Effect of a Single Inhalation of Laninamivir Octanoate in Children With Influenza

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**KEY WORDS**
laninamivir; zanamivir; neuraminidase, influenza, child

**ABBREVIATIONS**
LO—laninamivir octanoate
NAI—neuraminidase inhibitor
OT—oseltamivir
ZN—zanamivir

Dr Katsumi designed the study, analyzed the data, and drafted the article; Dr Otabe examined many pediatric patients in the study as a leader of clinical doctors; Dr Matsui examined many pediatric patients in the study as a subleader of clinical doctors; Drs Kidowaki, Mibayashi, and Tsuma examined many pediatric patients in the study as a clinical doctor; and Dr Ito designed the study and revised the article.

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**WHAT’S KNOWN ON THIS SUBJECT:** A single inhalation of laninamivir octanoate has previously been shown to be as effective as repeated doses of zanamivir in vitro and in vivo, but it is not known whether this is also the case for children.

**WHAT THIS STUDY ADDS:** Median time to fever resolution was not significantly different between laninamivir octanoate and zanamivir for pediatric patients with influenza. The severity of influenza symptoms and the frequency of complications were similar in the 2 groups.

**abstract**

**OBJECTIVE:** The purpose of this study was to compare the efficiency and safety of a new neuraminidase inhibitor, laninamivir octanoate (LO), with zanamivir (ZN) in pediatric patients with influenza.

**METHODS:** One hundred twelve pediatric patients ≤15 years, diagnosed with a rapid diagnostic test as having influenza from January to May 2011, were randomly assigned to the LO group or the ZN group, and their parents were asked to complete a questionnaire during the recovery at home. The LO group was instructed to inhale LO once (20 or 40 mg depending on age), and the ZN group was instructed to inhale ZN (20 mg) twice daily for 5 days.

**RESULTS:** The LO group (n = 55) and the ZN group (n = 57) were well balanced. Finally, 44 patients in the LO group and 41 patients in the ZN group could be evaluated. Median times to fever resolution after initial treatment were 36 hours in the LO group and 37 hours in the ZN group. No differences were observed between the 2 groups with respect to the frequencies of asthmatic symptoms, pneumonia, gastrointestinal symptoms, or abnormal behaviors. Six younger children could not inhale LO well for technical reasons.

**CONCLUSIONS:** Our data suggest that the efficiency and safety of LO are the same as those of ZN in pediatric patients with influenza but that LO may be more convenient than ZN because it requires only a single inhalation. However, younger patients may not inhale LO efficiently.

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Neuraminidase inhibitors (NAIs) have been reported to be effective in preventing severe illness in patients with influenza A (H1N1) 2009 virus infection.\(^1\) \(^2\) In Japan, early treatment of life-threatening cases of influenza with NAIs is recommended. Zanamivir (ZN) is a conventional NAI that, when inhaled as a powder, alleviates the symptoms of pediatric patients with influenza.\(^3\) Another NAI that is used to treat influenza, Oseltamivir (OT), is not recommended for children above the age of 10 years by the Japanese Ministry of Health, Labor and Welfare because it is suspected to induce abnormal behaviors. Therefore, until recently, ZN was the only NAI available to these patients in Japan.

A new orally inhaled NAI, laninamivir octanoate (LO), an octanoyl ester prodrug of Laninamivir, was developed by Daiichi Sankyo (Tokyo, Japan). In vitro experiments, LO inhibited the neuraminidase activities of various types of influenza A, including influenza A (H1N1) 2009 virus, highly pathogenic avian H5N1 viruses, B influenza viruses, and OT-resistant viruses.\(^4\) \(^5\) After intranasal administration of LO to mice, LO was efficiently converted to laninamivir, an active form of a long-acting NAI, by hydrolases such as carboxylesterase in the trachea and lung. Laninamivir binds to the neuraminidase of influenza virus more tightly than do other NAIs and can inhibit both infection and proliferation of influenza virus in these tissues for a few days.\(^6\) \(^7\) In a mouse influenza virus infection model, a single inhalation of LO reduced the influenza virus titer in the lungs by approximately the same amount as repeated inhalations of ZN.\(^8\) In previous clinical trials, a single inhalation of LO was estimated to be as effective as repeated doses of OT.\(^9\) \(^10\) The first of these 2 studies\(^8\) was published in June 2010. Subsequently, in October 2010, LO was approved for pediatric and adult patients with influenza in Japan.\(^11\)

However, LO has not yet been compared with ZN clinically. Our purpose for this study was to compare LO and ZN with respect to median time to fever resolution, the occurrence of other symptoms, and compliance in pediatric patients with influenza.

