〈Original Article〉

Comparative analysis of laninamivir octanoate hydrate in inhalation suspension set and other anti-influenza drugs in treating influenza in children

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Purpose: Laninamivir octanoate hydrate is a long-acting neuraminidase inhibitor but may not be effective in infants, who generally experience inhalation difficulty. No study has compared the clinical profiles of Laninamivir Nebulizer, the inhalation suspension set form of this drug, and other anti-influenza drugs and different patient statuses. Here, we compared the effectiveness and adverse events of Laninamivir Nebulizer inhalation and treatment with those of other anti-influenza drugs.

Patients and Methods: One hundred twenty-six children with influenza were divided into the following groups according to their therapeutic scheme: Laninamivir Nebulizer, all other drugs except for Laninamivir Nebulizer, Laninamivir, and Oseltamivir. The primary endpoints of the present study were time to resolution of fever and rates of household members with secondary infection. Adverse events were also analyzed.

Results: According to the Log rank test results, the mean time to resolution of fever for the Laninamivir Nebulizer group did not significantly differ from that for the Other drugs, Laninamivir, and Oseltamivir groups for both influenza A and B subtypes. The hazard ratio of the time to resolution of fever for the Laninamivir Nebulizer group did not significantly differ from that for the Other drugs, Laninamivir, and Oseltamivir groups for both influenza A and B and in the influenza A cohort. However, the mean time to resolution of fever for the Laninamivir Nebulizer group was significantly shorter than that for the Other drugs (Laninamivir Nebulizer vs. Other drugs groups = 51.1 ± 4.8 and 70.8 ± 8.1 h, respectively, $p = 0.0133^{*}$), Laninamivir (Laninamivir Nebulizer vs. Laninamivir groups = 51.2 ± 4.8 and 71.8 ± 10.0 h, respectively, $p = 0.0454^{*}$), and Oseltamivir

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(Laninamivir Nebulizer vs. Oseltamivir group = 51.1 ± 4.8 and 94.5 ± 14.2 h, respectively, $p = 0.0015^*$) groups in the influenza B cohort. The hazard ratio for time to resolution for the Laninamivir Nebulizer group was significantly greater than that for the Other drugs (Laninamivir Nebulizer group = 1.87 [95% CI: 1.05–3.35], $p = 0.0347^*$] and Oseltamivir (Laninamivir Nebulizer group = 3.38 [95% CI: 1.27–9.00], $p = 0.0151^*$] groups in the influenza B cohort. Both the hazard ratio of the rate of household members with secondary infection and the odds ratio did not significantly differ between the Laninamivir Nebulizer and other drug treatment groups. Although 11.8% (6/51) of the patients cried during nebulizer-mediated inhalation in the Laninamivir Nebulizer group, effectiveness, household transmission, and adverse events did not significantly differ between patients who cried and those who did not during nebulizer-mediated inhalation.

Conclusions: Clinical profiles of the Laninamivir Nebulizer group were equivalent to those of other anti-influenza drug treatment groups. Laninamivir Nebulizer may be a good therapeutic option for infants with influenza and inhalation difficulty.

Key words : Laninamivir octanoate hydrate, inhalation, nebulizer, influenza, children

Introduction

In Japan, in the last three winters (2016/2017, 2017/2018, and 2019/2020 seasons), approximately 10–20 million people contracted influenza, and nearly 10% of them comprised children aged less than 5 years[1–3]. Among the children with influenza treated at Ando Clinic (Narashino City, Chiba, Japan), nearly 35–50% were less than 5–7 years of age[4–6]. Children are usually treated with oseltamivir since it is a classic conventional drug and can be administered in dry powdered form. However, small children frequently cannot take this dry powder because of its taste. Moreover, oseltamivir-resistant viruses have been reported[7,8]. Laninamivir octanoate hydrate (laninamivir) is an octanoyl prodrug and a neuraminidase inhibitor effective against both influenza A and B viruses as well as highly pathogenic avian H5N1 and oseltamivir-resistant viruses[7,8]. A single dose of laninamivir inhaled using a dry powder inhaler is effective and well-tolerated by both children and adults for treatment[9,10] and prophylaxis[11,12] of influenza. A proper inhalation technique is crucial for effective inhalation of laninamivir. Ensuring effective delivery is challenging without training. Therefore, laninamivir may not be sufficiently effective in patients with inhalation difficulty, such as infants. For laninamivir, an inhalation suspension set (Laninamivir Nebulizer) is available as a kit using a nebulizer, which was launched on October 25, 2019[13]. This form of laninamivir is easy to inhale for patients such as infants, who are generally non-cooperative during the administration of other forms of drugs. However, only one study

concerning the use of Laninamivir Nebulizer among adults, primarily examining its pharmacokinetics, has been published so far[14]. A study on the safety and efficacy of Laninamivir Nebulizer in children under the age of 5 years based on post-market surveillance data was recently published[13]. However, no study has compared the efficacy of Laninamivir Nebulizer with that of other anti-influenza drugs. In this study, Laninamivir Nebulizer was compared with other neuraminidase inhibitors used for treating influenza in terms of effectiveness, household transmission of secondary influenza virus infection, and adverse events during the 2019–2020 flu season. Additionally, the effectiveness of Laninamivir Nebulizer in the context of patients' statuses (crying or non-crying) was prospectively examined because it may be difficult for small, crying patients to properly inhale laninamivir.

Patients and Methods

Patients and data collection

This study was designed as a prospective cohort study. The patients and/or their parents were informed of the study design. Included were children diagnosed positive for influenza after a rapid influenza diagnostic test (RIDT) at the Ando Clinic (Narashino City, Chiba, Japan) during the 2019–2020 flu season. Excluded were patients who had already began treatment for influenza in another hospital. The patients were divided into the following four groups: 1) Laninamivir Nebulizer—patients treated with Laninamivir Nebulizer; 2) Other drugs—patients treated with other anti-influenza drugs, namely laninamivir and oseltamivir powder; 3) Laninamivir—patients treated with laninamivir; and 4) Oseltamivir—patients treated with oseltamivir phosphate (Oseltamivir). Patients treated with anti-influenza drugs other than those mentioned above were not analyzed owing to the small sample size. During presentation, the following clinical information was collected: sex, age, type of influenza, vaccination status for the quadrivalent influenza vaccine, comorbidities, body temperature, time from onset, and type of anti-influenza drugs administered. Comorbidities were defined as conditions that may affect the immune status[15]. The following comorbidities were considered: chronic pulmonary, cardiovascular (excluding hypertension), renal, liver, hematologic, and neurological disorders, diabetes mellitus, autoimmune disorders, congenital anomaly, and cancer[15]. Data regarding time to resolution of fever, adverse events of anti-influenza drugs, and household members with secondary influenza virus infection were collected at follow-up or by telephone interview.

