Duration of fever and other symptoms after laninamivir octanoate hydrate inhalation over eight influenza seasons

Naoki Tani[1], Naoki Kawai[2], Hideyuki Ikematsu[3], Takuma Bando[2], Norio Iwaki[2], Yoshio Takasaki[4], Shizuo Shindo[2], Yong Chong[1], and Seizaburo Kashiwagi[5]

[1]Kyushu University Graduate School of Medical Sciences
[2]Japan Physicians Association
[3]Affiliation not available
[4]Takasaki Children's Clinic
[5]Japan Physicians Association,

July 24, 2020

Abstract

Background: Laninamivir octanoate hydrate (laninamivir) is a commonly used drug for influenza virus. This study is part of our long-term, systematic surveillance to monitor its effectiveness. Methods: We investigated the duration of fever and other symptoms after laninamivir inhalation for the outpatients in the Japanese 2017/18 and 2018/19 influenza seasons, then compared the results with those of the previous six seasons. Results: The number of laboratory confirmed patients analyzed was 111 in the 2017/18 season and 84 in 2018/19. The median duration of fever for B was significantly longer than for A in the 2017/18 season (p = 0.0182). In the 2018/19 season, when we could compare only between A subtypes, the median duration of fever was significantly longer for A (H3N2) (p = 0.0290). In contrast, the differences in the median duration of other symptoms were not significant. With the previous six seasons added, we evaluated the data of 1,473 patients over eight sequential influenza seasons. Seasonal differences were observed in the prevailing types/subtypes. The median duration of fever among the types/subtypes was significantly different in some seasons, and it was generally longer for B than for A. The difference in the duration of fever among the eight seasons was all within 24 hrs, and it was statistically significant only for A (H3N2). Conclusions: These results indicate the continuing clinical effectiveness of laninamivir against all types/subtypes of influenza virus, despite its broad use in Japan. Longer duration of fever for B than for A was observed after laninamivir inhalation.

Title: Duration of fever and other symptoms after laninamivir octanoate hydrate inhalation over eight influenza seasons

Running title: The continued effectiveness of laninamivir in Japan

Naoki Tani[a], Naoki Kawai[b, d], Hideyuki Ikematsu[b, c], Takuma Bando[b], Norio Iwaki[b], Yoshio Takasaki[b, e], Shizuo Shindo[b, f], Yong Chong[a], Seizaburo Kashiwagi[b]

[a] Medicine and Biosystemic Science, Kyushu University Graduate School of Medical Sciences, Fukuoka Japan

[b] Japan Physicians Association, Tokyo, Japan

[c] Ricerca Clinica Co., Fukuoka, Japan

[d] Kawai Clinic, Gifu, Japan

[e] Takasaki Clinic: Pediatrics & Child Health

[f] SHINDO CHILDREN'S CLINIC

Corresponding author: Naoki Tani

Medicine and Biosystemic Science, Kyushu University Graduate School of Medical Sciences, 3-1-1, Maidashi, Higashi-ku Fukuoka-shi, Fukuoka, 812-8582, Japan

Tel.: +81-92-642-5229

Fax: +81-92-642-5247

Present address: Medicine and Biosystemic Science, Kyushu University Graduate School of Medical Sciences, 3-1-1, Maidashi, Higashi-ku Fukuoka-shi, Fukuoka, 812-8582, Japan

Tel.: +81-92-642-5229

Fax: +81-92-642-5247

E-mail:*nao_taniyan@icloud.com*

Acknowledgments

We thank the following doctors for participating in this study:

Dr.Mariko Echizen (Kawai Clinic), Dr. Kouichi Mochizuki (MOCHIZUKI NAIKA clinic), Dr. Hiroshi Ukai (UKAI CLINIC), Dr. Takashi Kawashima (Kawashima Medical Clinic) , Dr. Norio Iwaki (Iwaki's Clinic), Dr. Kenichi Doniwa (Clinic Doniwa), Dr. Takuma Bando(Bando Clinic),Dr. Shinro Matsuura (Matsuura Clinic), Dr. Osame Tanaka (Tokujikai Tanaka clinic), Dr. Tetsunari Maeda (Sakura Clinic), Dr. Wataru Ikematsu(Higashihie Internal Clinic), Dr. Ryuji Shimamura(Shimamura Medical Cliic), Dr. Keigo Shibao (Shibao clinic), Dr. Yuji Yamashita (Yamashita Pediatrics Clinic), Dr. Takato Yokoyama (Yokoyama Children's Clinic), Dr. Minako Iwaya(Iwaya Pediatrics Clinic), Dr. Yumi Kiyomatsu (Kiyomatsu Pediatrics Clinic).

