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 oral oseltamivir, which is advantageous in terms of adherence. However, the clinical efficacy of peramivir remains unclear. Laninamivir exerts its neuraminidase inhibitory activity against 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 influenza remains isolated, which is advantageous in terms of medication adherence. However, the clinical efficacy of peramivir remains unclear.

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 as 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 influenza 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 obtained from rapid antigen test, in the presence of signs and symptoms of influenza-like illness, including fever, headache, muscle pain, diarrhea, and respiratory failure, without other focal signs of infection. Fewer than 10% of all axillar temperature was ≥ 37.0 °C. Patients who were febrile for ≥48 hours on the first day were excluded from this study. Patients were randomized equally to receive either oral oseltamivir (75 mg twice daily for 5 days), intravenous peramivir (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.

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 symptoms, independent groups, chi-square test, Fisher’s exact test, or Mann-Whitney U test with Bonferroni adjustment was used to analyze categorical data, as appropriate. All P values were calculated 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,

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 single-dose 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.