Diagnosis of influenza

Nasopharyngeal swabs were obtained from all patients and tested using the ImunoAce™ Flu test kit (TAUNS Laboratories, Inc., Shizuoka, Japan). The ImunoAce™ Flu test can detect and differentiate between influenza A and B virus, with high positive (influenza A: 100%, influenza B:

100%) and negative (influenza A: 98.7%, influenza B: 99.3%) concordance rates, as demonstrated using a viral isolation culture (from package insert)[6].

Anti-influenza drugs

Laninamivir Nebulizer was administered as one dose at 160 mg suspended in 2 mL saline using a nebulizer on day 1 in an isolated examination room. Laninamivir was administered as one dose of 20 mg (＜10 years) or 40 mg (≥10 years) by inhalation in powder form on day 1. Oseltamivir was administered in two doses of 3 mg/kg (＜1 year) or 2 mg/kg (≥ 1 year, maximum dose: 75 mg) orally on days 1–5. Zanamivir hydrate (zanamivir) was administered in two doses of 10 mg by inhalation on days 1–5. Peramivir hydrate (peramivir) was administered as one dose of 10 mg/kg intravenously for more than 15 mins on day 1 (maximum dose: 600 mg/day). Baloxavir marboxil (baloxavir) was administered as one dose of 10 mg (＜12 years: bodyweight ≥10 kg and ＜20 kg), 20 mg (＜12 years: bodyweight ≥20 kg and ＜40 kg), or 40 mg (≥12 years: bodyweight ≥40 kg) orally on day 1.

Analysis of drug effectiveness

The primary endpoint for treatment effectiveness was time to resolution of fever. Time to resolution of fever was defined as the time from the patient's first presentation to the time at which the body temperature of the patient returned to less than 37.5℃ (or in which the body temperature of each patient returned to the normal range) and remained stable for at least 24 h. Patients who required withdrawal and drug change owing to ineffectiveness or adverse events related to anti-influenza drugs were excluded from the analysis of household transmission. Patients who consulted a secondary hospital owing to ineffectiveness or adverse events of anti-influenza drugs were also excluded from the analysis of household transmission. A drug was regarded as ineffective when fever and symptoms continued for more than 72 h. When the patients could not be followed up at the clinic before the resolution of fever or symptoms, they were not included in this analysis.

Analysis of household transmission of influenza virus infection

Household transmission was defined as the occurrence of secondary infection among residual uninfected household members within the time interval from the presentation of the first patient to the occurrence of secondary infection, which was ≥ 1 day and ≤ 7 days, respectively[16,17]. The risk of household transmission anti-influenza drug intake was estimated based on the household transmission rate, defined as the number of secondarily infected household members divided by the number of residual uninfected household members × 100[16]. Index patients were defined as the first patient from each household diagnosed with influenza in the 2019–2020 flu season at the Ando Clinic. Patients meeting the following criteria were included: those diagnosed positive for

influenza after RIDT and treated with anti-influenza drugs.

The following patients were excluded: 1) index patients with household members already diagnosed with influenza 2 weeks before the first visit; 2) patients who were a family member of the index patient (since the analysis in this study was based on the family as a unit); 3) patients who required withdrawal and change of drugs owing to ineffectiveness of or adverse events caused by anti-influenza drugs; 4) patients with no residual family member; and 5) patients who could not be followed up before the resolution of fever or symptoms (these cases were regarded as dropped).

Statistical analyses

Sample-size calculation was not performed. The Mann–Whitney U test was used to compare continuous variables (i.e., age, body temperature, and time from onset) between groups. Fisher's exact test was used to compare nominal variables (i.e., sex, type of influenza, and presence or absence of both vaccination and comorbidities). For analyses of time to resolution of fever and rate of household transmission, a Log rank test was used to compare the Laninamivir Nebulizer and Other drugs groups. Cox proportional hazards regression was used for multivariable analysis. Hazard ratios were adjusted for sex, age, and the subtype of influenza (A and B). To analyze the prevalence of adverse events, Fisher's exact test was used. Logistic regression analysis was used for calculating the odds ratio of adverse events. Odds ratios of adverse events were adjusted for sex, age, and subtype of influenza (A and B). Any adverse events during the clinical course, including delirium, confusion, hallucinations, vomiting, diarrhea, anorexia, eyelid function disorder, chest pain, and/or rash maculopapular, were recorded for all patients. The nomenclature was in accordance with the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 (along with Medical Dictionary for Regulatory Activities: MedDRA version 21.0)[18]. The prevalence of adverse events was defined as the number of cases with adverse events divided by the total number of cases. Odds ratios of adverse events were adjusted for sex and age and subtype of influenza (A and B). Overlapping was permitted (i.e., multiple adverse events could be associated with one case). A two-sided P-value < 0.05 indicated statistical significance. Statistical analyses were performed using JMP® 15.2 (Statistical Analysis Software, SAS Institute Inc., Cary, NC, USA).

Ethical statement

This study was conducted according to the tenets of the Declaration of Helsinki. Written informed consent was obtained from the patients, their parents, or both. Participants were recruited prospectively. The study design was approved by the Joint Institutional Review Board, and all patients were part of a previous study on influenza vaccine effectiveness (approval number: 14000050.20191220-4830)[19].

Results

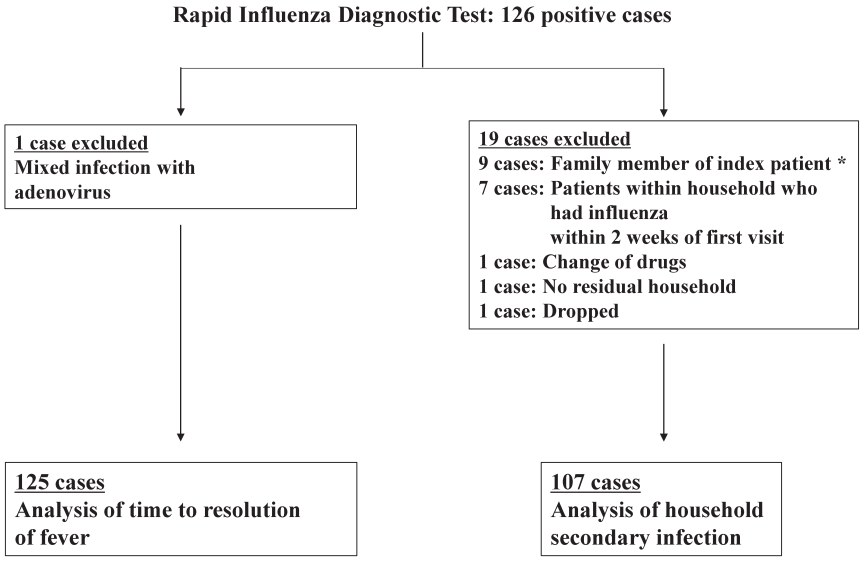
Patient characteristics

From December 21, 2019, to March 2, 2020, 126 patients with influenza were enrolled. As shown in Figs. 1 and 2 and Table 2, 126 cases of influenza were analyzed.