Funding

The work was supported by a research grant from Daiichi Sankyo Co., Ltd.

Abstract

Background: Laninamivir octanoate hydrate (laninamivir) is a commonly used drug for influenza virus. This study is part of our long-term, systematic surveillance to monitor its effectiveness.

Methods: We investigated the duration of fever and other symptoms after laninamivir inhalation for the outpatients in the Japanese 2017/18 and 2018/19 influenza seasons, then compared the results with those of the previous six seasons.

Results: The number of laboratory confirmed patients analyzed was 111 in the 2017/18 season and 84 in 2018/19. The median duration of fever for B was significantly longer than for A in the 2017/18 season ($p = 0.0182$). In the 2018/19 season, when we could compare only between A subtypes, the median duration of fever was significantly longer for A (H3N2) ($p = 0.0290$). In contrast, the differences in the median duration of other symptoms were not significant.

With the previous six seasons added, we evaluated the data of 1,473 patients over eight sequential influenza seasons. Seasonal differences were observed in the prevailing types/subtypes. The median duration of fever among the types/subtypes was significantly different in some seasons, and it was generally longer for B than for A. The difference in the duration of fever among the eight seasons was all within 24 hrs, and it was statistically significant only for A (H3N2).

Conclusions: These results indicate the continuing clinical effectiveness of laninamivir against all types/subtypes of influenza virus, despite its broad use in Japan. Longer duration of fever for B than for A was observed after laninamivir inhalation.

Keywords

Influenza; Laninamivir; Neuraminidase inhibitor; Fever; Symptom

Introduction

Seasonal influenza is epidemic every year, causing many deaths and much suffering. To counteract its fury, various anti-influenza drugs have been developed that show clinical effectiveness against influenza virus.

The neuraminidase inhibitors (NAIs) oseltamivir phosphate (Tamiflu®, oseltamivir), zanamivir hydrate (Relenza®, zanamivir), peramivir hydrate (Rapiacta®, peramivir), and laninamivir octanoate hydrate (Inavir®, laninamivir) are commonly used for the treatment of influenza in Japan. Moreover, a new anti-influenza virus drug of different mechanism, a cap-dependent endonuclease inhibitor, baloxavir marboxil (Xofluza®, baloxavir) was approved and became available from 2018[1,2].

The emergence of reduced susceptibility to anti-influenza drugs by virus mutation has been reported; H275Y mutated A(H1N1) and A(H1N1)pdm09 against oseltamivir and peramivir [3], and PA/I38X-substituted viruses against baloxavir [1,4]. We previously reported significant influence of H275Y mutation resulting in the decreased clinical effectiveness of oseltamivir for the H275Y mutated A(H1N1) virus [5,6].

Fortunately, these resistant viruses have not been predominant in seasonal influenza epidemics, but future mutation may allow the viruses to reduce the effectiveness of currently utilized anti-influenza virus drugs; thus, continuous investigation of viral susceptibility in vitro and their clinical effectiveness is quite important. Global surveillance of resistant viruses is a continuous effort [7–9]. Although their clinical effectiveness is also quite important, sufficient systematic surveillance has not been established.

Laninamivir, a long-acting neuraminidase inhibitor that requires only a single inhalation to complete treatment for influenza A and B, was approved in Japan in 2010 and is commonly used[10,11]. We have previously reported the duration of fever and other symptoms after the inhalation of laninamivir over six Japanese influenza seasons as a part of post-marketing surveillance [12]. As part of the surveillance program of the Japan Physicians Association Influenza Study Group to monitor the effectiveness of anti-influenza drugs, we did the present investigator initiated observational study of the duration of fever and other influenza symptoms of patients treated with anti-influenza drugs along with the 50% inhibitory concentration (IC50) in the Japanese 2017/18 and 2018/19 influenza seasons. In this paper, we analyze the duration of fever and other symptoms after the inhalation of laninamivir and compare the results to those of the previous six seasons.