METHODS

Study Design and Criteria for Enrollment

The study was a randomized controlled study conducted between January 2011 and May 2011 at our hospital. The institutional review board of our hospital approved the study protocol. Eligible patients were children up to the age of 15 years, which is the maximum age that our pediatric department accepts, who had an axillary temperature of 38.0°C or higher and who presented with respiratory symptoms (cough and/or sore throat) when recruited to the study. Influenza virus infection was diagnosed based on the results obtained with a rapid diagnostic test (Poctem Influenza A/B [Sysmex, Kobe, Japan]). According to the manufacturer, the sensitivity and specificity of the test are 83.8% and 92.3%, respectively, for influenza A, and 98.4% and 98.1% for influenza B. Patients were excluded from this study if (1) they were diagnosed by clinical symptoms alone in the presence of an influenza epidemic, (2) they had any chronic respiratory disease, cardiovascular disease, central nervous disorder, renal dysfunction, metabolic disorder, immune dysfunction, or other chronic comorbid condition except asthma, (3) they had a fever for more than 48 hours duration from the time of onset when they were diagnosed as having influenza, (4) their parents or clinician felt that the patients could not inhale the NAI well, and (5) they or their parents did not accept the assigned drug for any reason (these included a patient who did not want to be assigned an inhaled NAI, a patient that wanted OT, or a patient who did not want NAI treatment).

Method of Randomization and Drug Administration

Patients, who were diagnosed as having influenza A or B by the diagnostic test and who could inhale an NAI, were randomly assigned to 1 of the NAI groups as follows. First we received verbal consent from the parents (and also from the child if the child was old enough to understand based on their ability to understand during the medical interview) to administer LO or ZN, randomly assigned according to a day of the week, hour, and the examination room in advance. Then the patients and their parents were shown the selected NAI and how it was used and were asked whether the patient could inhale it. The parents were shown a questionnaire that was designed to be filled out at home. The drugs were given at home, and the symptoms were observed by the parents. All of the clinical examinations and drug prescriptions were considered as treatments by the Japanese public health system. Typically, families pay ~30% of the costs of the treatments. LO was administered as a single inhalation on the day that the patient was diagnosed. The dose of LO was 20 mg for patients <10 years of age and 40 mg for patients 10 to 15 years of age. ZN was administered at two 10-mg doses per day for 5 days. We asked them to evaluate the time to fever resolution without recent use of acetaminophen.

Questionnaire

The questionnaire asked about symptoms before and after drug administration, including gastrointestinal symptoms, asthmatic symptoms, pneumonia, abnormal behaviors, drug compliance and reasons for low compliance if applicable, and number of days absent from school or
preschool. Asthmatic symptoms were defined as coughing and wheezing diagnosed by a doctor. Abnormal behaviors were defined as symptoms advocated by the Ministry of Health, Labor, and Welfare in Japan\textsuperscript{12} and were listed on the questionnaire: (1) running suddenly without a specific purpose, (2) falling from a building, (3) dangerous behavior with a risk of fatal accident or harm to other persons, (4) meaningless speech without assessment of the situation, (5) sensations of fear, (6) visual hallucinations, (7) crying without a specific purpose, (8) marked excitement or panic, (9) skipping without a specific purpose, (10) delirious behavior, (11) moving without a specific purpose, and (12) meaningless behavior without a risk of fatal accident. Parents were instructed to mail the completed questionnaire to our hospital after the patient’s symptoms had completely resolved.

**Time to Fever Resolution**

In Japan, children who have influenza are not allowed to return to school until they have had 3 consecutive days without fever. Therefore, in this study, the end point was based on only fever and not other influenza symptoms such as cough or sore throat. The onset of fever was defined as the time when axillary temperature was first measured as 38.0°C or more. Time to fever resolution was defined as the time until the beginning of the first 12-hour period in which the axillary temperature returned to less than 37.5°C without recent use of acetaminophen.