Patient characteristics are summarized in Table 1. Anti-influenza drugs were administered as follows: Laninamivir Nebulizer, 51 patients; Other drugs, 75 patients (laninamivir [33], oseltamivir [28], zanamivir [7], peramivir [3], and baloxavir [4]).

Patients treated with Laninamivir Nebulizer (Laninamivir Nebulizer group) were significantly younger than those treated with other drugs (Other drugs group; median age of Laninamivir Nebulizer vs. Other drugs groups = 6 years vs. 9 years, $p = 0.0003$) and those treated with laninamivir (Laninamivir group; mean age of Laninamivir Nebulizer vs. Laninamivir groups = 6 vs. 10 years, $p < 0.0001$). The Laninamivir Nebulizer group had a significantly higher proportion of female patients than the Other drugs group (male : female ratio = 24 : 27 vs. 49 : 26, $p = 0.0456$). Furthermore, the Laninamivir Nebulizer group had a significantly higher proportion of influenza B patients than the Other drugs (influenza A : B ratio of Laninamivir Nebulizer vs. Other drugs groups = 18 : 33 vs. 51 : 24, $p = 0.0005$), Laninamivir (influenza A : B of Laninamivir Nebulizer vs. Other drugs groups = 18 : 33 vs. 22 : 11, $p = 0.0071$) and Oseltamivir (influenza A : B of Laninamivir Nebulizer vs. Other drugs groups = 18 : 33 vs. 20 : 8, $p = 0.0025$) groups. Other clinical factors (influenza vaccination status, presence or absence of comorbidities, body

Fig. 1. Flowchart of the study



* Index patient was the first patient from each household diagnosed with influenza at the clinic

Table 1. Patient characteristics

1) Laninamivir Nebulizer vs. Other drugs groups

		Anti-influenza drugs		
Characteristics	**Total**	**Laninamivir Nebulizer[a]**	**Other drugs[b]**	***P*-value**
Number (*n*)	126	51	75	—
Median age[c] (years) (range)	8 (0.5–15)	6 (0.5–14)	9 (1–15)	0.0003*
Sex (male : female)	73 : 53	24 : 27	49 : 26	0.0456*
Type of influenza (A : B)	69 : 57	18 : 33	51 : 24	0.0005*
Vaccination (yes : no)	53 : 73	19 : 32	34 : 41	0.4624
Comorbidity[d] (yes : no)	13 : 113	4 : 47	9 : 66	0.5585
Body temperature[e] (℃)	39.1 ± 0.1	39.1 ± 0.1	39.2 ± 0.1	0.6505
Time from onset[e] (hours)	23.3 ± 1.5	25.5 ± 2.4	21.8 ± 2.0	0.9444

2) Laninamivir Nebulizer vs. Laninamivir groups

		Anti-influenza drugs		
Characteristics	**Total**	**Laninamivir Nebulizer[a]**	**Laninamivir**	***P*-value**
Number (*n*)	84	51	33	—
Median age[c] (range)	8 (0.5–15)	6 (0.5–14)	10 (7–15)	<0.0001*
Sex (male : female)	46 : 38	24 : 27	22 : 11	0.1158
Type of influenza (A : B)	40 : 44	18 : 33	22 : 11	0.0071*
Vaccination (yes : no)	33 : 51	19 : 32	14 : 19	0.6544
Comorbidity[d] (yes : no)	6 : 78	4 : 47	2 : 31	1.0000
Body temperature (℃)	39.1 ± 0.1	39.1 ± 0.1	39.2 ± 0.1	0.7479
Time from onset (hours)	24.4 ± 2.0	25.5 ± 2.5	22.8 ± 3.2	0.6832

3) Laninamivir Nebulizer vs. Oseltamivir groups

		Anti-influenza drugs		
Characteristics	**Total**	**Laninamivir Nebulizer[a]**	**Oseltamivir**	***P*-value**
Number (*n*)	79	51	28	—
Mean age[c] (range)	6 (0.5–14)	6 (0.5–14)	5.5 (1–12)	0.2835
Sex (male : female)	42 : 37	24 : 27	18 : 10	0.1638
Type of influenza (A : B)	38 : 41	18 : 33	20 : 8	0.0025*
Vaccination (yes : no)	33 : 46	19 : 32	14 : 14	0.3420
Comorbidity[d] (yes : no)	9 : 70	4 : 47	5 : 23	0.2670
Body temperature (℃)	39.2±0.1	39.1±0.1	39.2±0.1	0.4083
Time from onset (hours)	24.3±2.2	25.5±2.7	22.1±3.7	0.8817

Laninamivir: Laninamivir octanoate hydrate
Oseltamivir: Oseltamivir phosphate
[a] Laninamivir nebulizer: Laninamivir octanoate hydrate inhalation using a nebulizer
[b] Other drugs include: 33: Laninamivir octanoate hydrate, 28: Oseltamivir phosphate, 7: Zanamivir hydrate, 3: Peramivir hydrate, and 4: Baloxavir marboxil.
[c] In the Laninamivir nebulizer group, there were two patients under 1 year of age (one patient was 6 months old and another was 9 months old).
[d] Comorbidities included bronchial asthma in 13 patients.
[e] Body temperature, time from onset: mean ± standard error

temperature, and time from onset) did not significantly differ between the Laninamivir Nebulizer and the other three groups (Table 1).

Effectiveness

Time to resolution of fever

Of the 125 patients, one patient was excluded for the analysis of time to resolution of fever because of mixed infection with adenovirus (Fig. 1). There were six censored cases because of the following reasons: four required a change of drugs before resolution of fever, and two consulted a secondary hospital before resolution of fever. These patients were included in the statistical analyses as censored cases.

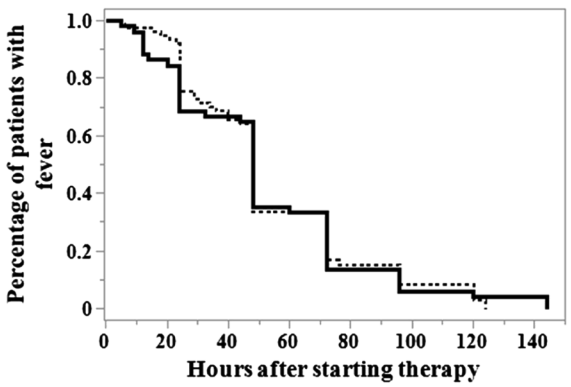
The mean time to resolution of fever for the Laninamivir Nebulizer group did not significantly differ from that for the Other drugs, Laninamivir, and Oseltamivir groups for both influenza A and B subtypes and in the influenza A cohort (Fig. 2a). The hazard ratio (referring to the adjusted hazard ratio in the following sentences) of time to resolution of fever for the Laninamivir Nebulizer group did not significantly differ from that for the Other drugs, Laninamivir, and Oseltamivir groups for both influenza A and B and in the influenza A cohort (Fig. 2a–b).

