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Clinical efficacy of new neuraminidase inhibitors, laninamivir and peramivir in patients with seasonal influenza; a randomized clinical trial

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Introduction

In Japan, influenza is currently treated with neuraminidase inhibitors, such as oseltamivir, zanamivir, laninamivir, and peramivir. Oseltamivir and zanamivir are available worldwide. In contrast, the new neuraminidase inhibitors, laninamivir and peramivir, are used in limited countries and their clinical efficacy for seasonal influenza remains unclear.

Peramivir is the only drug administered intravenously. Treatment for seasonal influenza is usually completed by a single dose, which is advantageous for medication adherence. However, the clinical efficacy of peramivir remains unclear.

laninamivir exerts its neuraminidase inhibitory activity against influenza A and B viruses, including oseltamivir-resistant viruses and the 2009 pandemic H1N1 virus. In addition, a major clinical benefit of this drug is that treatment for influenza can be completed by a single inhaled dose, which is convenient for both patients and physicians, and leads to improved compliance. However, the use of this drug is also limited to few countries.

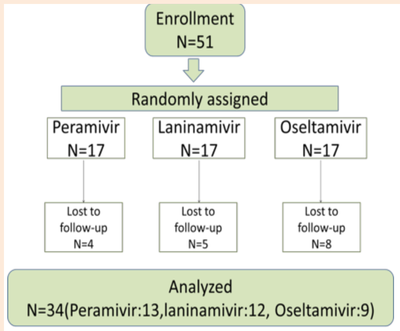
In this prospective randomized clinical trial, we compared the clinical efficacy of peramivir and laninamivir with that of oseltamivir for adult patients

Methods

This study was a randomized, controlled, single-center trial that compared the efficacy of three neuraminidase inhibitors, including oseltamivir, laninamivir, and peramivir. This prospective study was performed in accordance with the Helsinki Declaration of the World Medical Association and was approved by the ethical committee of Teikyo University School of Medicine(No. 12-167). Influenza patients who visited the outpatient clinic of Teikyo University Hospital, Tokyo, Japan in the flu season (November, December, January, February, March) between November 2013 and March 2015 were enrolled to this study. Written informed consent was obtained from all study participants. Influenza was diagnosed on the basis of a positive result of influenza rapid antigen test, in the presence of signs and symptoms of influenza-like illness, including fever, muscle pain, chills, sweating, headache, dry cough, and respiratory failure, without other focal signs of infection. Fever was defined as an axillary temperature of ≥37.0 ˚C. Patients who were febrile for ≥48 hours on the first hospital were excluded in this study. Patients were randomized equally to receive either oral oseltamivir (75 mg twice daily for 5 days), inhaled laninamivir (40 mg one dose), or intravenous peramivir (300 mg one dose). Demographic and clinical data, such as age, gender, maximum body temperature after disease onset, and time course of fever were collected on the first visit. Symptoms, such as cough, sore throat, nasal discharge, headache, muscle pain, joint pain, nausea/vomiting, and diarrhea, as well as body temperature, pulse rate, and type of influenza (influenza A or B), were also noted on the visit. After treatment for influenza, the clinical course of the symptoms was evaluated by a questionnaire. Patients who did not submit the questionnaire were excluded from this study.

The primary endpoint of this study was time to defervescence after treatment; the secondary endpoint was resolution of other symptoms. Time to defervescence was defined as the period when axillary temperature reached below 37.0 ˚C for more than two days. The results were compared among the three neuraminidase inhibitor groups and between the single-dose group (peramivir and laninamivir) and the multiple-dose group (oseltamivir).

The results were expressed as mean and standard deviation, unless otherwise indicated. For multiple comparisons of independent groups, chi-square test, Fisher's exact test, or Mann-Whitney U test with Bonferroni adjustment was used to analyze continuous and categorical data, as appropriate. All P values were two-sided and considered statistically significant at $p < 0.05$.



Results

The clinical background of the study population is summarized in Table 1. Duration of fever on the first visit was similar among the 3 groups: 24 hours in the oseltamivir group, 28.1 hours in the laninamivir group, and 25.9 hours in peramivir group. The other clinical characteristics and accompanying symptoms were likewise not significantly different among the 3 groups (Tables 1 and 2).

