The novel anti-influenza virus agent baloxavir marboxil is a selective inhibitor of an influenza cap-dependent endonuclease. Although a single oral dose in tablet form of baloxavir marboxil is expected to improve drug compliance and rapidly reduce viral titers for pediatric patients with influenza, there is a concern that baloxavir marboxil-resistant influenza A variants could be generated. In this study, we investigated the frequency of prescription and pharmacy revisits for baloxavir marboxil at an outpatient clinic compared with that of neuraminidase inhibitors in pediatric patients with influenza. A total of 475 pediatric patients who were infected with the influenza virus visited the pharmacy between December 2019 and March 2020. Baloxavir marboxil (n = 149), oseltamivir (n = 161) and laninamivir (n = 162) were mainly prescribed and only a few patients were treated with peramivir (n = 2) or zanamivir (n = 1). Baloxavir marboxil-, oseltamivir- and laninamivir-treated pediatric patients were enrolled, and a log-rank test showed that the revisits of pediatric patients who were taking baloxavir marboxil was lower than those for oseltamivir (p < 0.001). Moreover, Cox proportional hazards models also revealed that baloxavir marboxil decreased the risk of revisits in comparison to oseltamivir (hazard ratio 0.28, 95% confidence interval 0.11–0.70, p = 0.006), while no difference was found between laninamivir and baloxavir marboxil. Although there is a need to acquire appropriate and relevant information concerning resistant viruses, our results suggest that baloxavir marboxil may be a useful drug for treating pediatric patients with influenza infections.

Key words  influenza; pediatric patient; pharmacy; baloxavir marboxil; neuraminidase inhibitor

INTRODUCTION

Influenza is a viral infection that presents a high fever, headaches, joint pain, myalgia and a general malaise. In Japan, type A (H1N1 or H3N2) and type B influenza usually reach epidemic levels between December and March annually. The therapeutic strategy for the treatment of influenza includes the administration of a vaccine for prevention and anti-influenza drugs for treatment in cases of actual infections. While the vaccine decreases the onset risk and severity of influenza, patients who have influenza are usually treated with various types of anti-influenza drugs. Although anti-influenza drugs are roughly classified into neuraminidase inhibitors (oseltamivir, zanamivir, laninamivir and peramivir), acidic endonuclease inhibitors (baloxavir marboxil), an M2 protein inhibitor (amantadine) and a RNA polymerase inhibitor (favipiravir), neuraminidase inhibitors and baloxavir marboxil are administrated to most influenza patients.

Neuraminidase inhibitors induce the inactivation of neuraminidase and suppress the release of progeny influenza viruses from host cells. When neuraminidase inhibitors are administrated to pediatric patients with influenza, it has been reported that the administration of oseltamivir or zanamivir resulted in a decrease in the number of times that an antipyretic analgesic was needed, shortening hospitalization time and the period of viral shedding. However, because these drugs need to be taken twice a day for 5 d, non-compliance in dosing may be a problem. Whereas the dosing form of laninamivir is a dry powdered formulation that is inhaled and the patient receives a single dose only. In this regard, the probability of success for inhalations in pediatric patients under 9 years old was reported to be 88.9% and there was a concern that the therapeutic effect was decreased depending on the degree of inhalation. Although peramivir, which is administered intravenously, is superior to other neuraminidase inhibitors in terms of its absorption, there is a tendency to hesitate to use this drug because intravenous administration is invasive for influenza-infected pediatric patients in outpatient care but not patients who are hospitalized.

Baloxavir marboxil was released in 2018 and inhibits viral replication by inhibiting the cap-dependent endonuclease within the polymerase acid (PA) protein of influenza A and B. Baloxavir marboxil is highly convenient because it involves a single oral dose in tablet form and a phase III clinical
trial (T0822) for pediatric patients with influenza indicated that their time in the hospital was reduced and that is induced early viral reduction.\(^{13}\) On the other hand, this clinical trial also reported that baloxavir marboxil-resistant influenza A variants with a PA mutation (138T/M/F) emerged in 2.2–9.7% of adults and adolescents\(^{13}\) and another study also indicated that the mutation appeared in 23.4% of pediatric patients after being medicated with baloxavir marboxil.\(^{14}\) Furthermore, patients with this mutated influenza virus caused by baloxavir marboxil showed a prolonged virus detectability and a delay in the improvement of clinical symptoms.\(^{15}\) Therefore, in 2019, The Japanese Association for Infectious Diseases and the Japan Pediatric Society issued recommendations stating that the use of baloxavir marboxil needs to be carefully considered for pediatric patients under the age of 12 years.\(^{16,17}\)

Given these circumstances, there is presently few data available regarding the utilization and usefulness of baloxavir marboxil compared with other anti-influenza drugs in pediatric clinical practice.\(^{18}\) Therefore, in this study, we conducted a pharmacist-managed clinical investigation at pharmacies to survey the frequency of prescriptions for baloxavir marboxil and neuraminidase inhibitors for pediatric patients by medical practitioners of the region between December 2019 and March 2020. Moreover, because it was possibility that revisit to the pharmacy indicated the prolongation of influenza-associated symptoms, we also aimed to compare the frequency of revisits to the pharmacy within 7d in the case of baloxavir marboxil-treated pediatric patients with that for neuraminidase inhibitors.