However, the mean time to resolution of fever for the Laninamivir Nebulizer group was significantly lower than that for the Other drugs (Laninamivir Nebulizer vs. Other drugs groups = 51.1 ± 4.8 and 70.8 ± 8.1 h, respectively, $p = 0.0133^{*}$), Laninamivir (Laninamivir Nebulizer vs. Laninamivir groups = 51.2 ± 4.8 and 71.8 ± 10.0 h, respectively, $p = 0.0454^{*}$) and Oseltamivir (Laninamivir Nebulizer vs. Oseltamivir groups = 51.1 ± 4.8 and 94.5 ± 14.2 h, respectively, $p = 0.0015^{*}$) groups in the influenza B cohort (Fig. 2c). The hazard ratio for time to resolution for the Laninamivir Nebulizer group was significantly greater than that for the Other drugs (Laninamivir Nebulizer group = 1.87 [95% CI: 1.05–3.35], $p = 0.0347^{*}$] and Oseltamivir (Laninamivir Nebulizer group = 3.38 [95% CI: 1.27–9.00], $p = 0.0151^{*}$] groups in the influenza B cohort. The hazard ratio for time to resolution for the Laninamivir Nebulizer group did not significantly differ from that for the Laninamivir (Laninamivir Nebulizer group = 1.72 [95% CI: 0.78–3.80], $p = 0.1815$] group in the influenza B cohort (Fig. 2c).

Household transmission of influenza infection

The rate of household members with secondary infection in the Laninamivir Nebulizer group did not significantly differ from that in the Other drugs (Laninamivir Nebulizer vs. Other drugs groups = 7.0 ± 2.4 vs. 12.4 ± 3.1, $p = 0.3811$), Laninamivir (Laninamivir Nebulizer vs. Laninamivir groups = 7.0 ± 2.4 vs. 13.7 ± 5.1, $p = 0.4064$), and Oseltamivir (Laninamivir Nebulizer vs. Oseltamivir groups = 7.0 ± 2.4 vs. 15.5 ± 5.3, $p = 0.1509$) groups for both influenza A and B (Table 2).

Fig. 2a 1) Time to resolution of fever in Laninamivir Nebulizer vs. Other drugs (any influenza) groups

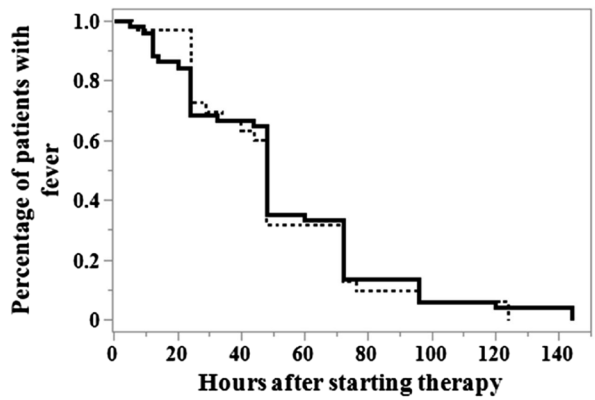


Hazard ratio (95% confidence interval)
1.24 (0.82-1.89) *P*-value 0.3134

Number of patients									Censored
Laninamivir Nebulizer	51	43	34	17	7	3	2	2	0
Other drugs	74	69	47	24	9	3	1	0	6

Any influenza		Time to resolution of fever		Hazard ratios of time to resolution of fever	
Drugs	n	Mean ± standard error	*P*-value	Hazard ratio (95% confidence interval)	*P*-value
Laninamivir Nebulizer vs. other drugs	51 vs. 74	52.1 ± 4.6 vs. 53.8 ± 3.6	0.9107	1.24 (0.82–1.89)	0.3134

Fig. 2a 2) Time to resolution of fever in Laninamivir Nebulizer vs. Laninamivir (any influenza) groups

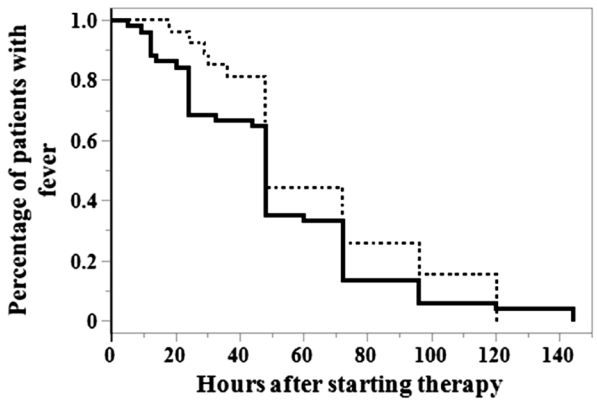


Hazard ratio (95% confidence interval)
1.13 (0.61-2.09) *P*-value 0.6916

Number of patients									Censored
Laninamivir Nebulizer	51	43	34	17	7	3	2	2	0
Laninamivir	33	32	20	10	3	1	1	0	2

Any influenza		Time to resolution of fever		Hazard ratios of time to resolution of fever	
Drugs	n	Mean ± standard error	*P*-value	Hazard ratio (95% confidence interval)	*P*-value
Laninamivir Nebulizer vs. Laninamivir	51 vs. 33	52.1 ± 4.6 vs. 51.3 ± 5.0	0.8296	1.13 (0.61–2.09)	0.6916

Fig. 2a 3) Time to resolution of fever in Laninamivir Nebulizer vs. Oseltamivir (any influenza) groups

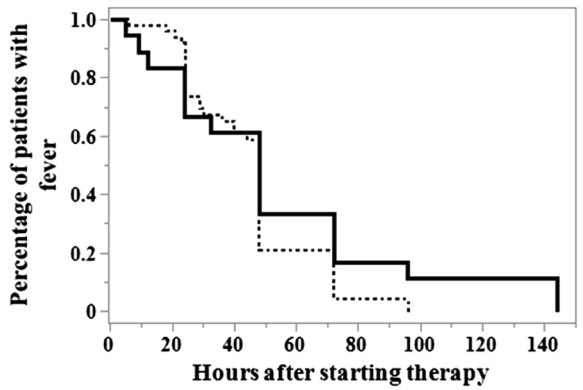


Hazard ratio (95% confidence interval)
1.44 (0.87-2.40) *P*-value 0.1565

Number of patients									Censored
Laninamivir Nebulizer	51	43	34	17	7	3	2	2	0
Oseltamivir	25	24	20	10	5	2	0	0	3

Any influenza		Time to resolution of fever		Hazard ratios of time to resolution of fever	
Drugs	n	Mean ± standard error	*P*-value	Hazard ratio (95% confidence interval)	*P*-value
Laninamivir Nebulizer vs. Oseltamivir	51 vs. 27	52.1 ± 4.6 vs. 61.8 ± 6.1	0.1463	1.44 (0.87–2.40)	0.1565

Fig. 2b 1) Time to resolution of fever in Laninamivir Nebulizer vs. Other drugs (influenza A) groups