2. Patients and methods

2.1. Patients

Patients who visited one of the participating clinics from November to April with upper respiratory tract symptoms and fever 37.5 or over were tested by a rapid influenza diagnosis test kit. Patients testing positive were enrolled after obtaining written informed consent. We excluded patients suspected of having other viral or secondary bacterial infections following influenza virus infection. This study has been approved by the ethical review board of Hara-Doi hospital, and registered with the UMIN-CTR (UMIN000030136).

Laninamivir was administered according to the recommended dosage: A single inhalation of 20 mg for patients under 10 years of age and a single inhalation of 40 mg for patients aged 10 years or over.

2.2. Study procedures

Most of the procedures used in this study were the same as those used in the previous post-marketing surveillance program done from 2011 to 2017. In brief, participating physicians asked each eligible patient to provide the following information by recording it in a patient diary: 1) Date and time of laninamivir inhalation, 2) Body temperature, date, and time of measurement (measured four times daily, for the seven days after inhalation), 3) Seven symptoms (headache, muscle/joint pain, fatigue, chills/sweating, nasal symptoms, sore throat, and cough) were rated on a 4-grade scale (0: free, 1: mild, 2: moderate, 3: severe)

and assessed at the time of body temperature measurement (at least four times daily for seven days), and 4) adverse events. The patients mailed or handed the completed patient diary to their physician.

The duration of fever was defined as the time from the inhalation of laninamivir to afebrile. The definition of afebrile used in this study is based on the Japanese Ministry of Health, Labor, and Welfare criteria that existed at the time of clinical trials for the development of anti-influenza drugs in Japan [10,11]. In these criteria, an afebrile adult is defined as having a temperature of 36.9 or lower for longer than 24 hours, while an afebrile child has a temperature of 37.4 or lower. Resolution of fever was defined as the time from the inhalation of laninamivir to the time that patients became afebrile. The duration of symptoms was defined as the time from inhalation until the patient noted improvement of all symptoms to a mild grade.

The parameters investigated at the initial visit were sex, presence/absence of pregnancy for women, age, type/subtype of influenza virus by virus isolation, date and time of onset of influenza (defined as when fever or chills first occurred), body temperature, severity of symptoms at the hospital visit, history of influenza vaccination, history of allergies and other diseases, date and time of inhalation and laninamivir dosage, and concomitant medications.

2.3. Influenza virus isolation and typing

Nasal aspirates, nasopharyngeal swabs, or self-blown nasal discharge were used for influenza virus isolation. We used a standard procedure to isolate influenza virus using Madin-Darby canine kidney (MDCK) -SIAT1 cells [13].

The type and subtype of the isolated virus was determined by reverse transcription polymerase chain reaction (RT-PCR) using type- and subtype-specific primers for the hemagglutinin gene[14]. The Yamagata and Victoria lineages of influenza B virus were discriminated by real-time RT-PCR using lineage specific primers and probes for the hemagglutinin gene [15].

2.4. Measurement of susceptibility of NAIs to virus isolates

As a marker of virus susceptibility to laninamivir, the IC50 of laninamivir for each influenza isolate was determined by a fluorescence-based neuraminidase inhibition assay as described elsewhere[16,17].

2.5. Statistical analysis

For the comparison of baseline characteristics among seasons, categorical data was analyzed using the chi-square test or Fisher's exact test, and continuous data was analyzed using analysis of variance (ANOVA). The Cox proportional hazards model was used for comparisons of the duration of fever or symptoms among the virus types/subtypes in the 2017/18 and 2018/19 seasons, between patients under 10 years and 10 years and over by virus type/subtype in the 2017/18 and 2018/19 seasons, and comparisons of the duration of fever or symptoms among seasons by virus type/subtype. The medians for the duration of fever and symptoms were calculated by the Kaplan-Meier method. Spearman's rank correlation coefficients were calculated to evaluate the correlation between the median fever duration and the factors relevant to it.

