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Original Article

Post-marketing safety evaluation of the intravenous anti-influenza neuraminidase inhibitor peramivir: A drug-use investigation in patients with high risk factors

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ABSTRACT

Peramivir, the only injectable anti-influenza neuraminidase inhibitor medically available in Japan at present, is considered first-line treatment in patients with high risk factors for influenza exacerbation. We conducted a drug-use investigation of peramivir in inpatients with high risk factors (old age, pregnancy, and underlying disease such as chronic respiratory disease) from January 2010 to March 2013. Data of 772 patients from 124 facilities across Japan were collected; peramivir's safety in 770 patients and effectiveness in 688 patients were examined. In total, 412 adverse events were observed in 219 patients (28.4%). Of these, 155 events were adverse drug reactions (ADRs) observed in 98 patients (12.7%). Major ADRs (≥2%) were increased aspartate aminotransferase (5.1%), increased alanine aminotransferase (3.8%) and decreased white blood cell count (2.5%). Fourteen serious ADRs were observed in 12 patients (1.6%). All serious ADRs were resolved or improved except for two events for which outcomes were unknown. Multivariate analyses revealed that ADR incidences were significantly associated with these four backgrounds of patients: medical history, no influenza vaccination, renal impairment and other infection(s). With regard to its effectiveness, the median time to alleviation of both influenza symptoms and fever was 3 days, including the first day of administration, which was the same as in other previous surveillance studies. This surveillance study indicated the safety of peramivir in the treatment of influenza inpatients with high risk factors under routine clinical settings.
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1. Introduction

Recent meta-analysis results have shown that treatment with anti-influenza neuraminidase inhibitor (NAI) at early disease stage (within 2 days of symptom onset) to inpatients infected by influenza A H1N1pdm09 virus results in significant reduction of mortality [1]. From these findings, early intervention with NAI can be expected to exert important efficacy in patients who require hospitalized care and may develop influenza exacerbation due to high risk factors (old age, pregnancy, and underlying disease such as chronic respiratory disease). At present, four NAIs are medically available in Japan (oseltamivir, zanamivir, peramivir and laninamivir). Of these, peramivir is the only injectable drug; reliable transfer of active ingredients during intravenous infusion should exhibit efficacy. Thus, peramivir is considered first-line treatment in patients with high risk factors who are given high dosage or administered repeatedly [2], although it is usually given as a single dose in patients whose disease conditions are relatively mild.

In fact, the efficacy/effectiveness and safety of peramivir has been reported from clinical trials [2–5] and post-marketing surveillance studies [6,7]; however, the outcome information on inpatients with high risk factors, if any, has been obtained from a limited number of patients as many were outpatients. Therefore, the efficacy and safety information of peramivir from clinical

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settings would provide better understanding for its useful intervention in inpatients with high risk factors.

We conducted a drug-use investigation of peramivir in inpatients with high risk factors from January 2010 to March 2013. 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).

This paper focuses on the results from an observational drug-use investigation performed in inpatients with high risk factors under routine clinical settings for the purpose of evaluating safety and effectiveness profiles of peramivir.

2. Patients and methods

2.1. Patients

We defined the target population as inpatients with influenza infection possessing high risk factors and surveyed them from 124 facilities during the period of January 2010 to March 2013. Patients with high risk factors were defined as those with at least one of the following characteristics: being pregnant, being ≥65 years old, and suffering from an underlying disease/complication that might exacerbate influenza infection such as chronic respiratory illness/heart disease/kidney disease/liver disease, neurological/neuromuscular disorder, blood dyscrasia, diabetes mellitus, and immunosuppression associated with disease or therapy.

2.2. Dosage and administration

The standard dose of peramivir is 300 or 600 mg/day for adult and 10 mg/kg/day, not to exceed 600 mg at a time, for children, given as an I.V. infusion for ≥15 min, respectively.

2.3. Surveillance study procedure

This surveillance study was implemented in the manner of a continuous investigation system, wherein the participating physicians were instructed to continuously complete survey forms of patients who were judged by the participating physicians as matching the target population described in "2.1. Patients" without exception until the patient number reached the requested quota (including retrospective cases). The physicians completed the survey forms, including baseline characteristics of the patients and the items related to adverse events (AEs) and effectiveness. Noting the presence/absence of the following AEs was required to ensure their detection: abnormal behavior, leukopenia/neutropenia, eosinophilia, diarrhea, nausea/vomiting, elevated aspartate aminotransferase (AST)/alanine aminotransferase (ALT), positive urine ketone bodies, anaphylactic symptoms, and psychiatric/neurological symptoms.

2.4. Safety evaluation criteria

AEs were defined as any unfavorable/unintended sign temporally associated with peramivir administration, whether or not considered related to peramivir. Adverse drug reactions (ADRs) were defined as AEs for which the causality of peramivir could not be ruled out as determined by the participating physicians or sponsor. Seriousness of AEs/ADRs was determined in accordance with the definition in the ICH-E2D guideline. ADR data were compiled according to the ICH Medical Dictionary for Regulatory Activities/J (Ver.16.1).

2.5. 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: normal condition, barely noticeable, bothersome, and unbearable. Symptom alleviation was considered to have occurred when all observed symptoms were scored "barely noticeable" or better. Fever alleviation was considered to have occurred when a maximum daily body temperature of <37 °C in adults (age ≥15 years) or <37.5 °C in children (age <15 years) was reached. And the time to symptom/fever alleviation was defined as the number of days from the start of peramivir administration to these endpoints.

2.6. Statistical analysis

The chi-square test was used to compare incidence rates of ADRs 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 factors showing significance in univariate analysis were further assessed as explanatory variables of a logistic regression model to determine the major factor(s) in ADRs. The response "unknown" was excluded from the 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. All of the various data analyses were performed using the SAS system (release 9.2).

3. Results

3.1. Baseline patient characteristics

We collected data of 772 patients from 124 facilities and examined safety in 770 patients and effectiveness in 688 patients (Fig. 1).

A total of 770 patients were analyzed for safety (Table 1), including one pregnant woman, 463 elderly (≥65 years) patients (60.1%), and 765 inpatients (99.4%). Influenza A and B accounted for 663 patients (86.1%) and 82 patients (10.6%), respectively. Among the 770 patients analyzed for safety, 617 patients (80.1%) possessed at least one of underlying diseases/complications classifiable as high risk factors. These underlying diseases/complications were classified into each high risk factor as follows: chronic respiratory disease (354 patients), immunosuppression associated with disease or therapy (348 patients), neurological disorders/neuromuscular disorders (158 patients), chronic heart disease (143 patients), diabetes mellitus (110 patients), chronic kidney disease (48 patients), chronic liver disease (12 patients) and blood dyscrasias (7 patients).

3.2. Safety

3.2.1. ADR incidence and type

In total, 412 AEs occurred in 219 (28.4%) of the 770 patients. AEs with an incidence of ≥3% were increased AST (9.2%), increased ALT (7.7%), and decreased white blood cell count (4.2%). One hundred twenty-five serious AEs occurred in 77 patients (10.0%). Serious AEs with an incidence of ≥1% were decreased neutrophil count (1.4%), pneumonia (1.4%), increased AST (1.3%), decreased white blood cell

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