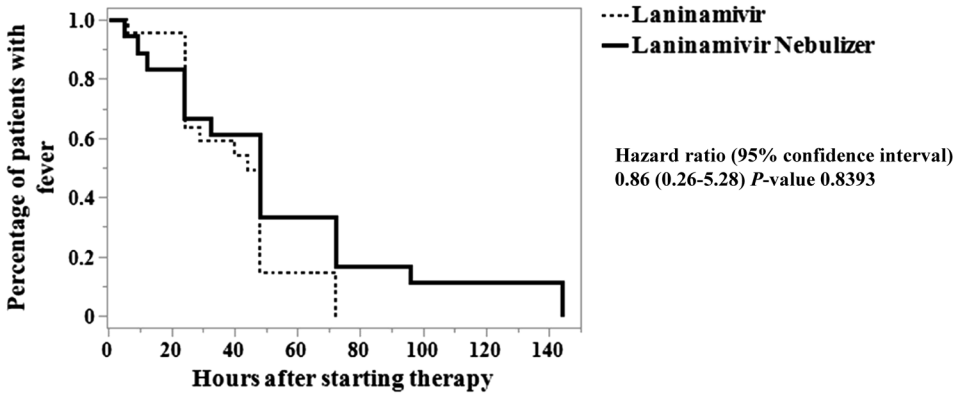


Hazard ratio (95% confidence interval)
0.92 (0.45-1.87) *P*-value 0.8224

Number of patients									Censored
Laninamivir Nebulizer	18	15	11	6	3	2	2	2	0
Other drugs	50	47	29	10	2	0	0	0	2

Influenza A		Time to resolution of fever		Hazard ratios of time to resolution of fever	
Drugs	n	Mean ± standard error	*P*-value	Hazard ratio (95% confidence interval)	*P*-value
Laninamivir Nebulizer vs. other drugs	18 vs. 50	53.9 ± 9.6 vs. 45.3 ± 2.9	0.2467	0.92 (0.45–1.87)	0.8224

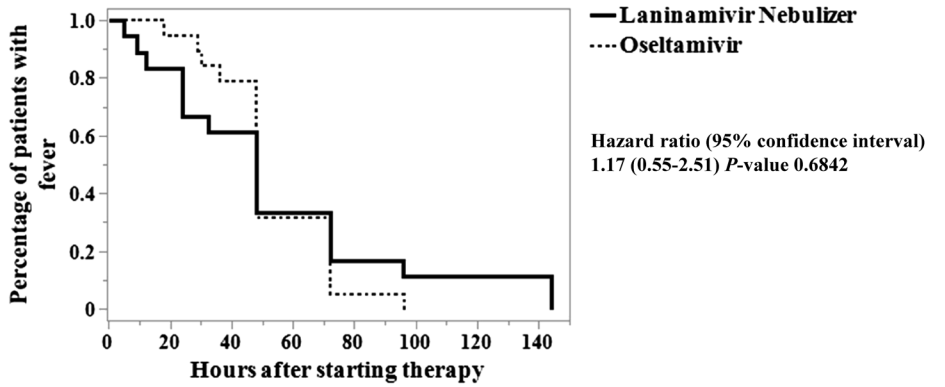
Fig. 2b 2) Time to resolution of fever in Laninamivir Nebulizer vs. Laninamivir (influenza A) groups



Number of patients									Censored
Laninamivir Nebulizer	18	15	11	6	3	2	2	2	0
Laninamivir	22	21	11	3	0	0	0	0	1

Influenza A		Time to resolution of fever		Hazard ratios of time to resolution of fever	
Drugs	n	Mean ± standard error	*P*-value	Hazard ratio (95% confidence interval)	*P*-value
Laninamivir Nebulizer vs. Laninamivir	18 vs. 22	53.9 ± 9.6 vs. 40.5 ± 3.9	0.1835	0.86 (0.26–5.28)	0.8393

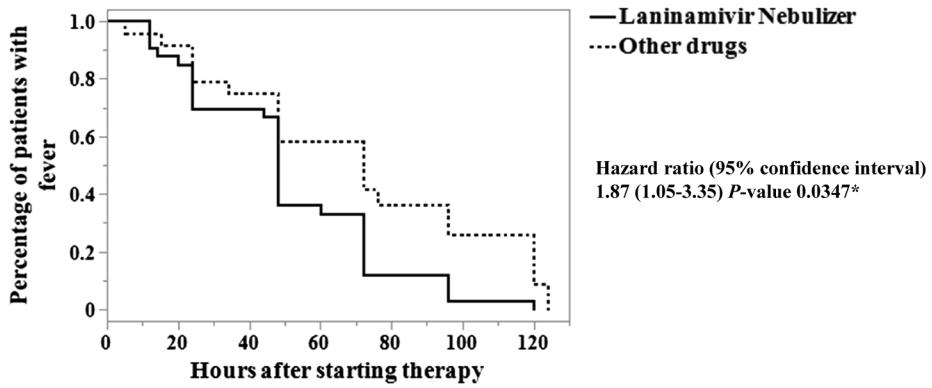
Fig. 2b 3) Time to resolution of fever in Laninamivir Nebulizer vs. Oseltamivir (influenza A) groups



Number of patients									Censored
Laninamivir Nebulizer	18	15	11	6	3	2	2	2	0
Oseltamivir	19	18	15	6	1	0	0	0	0

Influenza A		Time to resolution of fever		Hazard ratios of time to resolution of fever	
Drugs	n	Mean ± standard error	*P*-value	Hazard ratio (95% confidence interval)	*P*-value
Laninamivir Nebulizer vs. Oseltamivir	18 vs. 19	53.9 ± 9.6 vs. 52.7 ± 4.4	0.8983	1.17 (0.55–2.51)	0.6842

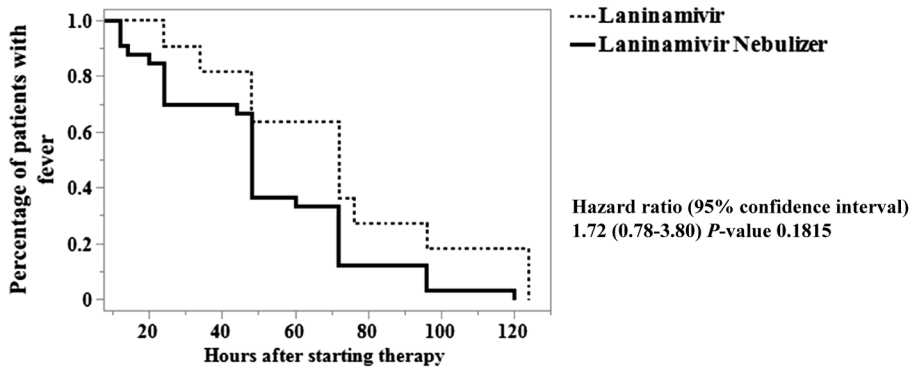
Fig. 2c 1) Time to resolution of fever in Laninamivir Nebulizer vs. Other drugs (influenza B) groups