**RESULTS**

**Patient Disposition and Characteristics**

Of 235 patients who were clinically diagnosed with influenza, 112 remained after exclusions and were assigned to the LO group (n = 55) or the ZN group (n = 57) (Fig 1). The baseline characteristics of the 2 groups were not significantly different with respect to age, time from onset of fever to beginning of treatment (Table 1). Of the 112 questionnaires, 100 were returned, including 44 patients in the LO group, 41 patients in the ZN group, and 15 patients whose compliance was judged from the questionnaires to be low.

**Clinical Outcome**

Approximately half of the 44 LO patients and approximately half of the 41 ZN patients resolved fever within 36 hours (Table 2). The median time to fever resolution in the LO patients (36 hours; n = 44) was nearly the same as that in the ZN patients (37 hours; n = 41). When the patients with low compliance were included, the median times for fever resolution for the LO group (36 hours; n = 52) and ZN group (37.5 hours; n = 48) were still not significantly different. When the patients with influenza A and patients with influenza B were examined separately, the times to fever resolution for the LO and ZN groups were also not significantly different. The two groups were not significantly different with respect to the number of days absent from school or preschool. The frequencies of asthmatic symptoms, pneumonia, gastrointestinal symptoms, and abnormal behaviors were similar in the 2 groups. None of the patients in either group required admission to our hospital for influenza virus infection. Only 2 abnormal behaviors (meaningless movements and sensations of fear) were observed in the patients (3 LO

**Statistical Analysis**

Statistical differences between the LO and ZN groups were evaluated by using Student’s t test. P < .05 was considered to indicate a statistically significant difference. All analyses were performed by using Excel 2003 (Microsoft, Tokyo, Japan) with the add-in software Statcel 2 (OMS Press, Saitama, Japan).
patients and 3 ZN patients), and they were not dangerous, did not require any treatment, and were spontaneously resolved within a few hours.

Time to fever resolution for younger patients was not significantly different from that for older patients in both the LO group (Fig 2A) and ZN group (Fig 2B).

**DISCUSSION**

Our results reveal that the clinical efficiency and safety of LO were similar to those of ZN. None of the eligible patients were admitted to hospital for any reason, although 1 of the patients excluded for chronic diseases was admitted with progression of Henoch-Schönlein purpura nephritis and influenza virus infection. Abnormal behaviors were observed in only a few of the LO and ZN patients and were not noticeably different in the 2 groups. These results suggest that patients 10 years of age and more, who are not allowed to be given OT in Japan, can be treated with LO.

The clinical efficiency of LO for patients with influenza A (H1N1) 2009 has not been reported, although the in vitro 50% inhibitory concentration of LO was the same as that of other NAs (including ZN) against influenza A (H1N1) 2009 viruses.\(^\text{13}\) When this study was conducted, the majority of patients with influenza A were infected with influenza A (H1N1) 2009,\(^\text{14}\) which suggests that most of our influenza A patients were infected with influenza A (H1N1) 2009. Thus, our results suggest that none of our study participants have been infected with a drug-resistant influenza
A (H1N1) 2009 virus. Further, time to fever resolution with LO was similar to that with ZN in influenza A (H1N1) 2009.

Some of the patients in both groups did not inhale deeply enough to receive the entire medication dose as we and their parents wanted. We assume that these patients did not get enough medicine. Incomplete inhalation of the single dose of LO may prolong fever more than failure to inhale ZN 1 time because ZN is inhaled 10 times more frequently than LO. However, the number of younger children in the LO group was too small to test this idea. Additional studies are needed to determine how incomplete LO inhalation affects time to fever resolution. At least for older pediatric patients with influenza, a single inhalation of LO was sufficient and may be more convenient than 10 inhalations of ZN for 5 days.

This study has some limitations. Assignment of patients to the 2 groups was not completely random because we did not know which drug the next patient would be given. The sample size was small, especially for younger pediatric patients. The results were evaluated by the parents, introducing possible bias.

**CONCLUSIONS**

The efficiency of LO against influenza appears to be the same as that of ZN. Although OT, ZN, and LO are effective for pediatric patients with influenza, LO may be more convenient because it requires only a single inhalation, especially for older pediatric patients.

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