all patients with an influenza-like illness are tested with rapid antigen tests, and they are treated with one of the NAIs when positive; this has become standard practice in clinics nationwide [7]. The clinical effectiveness of zanamivir, laninamivir, and peramivir has been tested mainly in clinical trials compared to the effect of either a placebo or oseltamivir [1,8–14], and there have been few studies in which the clinical effectiveness of four NAIs (oseltamivir, zanamivir, laninamivir, and peramivir) was compared [15,16]. In the present study, we evaluated the clinical effectiveness of the four NAIs for children with influenza A and B by comparing the durations of fever after administration of the first doses of NAIs.

2. Patients and methods

2.1. Patients

Outpatients aged 0 months to 18 years who had an axillary temperature of 37.5 °C or higher were diagnosed as having influenza virus infection based on results obtained by a rapid antigen test. Patients were excluded from this study if the time from onset of fever to initiating administration was 48 h or more or if body temperature fell to less than 37.5 °C before starting administration. Patients who had bacterial infections (pneumonia, otitis media) were excluded. Patients diagnosed as having influenza were treated with one of the NAIs (oseltamivir, zanamivir, laninamivir, and peramivir) after obtaining informed consent from the children's parents. The decision regarding administration of NAIs was left to the discretion of the physician. Oseltamivir was administered at 2 mg/kg/dose (to a maximum of 75 mg/dose) twice daily for 5 days, zanamivir was administered by inhalation at 10 mg/dose twice daily for 5 days, laninamivir was administered as a single inhalation (20 mg for patients less than 10 years of age and 40 mg for patients 10 years of age or more) and peramivir was administered intravenously at 10 mg/kg once daily (to a maximum of 600 mg/dose).

2.2. Study procedures

A prospective, multicenter observational study was conducted in the 2014–2015, 2015–2016 and 2016–2017 influenza seasons at 25 pediatric clinics and in departments of pediatrics in 11 hospitals in Hokkaido, Japan.

The age and sex of each patient and the date and results of the rapid diagnostic test were recorded by physicians. The time of onset (the first time that the patient had a fever of more than 37.5 °C), vaccination status, selection of NAIs, date and time of first administration of NAIs, and total number of administrations of NAIs were recorded by the parents of children. The parents were also instructed to take their children's axillary body temperatures at least four times daily and to plot the body temperatures on a graph with temperature on the vertical axis and time on the horizontal axis. The time at which a temperature of less than 37.5 °C was attained and maintained for more than 48 h was defined as the time when the patient became afebrile. If a patient's temperature decreased to less than 37.5 °C and remained less than 37.5 °C for more than 24 h but later increased to more than 37.5 °C, the patient was considered to have biphasic fever. All ethical approval for this study was obtained from the Institutional Review Board of Hokkaido University Hospital for Clinical Research (0140172).

2.3. Real-time reverse transcription PCR

Real-time reverse transcription PCR for detection of influenza A and B viruses was performed according to the referenced protocol [17].

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