Number of patients								Censored
Laninamivir Nebulizer	33	28	23	11	4	1	0	0
Other drugs	24	22	18	14	7	3	1	4

Influenza B		Time to resolution of fever		Hazard ratios of time to resolution of fever	
Drugs	n	Mean ± standard error	*P*-value	Hazard ratio (95% confidence interval)	*P*-value
Laninamivir Nebulizer vs. other drugs	33 vs. 24	51.1 ± 4.8 vs. 70.8 ± 8.1	0.0133*	1.87 (1.05–3.35)	0.0347*

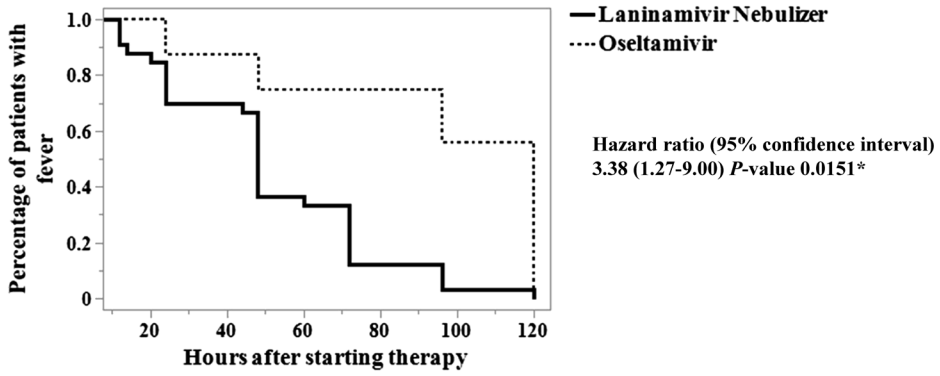
Fig. 2c 2) Time to resolution of fever in Laninamivir Nebulizer vs. Laninamivir (influenza B) groups



Number of patients								Censored
Laninamivir Nebulizer	33	28	23	11	4	1	0	0
Laninamivir	11	11	9	7	3	1	1	1

Influenza B		Time to resolution of fever		Hazard ratios of time to resolution of fever	
Drugs	n	Mean ± standard error	*P*-value	Hazard ratio (95% confidence interval)	*P*-value
Laninamivir Nebulizer vs. Other drugs	33 vs. 10	51.2 ± 4.8 vs. 71.8 ± 10.0	0.0454*	1.72 (0.78–3.80)	0.1815

Fig. 2c 3) Time to resolution of fever in Laninamivir Nebulizer vs. Oseltamivir (influenza B) groups



Number of patients								Censored
Laninamivir Nebulizer	33	28	23	11	4	1	0	0
Oseltamivir	8	8	7	6	4	2	0	3

Influenza B		Time to resolution of fever		Hazard ratios of time to resolution of fever	
Drugs	n	Mean ± standard error	*P*-value	Hazard ratio (95% confidence interval)	*P*-value
Laninamivir Nebulizer vs. Oseltamivir	33 vs. 8	51.1 ± 4.8 vs. 94.5 ± 14.2	0.0015*	3.38 (1.27–9.00)	0.0151*

The hazard ratio for the rate of household members with secondary infection in the Laninamivir Nebulizer group did not significantly differ from that in the Other drugs (Laninamivir Nebulizer group = 1.21 [95% CI: 0.77–1.90], $p = 0.4041$), Laninamivir (Laninamivir Nebulizer group = 1.19 [95% CI: 0.60–2.34], $p = 0.6172$), and Oseltamivir (Laninamivir Nebulizer group = 1.26 [95% CI: 0.71–2.24], $p = 0.4352$) groups for both influenza A and B (Table 2).

The rate of household members with secondary infection in the Laninamivir Nebulizer group did not significantly differ from that in the Other drugs (Laninamivir Nebulizer vs. Other drugs groups = 10.3 ± 5.8 vs. 10.3 ± 3.3, $p = 0.9279$), Laninamivir (Laninamivir Nebulizer vs. Laninamivir groups = 10.3 ± 5.8 vs. 13.8 ± 5.9, $p = 0.7423$), and Oseltamivir (Laninamivir Nebulizer vs. Oseltamivir groups = 10.3 ± 5.8 vs. 10.9 ± 5.3, $p = 0.9302$) groups in the influenza A cohort (Table 2).

The hazard ratio of the rate of household members with secondary infection in the Laninamivir Nebulizer group did not significantly differ from that in the Other drugs (Laninamivir Nebulizer group = 0.99 [95% CI: 0.47–2.08], $p = 0.9713$), Laninamivir (Laninamivir Nebulizer group = 1.48 [95% CI: 0.19–11.30], $p = 0.7061$), and Oseltamivir (Laninamivir Nebulizer group = 1.03 [95% CI: 0.48–2.21], $p = 0.9356$] groups for influenza A (Table 2).

The rate of household members with secondary infection in the Laninamivir Nebulizer group did not significantly differ from that in the Other drugs (Laninamivir Nebulizer group vs. Other drugs group = 5.6±2.3 vs. 17.2±6.7, $p = 0.1711$) and Laninamivir (Laninamivir Nebulizer

Table 2. Risk of secondary household transmission with anti-influenza drugs

		Rate of household members with secondary infection[a] (%)		Hazard ratio of the rate of household members with secondary infection[b]	
	n	Mean ± standard error	*P*-value	Hazard ratio (95% confidence interval)	*P*-value
Any influenza					
Laninamivir Nebulizer[c] vs. Other drugs group[d]	43 vs. 64	7.0 ± 2.4 vs. 12.4 ± 3.1	0.3811	1.21 (0.77–1.90)	0.4041
Laninamivir Nebulizer[c] vs. Laninamivir group	43 vs. 30	7.0 ± 2.4 vs. 13.7 ± 5.1	0.4064	1.19 (0.60–2.34)	0.6172
Laninamivir Nebulizer[c] vs. Oseltamivir group	43 vs. 21	7.0 ± 2.4 vs. 15.5 ± 5.3	0.1509	1.26 (0.71–2.24)	0.4352
Influenza A					
Laninamivir Nebulizer[c] vs. Other drugs group[d]	13 vs. 44	10.3 ± 5.8 vs. 10.3 ± 3.3	0.9279	0.99 (0.47–2.08)	0.9713
Laninamivir Nebulizer[c] vs. Laninamivir group	13 vs. 20	10.3 ± 5.8 vs. 13.8 ± 5.9	0.7423	1.48 (0.19–11.30)	0.7061
Laninamivir Nebulizer[c] vs. Oseltamivir group	13 vs. 16	10.3 ± 5.8 vs. 10.9 ± 5.3	0.9302	1.03 (0.48–2.21)	0.9356
Influenza B					
Laninamivir Nebulizer[c] vs. Other drugs group[d]	30 vs. 20	5.6 ± 2.3 vs. 17.2 ± 6.7	0.1711	1.40 (0.75–2.60)	0.2877
Laninamivir Nebulizer[c] vs. Laninamivir group	30 vs. 10	5.6 ± 2.3 vs. 13.3 ± 10.2	0.7227	1.14 (0.51–2.51)	0.7543
Laninamivir Nebulizer[c] vs. Oseltamivir group	30 vs. 5	5.6 ± 2.3 vs. 30.0 ± 13.3	0.0165 *	2.15 (0.63–7.28)	0.2196

