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Original article

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

Takuji Komeda [a, *], Shingo Ishii [a], Yumiko Itoh [a], Yasuyuki Ariyasu [a], Masaki Sanekata [a], Takayoshi Yoshikawa [a], Jingoro Shimada [b]

[a] Pharmacovigilance, Shionogi & Co., Ltd., 1-8 Doshomachi 3-chome, Chuo-ku, Osaka 541-0045, Japan
[b] Department of Microbiology, St. Marianna University School of Medicine, 2-16-1 Sugao, Miyamae-ku, Kawasaki, Kanagawa 216-8511, Japan

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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. We conducted a drug use investigation of peramivir from October 2010 to February 2012 and evaluated its safety and effectiveness under routine clinical settings. We collected data of 1309 patients from 189 facilities across Japan and examined safety in 1174 patients and effectiveness in 1158 patients. In total, 143 adverse events were observed with an incidence rate of 7.33% (86/1174). Of these, 78 events were adverse drug reactions (ADRs) with an incidence rate of 4.34% (51/1174). The most frequently reported ADRs were diarrhea, vomiting, and nausea, with incidence rates of 1.87% (22/1174), 0.85% (10/1174), and 0.68% (8/1174), respectively. Moreover, no ADR was reported as serious. ADR onset was within 3 days after the start of peramivir administration in 91.0% (71 events) of the 78 ADRs, and ADRs were resolved or improved within 7 days after onset in 96.2% (75 events) of the 78 ADRs. Neither patient characteristics nor treatment factors appeared to significantly affect drug safety. With regard to effectiveness, the median time to alleviation of both influenza symptoms and fever was 3 days, including the first day of administration. The present study demonstrates the safety and effectiveness of peramivir under routine clinical settings.

1. Introduction

Early administration of neuraminidase inhibitors (NAIs) has been reported to effectively prevent severe influenza virus infections [1–4]. The 2009 pandemic influenza virus A/H1N1 can cause severe pneumonia that requires mechanical ventilation [5,6]. The administration of oral or inhaled agents can be difficult in such severe cases and be problematic in infants and young children, which limits their clinical use. Thus, an intravenous formulation has been a much awaited alternative to enable early treatment with NAI in broader patient populations.

At present, peramivir is the only marketed intravenous NAI. Peramivir exhibits strong antiviral activity *in vitro* and *in vivo* by selectively inhibiting neuraminidase activity, suppressing the proliferation of type A and B influenza viruses [7–11]. After clinical trials confirmed the efficacy and safety of peramivir for influenza infections in adults [12–14], the approval of its manufacturing and marketing was granted and marketing started in January 2010. The present prospective observational drug use investigation was conducted from October 2010 to February 2012 to further assess the safety and effectiveness of peramivir under routine clinical settings. This post-marketing surveillance was required as a condition for approval by the Ministry of Health, Labour and Welfare (MHLW) and was conducted in compliance with the Good Post-Marketing Study Practices specified by the MHLW Ordinance No. 171 (December 20, 2004).

2. Patients and methods

2.1. Patients

All patients regardless of any characteristics (e.g., age) from 189 facilities, mainly comprising internal medicine, across Japan who

* Corresponding author. Tel.: +81 6 6209 6836; fax: +81 6 6233 2540.
E-mail address: takuji.komeda@shionogi.co.jp (T. Komeda).

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began to receive peramivir administration for influenza treatment were surveyed 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 in the package insert.

Adults: The usual dosage of peramivir is 300 mg/day, administered by a single intravenous drip infusion ≥15 min. The dosage for patients in whom symptoms may be aggravated because of complications and other reasons is 600 mg/day, administered by a single intravenous drip infusion ≥15 min. This administration may be repeated daily according to the symptoms. The dosage should be reduced according to the age and symptoms of the patient.

Children: The usual dosage of peramivir is 10 mg/kg/day, administered by a single intravenous drip infusion ≥15 min. Administrations may be repeated daily according to symptoms. The maximal dose should be 600 mg at a time.

