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Original article

Post-marketing safety and effectiveness evaluation of the intravenous anti-influenza neuraminidase inhibitor peramivir (II): A pediatric drug use investigation

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ABSTRACT

Peramivir is the only intravenous formulation among anti-influenza neuraminidase inhibitors currently available. Peramivir was approved for manufacturing and marketing in Japan in January 2010. In October 2010, an additional indication for pediatric use was approved. We conducted a pediatric drug use investigation of peramivir from October 2010 to February 2012 and evaluated its real-world safety and effectiveness in pediatric patients. We collected the data of 1254 peramivir-treated pediatric patients from 161 facilities across Japan and examined the safety in 1199 patients and effectiveness in 1188 patients. In total, 245 adverse events were observed with an incidence rate of 14.01% (168/1199). Of these, 115 events were adverse drug reactions (ADRs) with an incidence rate of 7.67% (92/1199). Common ADRs were diarrhea and abnormal behavior, with incidence rates of 2.50% (30/1199) and 2.25% (27/1199), respectively. Fourteen serious ADRs were observed in 12 patients (1.00%), including 5 cases each of abnormal behavior and neutrophil count decreased. While 87.0% (100 events) of ADRs occurred within 3 days after the initiation of peramivir administration, 87.8% (101 events) resolved or improved within 7 days after onset. Multivariate analyses indicated that the presence or absence of underlying diseases/complications was significantly related to ADR incidence. With regard to effectiveness, the median time to alleviation of both influenza symptoms and fever was 3 days, including the first day of administration. Thus, this study confirms the pediatric safety of peramivir without any concerns about effectiveness under routine clinical settings.

1. Introduction

Peramivir is the only intravenous formulation among anti-influenza neuraminidase inhibitors (NAIs) currently available. After clinical studies confirmed peramivir efficacy and safety for influenza in adults [1–3], manufacturing and marketing approval was granted in Japan in January 2010. Subsequently, a pediatric clinical study confirmed the efficacy and safety of peramivir for influenza in children [4]. An additional indication for pediatric use was approved in October 2010.

In addition to rhinorrhea, vomiting, abdominal pain, diarrhea, and neurological symptoms including febrile convulsions, severe complications such as encephalopathy are occasionally observed in pediatric influenza patients [5]. Therefore, it is important to consider safety in pediatric influenza treatment, particularly with regard to symptoms and possible complications.

Following the approval of the additional indication, we conducted a prospective observational drug use investigation of peramivir in children from October 2010 to February 2012 to assess its pediatric safety and effectiveness under routine clinical settings. This was required as a condition for approval by the Japanese Ministry of Health, Labour and Welfare (MHLW) and was conducted in compliance with the Good Post-Marketing Study Practice specified by the MHLW Ordinance No. 171 (December 20, 2004).

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2. Patients and methods

2.1. Patients

We surveyed children (<15 years) from 161 facilities, mainly comprising pediatrics, across Japan who began to receive peramivir administration for influenza treatment from October 2010 to February 2012.

2.2. Study drug

Peramivir hydrate was investigated.