Laninamivir: Laninamivir Octanoate Hydrate
Oseltamivir: Oseltamivir phosphate
Rate of household members with secondary infection: mean ± standard error
* Statistically significant
[a] Rate of household members with secondary infection was defined as the number of infected household members divided by the number of residual uninfected household members.
[b] Hazard ratios were adjusted for sex, age, and subtype of influenza (A vs. B) in any influenza.
Hazard ratios were adjusted for sex and age in both influenza A and B.
[c] Laninamivir Nebulizer: Laninamivir octanoate hydrate inhalation using a nebulizer
[d] Other drugs include laninamivir octanoate hydrate, oseltamivir phosphate, zanamivir hydrate, peramivir hydrate, and baloxavir marboxil.

group vs. Laninamivir group = 5.6±2.3 vs. 13.3±10.2, $p = 0.7227$) group. However, the rate of household members with secondary infection household transmission in the Laninamivir Nebulizer group was not significantly lower than that in the Oseltamivir group (Laninamivir Nebulizer group vs. Oseltamivir groups = 5.6±2.3 vs. 30.0±13.3, $p = 0.0165$) in the influenza B cohort (Table 2).

The hazard ratios of the rate of household members with secondary infection in the Laninamivir Nebulizer group did not significantly differ from those in the Other drugs group [Laninamivir Nebulizer group = 1.40 (95% CI: 0.75–2.60), $p = 0.2877$], Laninamivir group [Laninamivir Nebulizer group = 1.14 (95% CI: 0.51–2.51), $p = 0.7543$], and Oseltamivir group [Laninamivir Nebulizer group = 2.15 (95% CI: 0.63–7.28), $p = 0.2196$] in the influenza B cohort (Table 2).

Adverse events

The prevalence of adverse events in the Laninamivir Nebulizer group did not significantly differ from that in the Other drugs group [Laninamivir Nebulizer group vs. Other drugs groups = 9.8% (5/51) vs. 14.7% (11/75), $p = 0.5872$], Laninamivir group [Laninamivir Nebulizer group vs. Laninamivir groups = 9.8% (5/51) vs. 18.2% (6/33), $p = 0.3278$], and Oseltamivir group [Laninamivir Nebulizer group vs. Oseltamivir groups = 9.8% (5/51) vs. 7.1% (2/28), $p = 1.0000$] (Table 3-1)).

In the logistic regression analysis, the odds ratio of adverse events in the Laninamivir Nebu-

Table 3. Adverse events

1) Prevalence and odds ratio

		Prevalence of adverse events (%)[a] (%)		Odds ratio of adverse events[b]	
	n	Mean ± standard error	*P*-value	Odds ratio (95% confidence interval)	*P*-value
Laninamivir Nebulizerc vs. Other drugs groupd	51 vs. 75	9.8 (5/51) vs. 14.7 (11/75)	0.5872	0.71 (0.20–2.56)	0.6028
Laninamivir Nebulizerc vs. Laninamivir group	51 vs. 33	9.8 (5/51) vs. 18.2 (6/33)	0.3278	0.46 (0.07–2.95)	0.4154
Laninamivir Nebulizerc vs. Oseltamivir group	51 vs. 28	9.8 (5/51) vs. 7.1 (2/28)	1.0000	2.15 (0.34–13.82)	0.4186

2) Details of adverse events[c]

	Adverse events (outcome)		
	Spontaneous remission	Improved by medication	Admission
Laninamivir Nebulizer[a]	2: Delirium 2: Diarrhea 1: Anorexia 1: Eyelid function disorder	None	None
Laninamivir	2: Diarrhea 2: Delirium 1: Confusion	1: Diarrhea 1: Vomiting 1: Chest pain	None
Oseltamivir	1: Delirium	None	1: Rash maculopapular
Zanamivir	1: Diarrhea	None	None
Peramivir	1: Delirium	None	None
Baloxavir	1: Hallucinations	None	None

3) Details of adverse events[c]

	Adverse events (outcome)		
	Spontaneous remission	Improved by medication	Admission
Laninamivir Nebulizer[a]	2: Delirium 2: Diarrhea 1: Anorexia 1: Eyelid function disorder	None	None
Laninamivir	2: Diarrhea 2: Delirium 1: Confusion	1: Diarrhea 1: Vomiting 1: Chest pain	None
Oseltamivir	1: Delirium	None	1: Rash maculopapular
Zanamivir	1: Diarrhea	None	None
Peramivir	1: Delirium	None	None
Baloxavir	1: Hallucinations	None	None

Laninamivir: Laninamivir octanoate hydrate
Oseltamivir: Oseltamivir phosphate
* Statistically significant
[a] Prevalence of adverse events was defined as the number of cases with adverse events divided by the total number of cases.
[b] Laninamivir Nebulizer: Laninamivir octanoate hydrate inhalation using a nebulizer
[c] Other drugs include laninamivir octanoate hydrate, oseltamivir phosphate, zanamivir hydrate, peramivir hydrate, and baloxavir marboxil.
[d] Odds ratios of adverse events were adjusted for sex and age.
[e] Overlapping, yes (i.e., one case may show multiple adverse events).

Table 4. Effectiveness and adverse events in the Laninamivir Nebulizer group during nebulizer-mediated inhalation depending on the patients' status

1) Effectiveness

Time to resolution of fever[a]	n	Mean ± standard error	P-value	Hazard ratio (95% confidence interval)[b]	P-value
Crying during Nebulizer treatment[c] vs. No crying during Nebulizer treatment[d]	6 vs. 45	64.0 ± 16.0 vs. 50.5 ± 4.7	0.4990	0.78 (0.28–2.14)	0.6246

2) Household transmission

Rate of household members with secondary infection[f]	n	Mean ± standard error	P-value	Hazard ratio (95% confidence interval)[b]	P-value
Crying during Nebulizer treatmentc vs. No crying during Nebulizer treatment[d]	4 vs. 39	0.0 ± 0.0 vs. 7.7 ± 2.6	0.3211	1.77 (0.49–6.45)	0.3870

3) Adverse events

Adverse events	n	Prevalence of adverse events (%)[h]	P-value	Odds ratio (95% confidence interval)[i]	P-value
Crying during Nebulizer treatment[c] vs. No crying during Nebulizer treatment[d]	6 vs. 45	16.7 (1/6) vs. 8.9 (4/45)	0.4799	1.16 (0.06–23.46)	0.9227