The level of significance was set at <0.05 two-sided. Because the study is exploratory, multiplicity adjustments were not performed. All analyses were performed using the SAS system, Release 9.4.

3. Results

3.1. Patients

A total of 152 patients treated with laninamivir in the 2017/18 season and 91 in the 2018/19 season were enrolled at the 19 participating institutions listed in acknowledgements. There was no missing data in either season. The data of 41 patients in the 2017/18 season and seven in the 2018/19 season were excluded from the analysis of duration of fever and symptoms because the body temperature at first visit was under 37.5 or unknown or because of undetermined viral type/subtype, leaving the data of 111 patients in the 2017/18 season and 84 patients in the 2018/19 season available for analysis. Including the previous six seasons, the data of 1,473 patients was available for the comparative analysis of the eight seasons.

3.2. Baseline clinical characteristics

The baseline clinical characteristics of the patients in the 2017/18 and 2018/19 seasons are listed in Table 1. In the 2017/18 season, the data for the Yamagata and Victoria lineages were combined because there was only one patient with Victoria. A (H1N1)pdm09, A (H3N2), and B were found in specimen from 14, 45, and 52 patients in the 2017/18 season and in 22, 62, and 0 in the 2018/19 season.

There were no significant differences in age distribution by virus type/subtype in the 2017/18 season ($p = 0.0984$, ANOVA). In contrast, the mean age of A (H3N2) patients was significantly higher than that of A (H1N1)pdm09 patients in the 2018/19 season ($p = 0.0151$, ANOVA).

The percentages of vaccinated patients ranged from 21.2% to 40.0% in these two seasons, with no statistical significance among the types/subtypes ($p = 0.1162$ in the 2017/18 season and $p = 0.7911$ in the 2018/19 season, Fisher's exact test).

The mean time from symptom onset to laninamivir inhalation ranged from 12.1 to 21.3 hours in both seasons, without significant differences among the types/subtypes ($p = 0.2813$ in the 2017/18 season and $p = 0.2698$ in the 2018/19 season, ANOVA).

The body temperature at initial visit was not significantly different by virus type/subtype ($p = 0.3197$ in the 2017/18 season and $p = 0.7146$ in the 2018/19 season, ANOVA).

There was no significant difference in the influenza symptom scores at initial visit among the virus types/subtypes in the 2017/18 season ($p = 0.4134$, ANOVA), and the score of A (H3N2) patients (9.9 points) in the 2018/19 season was higher than that of A (H1N1)pdm09 patients (7.9 points) ($p = 0.0393$, ANOVA).

3.3. Duration of fever and other symptoms in the 2017/18 and 2018/19 seasons

The median durations of fever and symptoms after laninamivir inhalation are listed by age in Table 2.

In the 2017/18 season, the number of the patients aged under 10 years was so small that the median duration of fever and other symptoms was similar between all participants and the patients aged 10 years and over. The median duration of fever was significantly longer for B than for A ($p = 0.0182$ for all participants and $p = 0.0408$ for the patients aged 10 years and over, ANOVA). There was little difference between the A subtypes. In contrast, the median duration of other symptoms for all participants was longest for A (H1N1)pdm09, followed by B then A(H3N2), but with no significant difference ($p = 0.2153$ for all participants and $p = 0.0905$ for the patients aged 10 years and over, ANOVA).

No patients had B in the 2018/19 season. The median duration of fever and other symptoms for all participants and the patients aged under 10 years for A (H3N2) was longer than that for A (H1N1)pdm09. Significant differences were seen in the duration of fever for all participants and patients aged under 10 years. ($p = 0.0290$ and $p = 0.0246$, respectively, ANOVA). The median duration of fever and other symptoms for the A subtypes were almost the same for the patients aged 10 years and over.

3.4. Duration of fever and symptoms over eight influenza seasons

The median durations of fever and symptoms over the eight seasons are listed in Table 3 by virus type/subtype. Influenza B had a longer median duration of fever than the A subtypes in all seasons that B was analyzed, but a significant difference was seen only in the 2017/18 season ($p = 0.0182$, ANOVA). The median duration of symptoms for B was also longer than that for A except in the 2012/13 and 2017/18 seasons (only four B patients were registered in the 2012/13 season). A significant difference was seen only in the 2016/17 season ($p = 0.0342$).