2.3. Dosage and administration

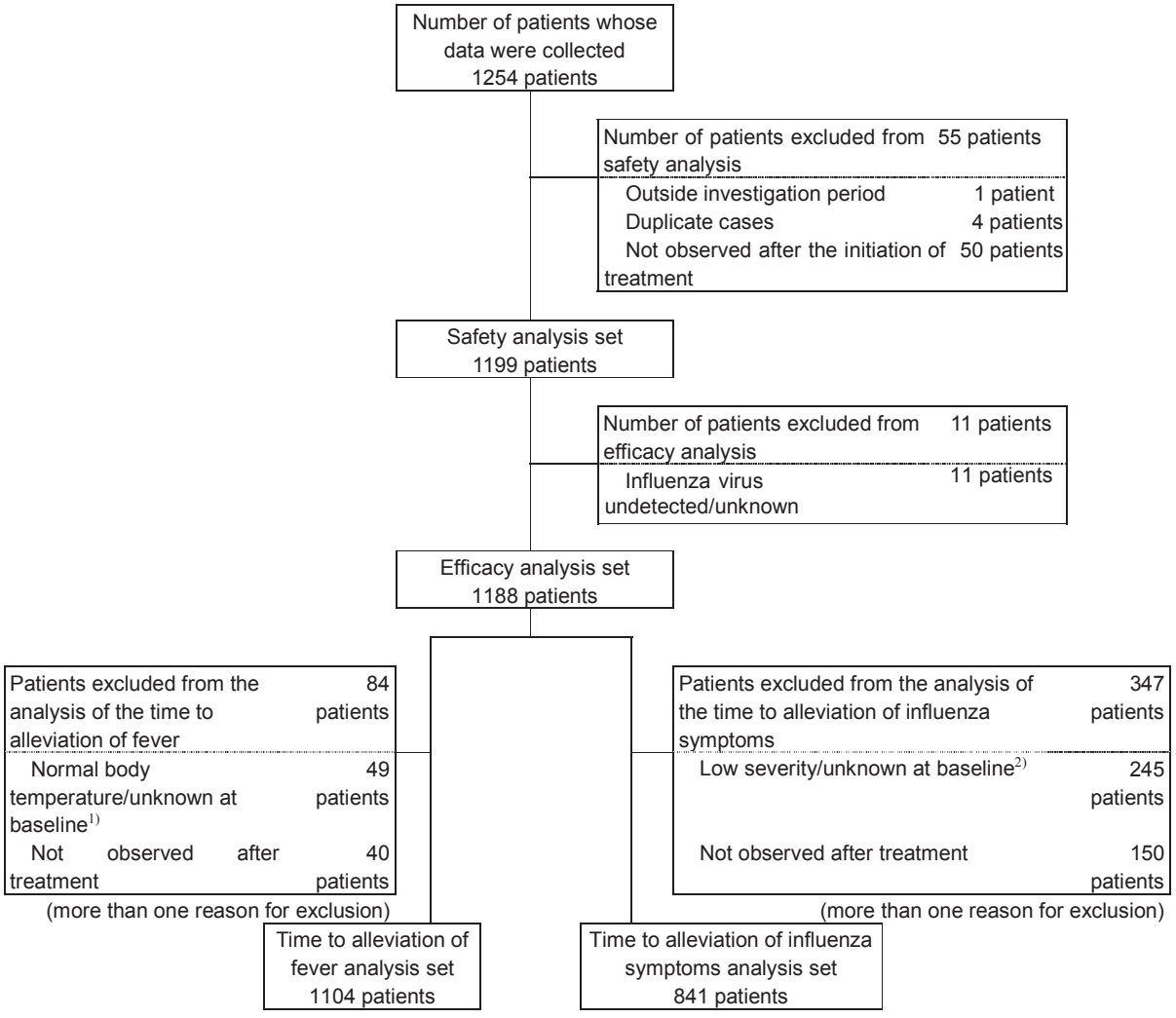
Peramivir was administered according to the dosage and administration specified on the package insert.

The usual dosage of peramivir for pediatric patients is 10 mg/kg/day, administered by a single intravenous drip infusion ≥15 min. Administrations may be repeated daily depending on the symptoms. The maximal dose should be 600 mg at a time.

2.4. Study procedure

This survey was implemented in a continuous investigation system, wherein the participating physicians were instructed to continuously complete survey forms without any exceptions until the patient number reached the requested quota. The physicians provided the following support to peramivir-treated patients and/or their guardians:

(1) They explained the necessity of surveying the safety and effectiveness of peramivir and requested for cooperation.
(2) They provided a peramivir safety and effectiveness check sheet and requested its completion.



1) Patients whose body temperatures were <37.5°C or unknown at baseline.

2) Patients whose severity of all influenza symptoms (cough, sore throat, headache, nasal congestion, feverish feeling or chills, muscle or joint pain, and fatigue) at baseline were either absent to mild or unknown, as assessed on a four-point scale [absent (normal condition), mild (barely noticeable), moderate (bothersome), and severe (unbearable)].

Fig. 1. Patient composition.