Time to resolution of fever, Time to resolution of the symptom: mean ± standard error
Laninamivir: Laninamivir octanoate hydrate
* Statistically significant
[a] Time to resolution of fever was defined as the time in which the body temperature of the patient returned to less than 37.5℃ and stabilized for at least 24 hours or the time in which the body temperature of each patient returned to the normal range and did not re-elevate.
[b] Hazard ratios were adjusted for sex, age, and subtype of influenza (A vs. B).
[c] Crying during Nebulizer treatment: Patients who cried during nebulizer-mediated inhalation
[d] No crying during Nebulizer treatment: Patients who did not cry during nebulizer-mediated inhalation
[e] Time to resolution of symptoms was defined as the time in which all symptoms of a patient disappeared except prolonged cough.
[f] Rate of household members with secondary infection was defined as the number of infected household members divided by the number of residual uninfected household members.
[g] Hazard ratios were adjusted for sex, age, and subtype of influenza (A vs. B).
[h] Prevalence of adverse events was defined as the number of cases with adverse events divided by the total number of cases.
[i] Odds ratios of adverse events were adjusted for sex and age.

lizer group did not significantly differ from that in the Other drugs group [Laninamivir Nebulizer group = 0.71 (95% CI: 0.20–2.56), $p = 0.6028$], Laninamivir group [Laninamivir Nebulizer group = 0.46 (95% CI: 0.07–2.95), $p = 0.4154$], and Oseltamivir group [Laninamivir Nebulizer group = 2.15 (95% CI: 0.34–13.82), $p = 0.4186$] (Table 3-1)). The details of adverse events are shown in Table 3-2.

Although six adverse events (2: delirium, 2: diarrhea, 1: anorexia, and 1: eyelid function disorder) occurred in the Laninamivir Nebulizer group, all patients recovered spontaneously without any medication. In the Other drugs group, there were no severe adverse events. However, three cases (1: diarrhea, 1: vomiting, and 1: chest pain) in the group treated with Laninamivir required

medication, and one case was admitted to a secondary hospital due to maculopapular rash in the group treated with Oseltamivir (Table 3-3).

In the Laninamivir Nebulizer group, 11.8% (6/51) of patients cried during nebulization (Table 4). However, no differences in effectiveness, household transmission rate, and adverse events were observed between patients who cried and patients who did not cry during nebulization (Table 4).

Discussion

Although the treatment by inhaling laninamivir and zanamivir in dry powder form is effective and well-tolerated, some patients, such as small children, cannot inhale this drug effectively. Moreover, the safety of baloxavir in children under 1 year of age has not been established, and a high prevalence of baloxavir-resistant strains has been reported in patients younger than 12 years, particularly for influenza A[20]. Since peramivir is used as an intravenous drip injection, some patients, such as small children, have to suffer pain. Additionally, fixation of the drip may be needed to prevent the children from removing the device. Oseltamivir is an orally administered drug and cannot be readily consumed by small children such as those under 1 year of age. Since Laninamivir Nebulizer does not present any of the abovementioned shortcomings, it is viable for use in younger patients such as small children younger than 1 year. The effectiveness and adverse events of Laninamivir Nebulizer were studied and compared with those of other anti-influenza drugs and different therapeutic statuses of patients, as no study has performed such an evaluation so far.

The mean time to resolution of fever in patients treated with Laninamivir Nebulizer was 52.1, 53.9, and 51.1 h in both influenza types, influenza A and influenza B, respectively. There were no significant differences in the time to resolution of fever between Laninamivir Nebulizer and the Other drugs, Laninamivir, and Oseltamivir groups for both influenza A and B subtypes and in the influenza A cohort. Although the hazard ratio of time to resolution of fever in the Laninamivir Nebulizer group did not significantly differ from that of the Other drugs, Laninamivir, and Oseltamivir groups for both influenza A and B subtypes and in the influenza A cohort, that of the Laninamivir Nebulizer group was significantly lower than that of the Other drugs and Oseltamivir groups for the influenza B cohort. These results suggest that Laninamivir Nebulizer may be more effective than other drugs (particularly oseltamivir) against influenza B. Furthermore, the mean time to resolution of fever of patients treated with Laninamivir Nebulizer was slightly longer than that reported previously[8]. The reasons for this difference remain unclear. The rate of household members with secondary infection in the Laninamivir Nebulizer group was 7.0%, 10.3%, and 5.6% for any influenza type, influenza A and influenza B, respectively. The effectiveness of Laninamivir Nebulizer did not significantly differ from that of other drugs in any influenza, influenza A and influenza B.

Although adverse events occurred in 9.8% of the cases in the Laninamivir Nebulizer group, all patients recovered spontaneously without any medication, and there was no significant difference in the prevalence of adverse events between the Laninamivir Nebulizer and Other drugs groups.

Although the rate of adverse events was greater than that reported previously, there were no serious adverse events[8]. This may be due to the small sample size of this study.

In addition, in the Laninamivir Nebulizer group, 11.8% of patients cried during nebulization. However, no differences in effectiveness, household transmission rate, and adverse events were observed between patients who cried and patients who did not cry during nebulization (Table 4). In this study, two patients in the Laninamivir Nebulizer group were under 1 year of age (one patient was 6 months old and another one was 9 months old). Therefore, laninamivir nebulization may be better suited for children below 1 year of age who cannot inhale the powder or consume oral dosage forms.

There are some limitations to the study that must be considered while interpreting the results. First, a relatively small number of patients were enrolled. Since the number of patients was small, it was not possible to compare the efficacy of Laninamivir Nebulizer with that of each anti-influenza drug. The duration of the influenza endemic in the 2019–2020 season was shorter than that in previous seasons. This may be because of the influence of the SARS-CoV-2 infection outbreak. A similar trend for influenza outbreaks was observed worldwide. Second, this study was conducted at a single center. Discordances in study results have been suggested between single and multiple centers[21]. However, this bias was inevitable. Third, data analysis using other statistical methods such as the Reed–Frost model may be more desirable for analyzing household transmission. However, the statistical software used in this study did not include this method. Fourth, the methods for collecting data were follow-up examination or telephonic interviews. The symptoms and features reported by the patients' parents could be subjective. However, this is an unavoidable limitation of such observational studies.

In conclusion, Laninamivir Nebulizer is safe and effective for both influenza A and B. Both the effectiveness and safety of the Laninamivir Nebulizer were found to be equivalent to those of other anti-influenza drugs. In addition, the Laninamivir Nebulizer showed comparable effectiveness, even in crying children. Novel drug identification for diseases affecting small children, such as influenza, should also consider individuals who cannot inhale powders or consume oral forms of medicine. Therefore, the Laninamivir Nebulizer can be a good therapeutic option for infants with influenza.

Acknowledgments

None.

Conflicts of interest

The author declares no potential conflict of interest.

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