The median durations of fever were similar for A (H1N1)pdm09 in the six seasons during which it was circulating, with no significant differences ($p = 0.2719$, ANOVA), but a significant difference was found in the median durations of symptoms ($p = 0.0432$, ANOVA).

Although the median durations of symptoms over the eight seasons for A (H3N2) were quite similar, with no significant difference (p = 0.0906, ANOVA), seasonal variations in the median duration of fever were apparent (p = 0.0103, ANOVA).

There were no significant differences in the median durations of fever or symptoms over the eight seasons for B (p = 0.0930 and p = 0.3686, respectively, ANOVA).

3.5. Resolution of fever over eight influenza seasons

The percentage of patients with fever by the time from the inhalation of laninamivir is shown in Fig. 1 (1 A (H1N1)pdm09, 2 A (H3N2), and 3 B). We eliminated the seasons in which the number of patients was under five from the analysis.

The resolution of fever after the inhalation of laninamivir was significantly different among the analyzed seasons for A (H1N1)pdm09 and A (H3N2) (p = 0.0037 and p = 0.0025, respectively, Cox regression), but was not significant for B (p = 0.0598, cox regression).

3.6. Factors relevant to fever duration; half maximal Inhibitory Concentration (IC50), age, and prevalence of types/subtypes

To consider the regulatory factors of fever duration for A (H3N2) that had significant differences by two statistical methods, we analyzed the median IC50 of laninamivir, the proportion of the type/subtype, and mean age by season and virus type/subtype (Table S1) [7]. We also did analysis of A (H1N1)pdm09 and B together. To evaluate the correlation between the median fever duration and these factors, we calculated Spearman's rank correlation coefficients and created scatter diagrams (Fig. S1-9). Although there were some high Spearman's rank correlation coefficients (e.g. between the median fever duration and the IC50 of H1N1pdm09, IC50 of B, and mean age of H3N2), we could not identify any obvious regulatory factor that might strongly influence the median fever duration.

4. Discussion

The mortality rate of patients with influenza in Japan is low compared with other countries. During the A (H1N1)pdm09 pandemic in 2009, the mortality rate in Japan was from one-11th to one-16th that of United Kingdom, Mexico, and United States [18]. The reasons are unclear, but good access to medical care and early administration of anti-influenza drugs may have contributed to the good outcomes.

Neuraminidase inhibitors should be administered within 48 hours and if possible within 12 hours from the onset of influenza like symptoms[19]. The mean time from symptom onset to laninamivir inhalation was within 24 hours in both the 2017/18 and 2018/19 seasons, similar to all of the previous seasons [20]. These results may be because most influenza patients in Japan visit clinics on the day they develop symptoms, which may contribute to the high effectiveness we found for neuraminidase inhibitors.

There have been few recent reports of differences in symptoms between influenza types/subtypes, particularly for A (H3N2) and A (H1N1)pdm09[21]. In the 2018/19 season there were no B patients, and the symptom score of A (H3N2) was significantly higher than that of A (H1N1)pdm09 (p = 0.0393, ANOVA). The score was also highest for A (H3N2) in the 2017/18 season, but without significance (p = 0.4134). These results suggest that the stronger symptoms of A(H3N2) patients commonly seen at the initial visit would be useful for discriminating A(H3N2) from the other subtypes.

The recommended dosage of almost all anti-influenza virus drugs differs by age. One previous study suggested that the dosage of oseltamivir for younger children was insufficient [22]. The effectiveness of the dosage of laninamivir used for younger children has not been reported. The recommended dosages of laninamivir are a single inhalation of 20mg for patients under 10 years of age and a single inhalation of 40mg for patients aged 10 years and over. No difference in the efficiency of laninamivir by age has been observed[10,23]. In the present study, there were no significant differences in duration of fever or symptoms for patients aged under 10 years and those 10 years and over in the latest two seasons (statistical data not shown). Although it is a limitation of this study that the number of young children, under 10 years, was too small to allow us to

adequately judge differences between the age groups, a comparable duration of fever and other symptoms was consistent through the previous six seasons. We found no significant difference between the age groups in the clinical effectiveness of laninamivir, even though there was a difference in the laninamivir dosage. To build on our results, another study including more young patients will be of much worth.

