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Original article

Spread of viral infection to family members from influenza patients treated with a neuraminidase inhibitor

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ABSTRACT

We compared the incidence rates of household secondary infection among influenza patients prescribed laninamivir, oseltamivir, or zanamivir (neuraminidase inhibitors), based on health-insurance claims data owned by Japan Medical Data Center (JMDC) which was consisting of medical information on patients who were prescribed an anti-influenza drug and their family members between October 2010 and July 2011. The date when an index case patient was prescribed laninamivir, oseltamivir or zanamivir for the first time was defined as "Day 1". If other members in the same family were prescribed laninamivir, oseltamivir, zanamivir, or peramivir during Days 3–8, we assumed any household secondary infection had occurred. The incidence rate was 11.0%, 14.3%, and 11.6% in index case patients prescribed laninamivir, oseltamivir, and zanamivir, respectively. The results of the logistic regression analysis revealed a significant difference between laninamivir and oseltamivir, while no significant difference was observed between laninamivir and zanamivir.

1. Introduction

Influenza begins with a high fever and other symptoms, after an incubation period of about 2 days following infection by the influenza virus. As current clinical practice in Japan, seasonal influenza is primarily treated with neuraminidase inhibitors, which suppress the growth of influenza viruses and promptly improve symptoms such as high fever by inhibiting viral reproduction. However, even if the fever backs to normal, the influenza virus does not completely disappear. Small numbers of influenza viruses are persistently present in recovered patients even several days after alleviation of fever; therefore, this causes the transmission of virus to family members or neighborhoods and is a serious concern throughout this period. It is currently uncertain how often secondary infection might occur in family members of an index case patient who receive a neuraminidase inhibitor, and how many influenza patients are concerned to spread virus and eventually infect to their family members [1].

Two neuraminidase inhibitors of the first generation, i.e. oseltamivir and zanamivir, established efficacy in treatment of influenza [2–5] and so far have been used in Japan. Since 2010, two novel drugs, i.e. peramivir as intravenous-drip infusion formulation and laninamivir as a single inhalation formulation were also available to overcome unmet medical needs of the patients [6–9]. At present, three of them, i.e. oseltamivir, zanamivir and laninamivir have also established efficacy in prevention of influenza [10–17].

The three drugs are predominantly used in outpatient practice in treatment of influenza, however, they are different in that the route of administration and number of doses, in addition, laninamivir's mechanism of action are slightly different from those of the other two agents [18]. Therefore, we focused on the first influenza-infected patient (index case) who was prescribed a neuraminidase inhibitor (laninamivir, oseltamivir or zanamivir) and investigated the incidence rates of household infection among patients prescribed each drug. We analyzed health-insurance claims data owned by Japan Medical Data Center (JMDC).

2. Methods

2.1. Database

Recently, some studies are conducted by using an automated health records database provided by JMDC [19–23]. In the present

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study, we also conducted a research using JMDC data. The primary purpose of the database was to accumulate patient receipts and apply to reimbursement of health care insurance and to survey medical several practices. From these health insurance societies, JMDC obtains all information from receipts issued by each medical institution, collects them on paper and on DVD, and register them into the database. The paper media are scanned as image data and digitized using an optical character reader (OCR).

JMDC data are anonymized and heavily encrypted by the Center's unique "irreversible anonymous aggregation technology". Although this study was exempted from the Ethical Guidelines for Epidemiological Research (Ministry of Education, Culture, Sports, Science and Technology and Ministry of Health, Labor and Welfare, 2002) because it is epidemiological research using only JMDC's anonymized data, we performed our analyses under adequate ethical strictures, e.g., by publishing only numerical data.