Table 1

	Oseltamivir	Laninamivir	Peramivir
Age, years (mean ± SD)	*40.4±9.84*	*36.2±10.0*	*43.6±15.3*
Gender (Female)	*6(66.7%)*	*9(75.0%)*	*7(53.8%)*
Maximum BT, ˚C (mean ± SD)	*38.8±0.61*	*38.5±0.64*	*38.6±0.55*
BT, ˚C (mean ± SD)	*38.2±1.14*	*37.7±0.50*	*37.9±0.53*
Duration of fever, hours(mean ± SD)	*24.0±12.0*	*28.1±17.3*	*25.9±22.8*
Pulse rate per min (mean ± SD)	*104±16.4*	*104±19.5*	*107±20.8*
Patients with influenza type A,	*8(88.9%)*	*10(83.3%)*	*10(76.9%)*
Comorbid conditions, n (%)			
Malignancy	*0(0.0%)*	*2(16.7%)*	*0(0.0%)*
Congestive heart failure	*0(0.0%)*	*0(0.0%)*	*0(0.0%)*
Diabetes mellitus	*0(0.0%)*	*1(8.3%)*	*2(15.4%)*
Chronic renal failure	*0(0.0%)*	*1(8.3%)*	*2(15.4%)*
Liver cirrhosis	*0(0.0%)*	*0(0.0%)*	*0(0.0%)*
Bronchia l asthma	*0(0.0%)*	*1(8.3%)*	*0(0.0%)*
Other airway diseases	*0(0.0%)*	*0(0.0%)*	*1(7.7%)*
Use of immunosuppressive	*1(11.1%)*	*1(8.3%)*	*0(0.0%)*
Immunosuppressive diseases	*1(11.1%)*	*0(0.0%)*	*0(0.0%)*

Table 2

N (%)	Oseltamivir (n=9)	Laninamivir (n=12)	Peramivir (n=13)
Cough	*8(88.9%)*	*10(83.3%)*	*11(84.6%)*
Sore throat	*8(88.9%)*	*9(75.0%)*	*6(46.2%)*
Nasal discharge	*8(88.9%)*	*10(83.3%)*	*8(61.5%)*
Headache	*8(88.9%)*	*10(83.3%)*	*9(69.2%)*
Muscle pain	*8(88.9%)*	*11(91.7%)*	*13(100%)*
Joint pain	*8(88.9%)*	*11(91.7%)*	*10(76.9%)*
Nausea/Vomiting	*4(44.4%)*	*3(25.0%)*	*4(30.8%)*
Diarrhea	*3(33.3%)*	*3(25.0%)*	*6(46.2%)*

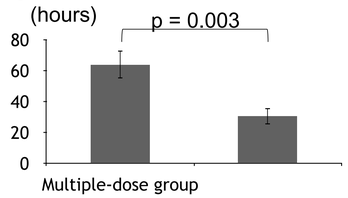
As shown in Figure 1, the average time to defervescence was significantly shorter in the peramivir group than in the oseltamivir group (24 hours vs. 64 hours, $p = 0.004$). The laninamivir group had shorter duration of fever (38 hours) than the oseltamivir group, but this difference was not significant ($p = 0.151$). There were no significant differences among the 3 groups in terms of resolution of other symptoms after treatment (data not shown).

Figure 1

Average time to defervescence after treatment for influenza. There was significant difference between oseltamivir group and peramivir group ($p = 0.004$) Laninamivir group tended to have shorter duration of fever, although not significantly different ($p = 0.151$)

As shown in Figure 2, the average time to defervescence was significantly shorter in the single-dose group than the multiple-dose group (30.7 hours vs. 64 hours, $p = 0.003$). There were no significant differences between the 2 groups in terms of resolution of other symptoms after treatment (data not shown).

Figure 2



There was significant difference between oseltamivir group and single-dose group in average time to defervescence after treatment ($p = 0.003$).

Conclusions

Our study showed that peramivir was valuable in patients with seasonal influenza. The blood concentration of peramivir peaks immediately after intravenous administration; in addition, this route easily leads to high concentration of the drug in serum. This may explain the superiority of peramivir compared to oseltamivir for the treatment of seasonal influenza.

In this study, we demonstrated that the average time to defervescence was approximately 24 hours shorter after laninamivir treatment than after oseltamivir treatment, although the difference was not significant. Considering drug compliance, the single-dose laninamivir might be clinically more advantageous than the multiple-dose oseltamivir.