It is important to constantly monitor the effectiveness of anti-influenza virus drugs. Surveillance of resistant viruses has shown no increase [7–9], but to our knowledge, no surveillance of clinical effectiveness has been carried out on a large scale.

Although there were no significant differences of resolution of fever after the inhalation of laninamivir among seasons in our previous study, we found significant differences among seasons in this study (Fig 1, 2, and 3). The seasonal variation in the median duration of fever was significant for A(H3N2) ($p = 0.0103$, ANOVA), but not for A(H1N1) or B (Table 3). No obvious regulatory factors that might affect the median fever duration were identified, possibly because the number of variables was not sufficient and some outliers existed.

These seasonal differences may reflect changes of viral nature conferred by the accumulation of mutations. The therapeutic effect of laninamivir was confirmed to have been sustained throughout the seasons, as shown by our results for the duration of fever and other symptoms. The clinical significance of these seasonal differences in the types/subtypes are subtle and may not be recognized by most physicians, but they are important. No safety issues with laninamivir have been found (data not shown), and continuation of the broad use of laninamivir should not be problematic.

Differences in the clinical effectiveness of NAIs by virus type/subtype are of great concern in the clinical setting. The duration of fever of B patients was consistently longer than that of A patients in the studied seasons (Table 3), but the difference was not significant until the 2017/18 season. A longer duration of fever has been reported for B than for A when patients are treated with oseltamivir [24]. Our results for patients treated with laninamivir are similar to previous results for patients treated with oseltamivir. The higher IC50 of B compared to A for NAIs [7], or the virulence of B may be responsible for these results, but the exact mechanism is unknown.

No difference in the clinical effect of laninamivir for A (H3N2) or A (H1N1) pdm09 was found. The 2018/19 season was interesting because there were no patients with B; thus, we were able to compare the A subtypes without its influence. Our findings showed that the duration of fever was significantly longer for A (H3N2) than for A (H1N1)pdm09 ($p = 0.0290$, ANOVA). However, the duration of fever varies by subtype every year, so knowing which subtype in the past had longer duration of fever has little clinical impact at present. Further study is necessary, but we can say with confidence that the effectiveness of laninamivir is comparable for A (H1N1)pdm09 and A (H3N2).

The main limitation of this study is that the results obtained were observational, thus the influence of age and other factors could not be eliminated by multiple adjustments. Prospective controlled studies will be important.

In conclusion, from these results of the two most recent seasons and those of the previous six, the clinical effectiveness of laninamivir was confirmed to have continued over the eight seasons against all influenza types/subtypes, without signs of elongation of fever or other symptoms, despite its broad use in Japan.

For patients treated with laninamivir, the median duration of fever for B was longer than for A, similar to oseltamivir.

Because of the rapidly changing epidemic influenza virus strains and the possibility of the appearance of new types of influenza virus, continuous surveillance of both resistant virus emergence and the clinical effectiveness of anti-influenza drugs against the circulating viruses will continue to be important.

Author contributors

All the authors designed the study. Naoki Tani, Naoki Kawai, Hideyuki Ikematsu, Yong Chong contributed to the data extraction process and analysis. Naoki Tani wrote the first draft of article. All the authors

revised the article and approved the final version.

Conflict of interest

This investigation was sponsored by Daiichi Sankyo Co., Ltd. H. Ikematsu has received honoraria from Daiichi Sankyo Co., Ltd for medical advice.

References

1. Hayden FG, Sugaya N, Hirotsu N, et al. Baloxavir marboxil for uncomplicated influenza in adults and adolescents. N Engl J Med 2018;379:913-923.

2. O'Hanlon R, Shaw ML. Baloxavir marboxil: the new influenza drug on the market. Curr Opin Virol 2019;35:14-18.

3. Chan PA, Connell NT, Gabonay AM, et al. Oseltamivir-resistant 2009-2010 pandemic influenza A (H1N1) in an immunocompromised patient. Clin Microbiol Infect 2010;16:1576-1578.