2.2. Data collected from the database

We used drug and insurance subscriber data in the JMDC database. The drug data included information on patients who were prescribed anti-influenza drugs between October 2010 and July 2011. The subscriber data included information on patients who were described in the drug data, as well as their family members. Anti-influenza drugs were defined as those for which the first 5 digits of the anatomical classification system (ATC) code in the JMDC database are J05B4: oseltamivir, zanamivir, peramivir, and laninamivir which are shown in Table 1. The drug data consisted of health-insurance claims category, family ID, subscriber ID, year and month of visit, year and month of birth of the subscriber, gender of the subscriber, ATC code, brand name, dispensing date, and number of beds in the prescriber's institute. The subscriber data consisted of family ID, subscriber ID, year and month of birth of the subscriber, and gender of the subscriber.

2.3. Definition of exposure and outcome

The date when an index case patient was prescribed laninamivir, oseltamivir, or zanamivir for the first time was defined as Day 1. Peramivir was excluded from the study because it is administered by drip infusion and is therefore rarely used in outpatient practice.

The definition of each outcome is shown in Table 2. If other members in the same family were prescribed laninamivir, oseltamivir, zanamivir, or peramivir during Days 3–8, we assumed any household secondary infection had occurred.

2.4. Statistical analysis

A logistic regression model with either occurrence of household infection or not as an outcome variable, and drug and background factors as the explanatory variables was applied to estimate the odds ratio and its 95% confidence interval (CI) between laninamivir and oseltamivir or between laninamivir and zanamivir for the rate of household secondary infection. The background factors were age, gender, family size, medical care facility, and dispense period of the index case. Formula of the logistic regression model is shown below:

$$\ln(P/(1-P)) = \beta_0 + \beta_1 x_1 + \beta_2 x_2 + \ldots + \beta_k x_k$$

P: Rate of household infection,
$x_1,\ldots,x_k$: Drug and background factors,
$\beta_0,\ldots,\beta_k$: Coefficient of regression

Subgroup analysis stratified by demography, family size, medical care facility and dispense period of the index case was also performed. In order to evaluate the robustness and consistency of the result, we also performed analyses using five different evaluation periods defined as Days 3–6, Days 3–7, Days 2–6, Days 2–7, and Days 2–8.

The statistical significance level was defined as 5% and all tests were two-sided. All the analyses were performed using SAS® Release 9.2 (SAS Institute Inc., Carey, NC, USA).

Table 1
Neuraminidase inhibitors used for treatment of influenza in Japan.

Generic name	Oseltamivir	Zanamivir	Peramivir	Laninamivir
Brand name	Tamiflu®	Relenza®	Rapiacta®	Inavir®
Approval year	2001	2001	2010	2010
Route of administration	Oral	Inhalation	Drip infusion	Inhalation
Treatment period	Twice daily for 5 days	Twice daily for 5 days	Once daily	Single inhalation

Table 2
Definition of outcome.

	Day 1–2	Days 3–8	Day 9-	Household secondary infection
Family A		X		Yes
Family B				No
Family C	X			No
Family D			X	No

X: Date of prescription.

3. Results

3.1. Study population

A flow chart for families is shown in Fig. 1. In the JMDC database, a total of 58,076 families included a patient who was prescribed an anti-influenza drug during our study period. We analyzed 24,726 of these families: 6362 treated with laninamivir, 12,142 with oseltamivir, and 6222 with zanamivir. The reasons for exclusion from the analysis were as follows: missing a dispensing date 23,670; no other members in the same family ID 8204; index case prescribed two or more anti-influenza drugs 31; or two or more initially infected patients in the same household 1378. Furthermore, because the purpose of the study was to investigate household secondary infection, hospitalized patients 67 were excluded from the analysis.

3.2. Baseline characteristics of patients

Baseline characteristics of the index cases are shown in Table 3. In each characteristics, comparisons among three groups are statistically significant ($P < 0.0001$) by using analysis of variance (ANOVA) for quantitative data and chi-squared test for categorical data. In actual, however, when there are large samples, the statistically-significant differences are shown in case of small differences.

The average age of the family members of the index case was 27.9, 25.7 and 29.4 years old for laninamivir, oseltamivir, and zanamivir respectively. Women accounted for 50% of family members in each drug group.