2.4. Study procedure

This study was implemented in a continuous investigation system, wherein the participating physicians were instructed to continuously complete survey forms without exception 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 to complete it.

The participating patients completed the check sheet with regard to details such as time course of symptoms and daily maximum body temperature, and returned the sheet at the next hospital visit or posted it to the physician.

The physicians completed the survey forms, including the items related to adverse events (AEs) and effectiveness, by referring to the check sheets for all patients promptly after completing the observation period, including for those who did not provide adequate safety information because of failure to revisit after the first time or to submit the check sheet.

2.5. Attributes investigated

The following information was recorded for each patient: gender (status of pregnancy or nursing in women), age, body weight, date of onset, virus type (test results using rapid diagnostic kits), virus subtype, inpatient or outpatient status at the start of peramivir administration, smoking status, influenza vaccination status, medical history, underlying diseases/complications, allergies, peramivir usage, concomitant drugs, daily maximum body temperature (using unspecified methods), presence of influenza encephalopathy, use of mechanical ventilation, influenza symptoms, outcome of influenza infection, AEs, and laboratory test results. Among AEs, the presence or absence of abnormal behavior, leukopenia/neutropenia, eosinophilia, diarrhea, nausea/vomiting, elevated aspartate aminotransferase/alanine aminotransferase, positive urine ketone bodies, anaphylactic symptoms, and psychiatric/neurological symptoms were compulsory items on the survey form to ensure their detection.

2.6. Safety evaluation criteria

AEs were defined as all untoward or unintended signs (including abnormal laboratory test results), symptoms, or diseases occurring following peramivir administration, regardless of the causality. Adverse drug reactions (ADRs) were defined as AEs whose causality to peramivir could not be ruled out, i.e., those other than "unrelated," as determined by the participating physicians or sponsor. The ADR incidence rate was calculated as follows:

(number of patients with ADR/total number of patients evaluated for safety) × 100

ADR data are compiled according to the ICH Medical Dictionary for Regulatory Activities/J (Ver.15.1).

2.7. Effectiveness evaluation criteria

Effectiveness was evaluated as the time to alleviation of influenza symptoms and fever. The severity of influenza symptoms, including cough, sore throat, headache, nasal congestion, feverish feeling or chills, muscle or joint pain, and fatigue, were evaluated on a four-point scale as follows: absent (normal condition), mild (barely noticeable), moderate (bothersome), and severe (unbearable). Symptom alleviation was considered when all the observed symptoms were scored "mild" or better, and the number of days between the start of peramivir administration and first day of alleviation was considered as the time to alleviation. Fever alleviation was defined as a maximum daily body temperature of <37 °C in adults (age, ≥15 years) or <37.5 °C in children (age, <15 years), and the number of days to this endpoint from the start of peramivir administration was considered as the time to alleviation.

2.8. Statistical analysis

The chi-square test was used to compare ADR incidence rates between categories of patient characteristics and treatment factors. For ordinal variables for which the chi-square test detected significant differences, the Cochran–Armitage test for trend was used. To assess whether the observed differences were proportional to the category order, the goodness of fit test was used. The response "unknown" was excluded from data analysis. Effectiveness was assessed by first calculating the median time (days) to alleviation of influenza symptoms and fever and then obtaining Kaplan–Meier curves showing the time course of the proportion of patients remaining symptomatic. A two-sided significance level of 5% was used throughout.

3. Results

3.1. Study population

We collected data of 1309 patients from 189 facilities. Fig. 1 shows the numbers of patients included and excluded from each assessment. Of the 1309 patients, safety was evaluated in 1174 patients, excluding 133 patients. Effectiveness was assessed in 1158 of the 1174 patients evaluated for safety, excluding 16 patients. Time to symptom alleviation was assessed in 953 patients, excluding 205 patients. Time to fever alleviation was analyzed in 1073 patients, excluding 85 patients.

3.2. Baseline patient characteristics

Table 1 shows the characteristics of the 1174 patients analyzed for safety. Of these, 47.7% (560/1174) were males and 52.2% (613/