4. Hirotsu N, Sakaguchi H, Sato C, et al. Baloxavir Marboxil in Japanese Pediatric Patients With Influenza : Safety and Clinical and Virologic Outcomes. Clin Infect Dis 2019;ciz908.

5. Kawai N, Ikematsu H, Iwaki N, Kondou K. Clinical effectiveness of oseltamivir for influenza A (H1N1) virus with H274Y neuraminidase mutation. J Infect 2009;59:207-212.

6. Kawai N, Ikematsu H, Hirotsu N, et al. Clinical Effectiveness of Oseltamivir and Zanamivir for Treatment of Influenza A Virus Subtype H1N1 with the H274Y Mutation : A Japanese , Multicenter Study of the 2007–2008 and 2008–2009 Influenza Seasons. Clin Infect Dis 2009;49:1828-1835.

7. Ikematsu H, Kawai N, Chong Y, Bando T, Iwaki N, Kashiwagi S. In vitro neuraminidase inhibitory concentration (IC50) of four neuraminidase inhibitors in the Japanese 2017–18 season: Comparison with the 2010–11 to 2016–17 seasons. J Infect Chemother 2019;25:649-652.

8. Antiviral resistance surveillance in Japan (as of April 30, 2020), https://www.niid.go.jp/niid/en/influ-resist-e.html. Accessed June 02, 2020.

9. Takashita E, Daniels RS, Fujisaki S, et al. Global update on the susceptibilities of human influenza viruses to neuraminidase inhibitors and the cap-dependent endonuclease inhibitor baloxavir, 2017–2018. Antiviral Res 2020;175:104718.

10. Sugaya N, Ohashi Y. Long-Acting Neuraminidase Inhibitor Laninamivir Octanoate (CS-8958) versus Oseltamivir as Treatment for Children with Influenza Virus Infection. Antimicrob Agents Chemother 2010;54:2575-2582.

11. Watanabe A, Chang S, Kim MJ, Chu DW, Ohashi Y. Long-Acting Neuraminidase Inhibitor Laninamivir Octanoate versus Oseltamivir for Treatment of Influenza : A Double-Blind , Randomized , Noninferiority Clinical Trial. Clin Infect Dis 2010;51:1167-1175.

12. Ikematsu H, Kawai N, Iwaki N, Kashiwagi S. Duration of fever and other symptoms after the inhalation of laninamivir octanoate hydrate in the 2016/17 Japanese influenza season; comparison with the 2011/12 to 2015/16 seasons. J Infect Chemother 2018;24:718-724.

13. Oh DY, Barr IG, Mosse JA, Laurie KL. MDCK-SIAT1 Cells Show Improved Isolation Rates for Recent Human Influenza Viruses Compared to Conventional MDCK Cells. J Clin Microbiol 2008;46:2189-2194.

14. Stockton J, Ellis JS, Saville M, Clewley JP. Multiplex PCR for typing and subtyping influenza and respiratory syncytial viruses. J Clin Microbiol 1998;36:2990-2995.

15. Nakauchi M, Takayama I, Takahashi H, et al. Real-time RT-PCR assays for discriminating influenza B virus Yamagata and Victoria lineages. J Virol Methods 2014;205:110-115.

16. Yamashita M, Tomozawa T, Kakuta M, Tokumitsu A, Nasu H, Kubo S. CS-8958, a prodrug of the new neuraminidase inhibitor R-125489, shows long-acting anti-influenza virus activity. Antimicrob Agents Chemother 2009;53:186-192.

17. Ikematsu H, Kawai N, Iwaki N, Kashiwagi S. In vitro neuraminidase inhibitory activity of four neuraminidase inhibitors against clinical isolates of influenza virus in the Japanese 2012-2013 season. J Infect Chemother 2015;21:39-42.

18. Transmission dynamics and impact of pandemic influenza A (H1N1) 2009 virus. Wkly Epidemiol Rec 2009;84:477-484.

19. Mar C Del, Doshi P, Hama R, et al. Neuraminidase inhibitors for influenza complications. Lancet 2014;384:1260-1261.

20. Ikematsu H, Kawai N, Iwaki N, Kashiwagi S. Duration of fever and other symptoms after the inhalation of laninamivir octanoate hydrate for influenza treatment ; comparison among the four Japanese influenza seasons from 2011/2012 to 2014/2015. J Infect Chemother 2016;22:605-610.

21. Caini S, Kroneman M, Wiegers T, El Guerche-Seblain C, Paget J. Clinical characteristics and severity of influenza infections by virus type, subtype, and lineage: A systematic literature review. Influenza Other Respi Viruses 2018;12:780-792.

22. Osage C, Barrett J, Hill G, et al. Pharmacokinetics and dosage recommendations for an oseltamivir oral suspension for the treatment of influenza in children. Paediatr Drugs 2001;3:229-236.

23. Ikematsu H, Kawai N, Iwaki N, Kashiwagi S. Duration of fever and other symptoms after the inhalation of laninamivir octanoate hydrate; comparison of the 2011/12 to 2015/16 Japanese influenza seasons. J Infect Chemother 2017;23:627-633.

24. Naoki Kawai, Hideyuki Ikematsu, Norio Iwaki, Tetsunari Maeda, Takashi Kawashima, Nobuo Hirotsu SK. Comparison of the Effectiveness of Zanamivir and Oseltamivir Against Influenza A/H1N1, A/H3N2, and B. Clin Infect Dis 2009;48:994-996.

Tables

Table 1: Baseline clinical characteristics.

Table 2: Duration of fever and other symptoms after laninamivir inhalation.

Table 3: Duration of fever and symptoms over eight seasons.

Figure legends

Figure 1: Percentage of A (H1N1)pdm09 patients with fever after laninamivir inhalation in the 2013/14, 2015/16, 2016/17, 2017/18 and 2018/19 seasons.

Figure 2: Percentage of A (H3N2) patients with fever after laninamivir inhalation in the 2011/12, 2012/13, 2013/14, 2014/15, 2015/16, 2016/17, 2017/18 and 2018/19 seasons.

Figure 3: Percentage of B patients with fever after laninamivir inhalation in the 2011/12, 2013/14, 2014/15, 2015/16, 2016/17 and 2017/18 seasons.

Appendices

Table S1: Factors correlated with median of fever duration over the eight seasons studied.

Figure S1: Scatter plot of IC50 and fever duration of A (H1N1)pdm09.

Figure S2: Scatter plot of IC50 and fever duration of A (H3N2).

Figure S3: Scatter plot of IC50 and fever duration of B.

Figure S4: Scatter plot of mean age and fever duration of A (H1N1)pdm09.

Figure S5: Scatter plot of mean age and fever duration of A (H3N2).

Figure S6: Scatter plot of mean age and fever duration of B.

Figure S7: Scatter plot of the prevalence of the types/subtypes and fever duration of A (H1N1)pdm09.

Figure S8: Scatter plot of the prevalence of the types/subtypes and fever duration of A (H3N2).

Figure S9: Scatter plot of the prevalence of the types/subtypes and fever duration of B.

Hosted file

`table1.xlsx` available at https://authorea.com/users/345840/articles/471936-duration-of-fever-and-other-symptoms-after-laninamivir-octanoate-hydrate-inhalation-over-eight-influenza-seasons

Hosted file

`table2.xlsx` available at https://authorea.com/users/345840/articles/471936-duration-of-fever-and-other-symptoms-after-laninamivir-octanoate-hydrate-inhalation-over-eight-influenza-seasons

Hosted file

`table3.xlsx` available at https://authorea.com/users/345840/articles/471936-duration-of-fever-and-other-symptoms-after-laninamivir-octanoate-hydrate-inhalation-over-eight-influenza-seasons

Hosted file

`fig1.xlsx` available at https://authorea.com/users/345840/articles/471936-duration-of-fever-and-other-symptoms-after-laninamivir-octanoate-hydrate-inhalation-over-eight-influenza-seasons

Hosted file

`fig2.xlsx` available at https://authorea.com/users/345840/articles/471936-duration-of-fever-and-other-symptoms-after-laninamivir-octanoate-hydrate-inhalation-over-eight-influenza-seasons

Hosted file

`fig3.xlsx` available at https://authorea.com/users/345840/articles/471936-duration-of-fever-and-other-symptoms-after-laninamivir-octanoate-hydrate-inhalation-over-eight-influenza-seasons