PATIENTS AND METHODS

Ethics Approval Our study was conducted according to the Declaration of Helsinki and the ethical guidelines for Medical and Health Research Involving Human Subjects of the Ministry of Health, Labour and Welfare of Japan. Written informed consent was obtained from patients and the parents for participation in this study. The study was approved by the institution ethics review board of Research Ethics Committee of Kagoshima Pharmaceutical Association (Approval No. 1913).

Patients Four hundred and seventy five influenza pediatric patients between the ages of 1 and 14 years who had visited the Fleur (Kagoshima, Japan), Pokapoka (Kagoshima, Japan) and Cinnamon (Kagoshima, Japan) pharmacies between December 2019 and March 2020 were recruited for the study. If they were treated with peramivir (n = 2) or zanamivir (n = 1) as anti-influenza agents, they were excluded because of the small number of cases. Finally, 472 influenza patients were analyzed.

Data Collection At the first visit to pharmacies, information concerning influenza vaccinations, the type of influenza, and the hour between the first clinical symptom and the pharmacy visit were collected by interviews with a pharmacist. Electronic drug records were reviewed to extract age, sex, the types of anti-influenza drugs and concomitant drugs which were antipyretic analgesic and antitussive expectorants including beta 2-adrenergic receptor stimulating agents. When the pediatric patients with influenza revisited the pharmacy, the time (in hours) difference between the first visit and the revisit were calculated and the prescription contents obtained at the revisit were also recorded.

Statistical Analysis This study was an observational study. Sample size was determined by considering the number of visitors to three pharmacies during the survey period. To ascertain the normal distribution of variables, the Shapiro–Wilk’s test was performed. For univariate analysis, a one-way ANOVA or the Kruskal–Wallis test was used. Additionally, for categorical variables, Fisher’s exact test or pairwise Fisher’s exact test with the Bonferroni correction was performed. Regarding the variables of vaccination and types of influenza viruses, we categorized the missing information as, “unknown” without the imputation method. Because the activity of the influenza virus in young children can persist from the onset through 7d,\(^{19}\) we defined the event (revisit) when the patients with influenza revisited the pharmacy as 7d (168h). Cumulative incidence of revisits to the pharmacy were estimated using Kaplan–Meier method, and the log-rank test was performed to compare two groups with the Bonferroni correction. To evaluate the difference between the baloxavir marboxil- and the oseltamivir- or laninamivir-treated group, we employed cox proportional hazard models with the inverse probability of treatment weighting (IPTW) and robust standard errors using a propensity score (PS) to correct for potential confounding factors that may affect the treatment assignment. For multivariable modeling, PS was estimated by a logistic model, and age, sex, vaccination, types of influenza viruses, hours between the first clinical symptom and the pharmacy visit, the use of antipyretic analgesic and antitussive expectorant were used as background factors. The statistical analyses were conducted using the R software, version 3.6.2 (The R Foundation for Statistical Computing, Vienna, Austria). Values of p < 0.05 were considered significant.

RESULTS

Patient Characteristics Patients characteristics are presented in Table 1. Because there were a few cases in which peramivir (n = 2) or zanamivir (n = 1) were administered, these groups were excluded. One hundred and forty nine baloxavir marboxil-, 161 oseltamivir-, and 162 laninamivir-treated pediatric patients were enrolled. The frequency of prescription patients between the three groups were similar. While there were significant differences in age (p < 0.001), the presence or absence of vaccination (p < 0.001), types of influenza (p = 0.001) and the use of antipyretic analgesic (p < 0.001) between the three groups were recorded. We investigated the number of pharmacy revisit in each group (Table 2). The results indicated that the number of revisits for the baloxavir marboxil group were significantly lower than that for the oseltamivir group (p < 0.001) but not for the laninamivir group (p = 0.79).

Time-to-Event Analysis We next investigated the time difference between the first visit and the revisit to the pharmacy in each group and Kaplan–Meier curves were constructed to determine the difference in the cumulative incidence of revisits to the pharmacy between the three groups (Fig. 1). The log-rank test revealed a significantly lower incidence of revisits in the baloxavir marboxil-treated group in comparison to that for the oseltamivir-treated group (p < 0.001). There was no difference between the baloxavir marboxil- and the laninamivir-treated group (p = 0.68). We employed Cox pro-
portional hazard models with IPTW using PS. The propensity score was calculated using the logistic regression model, in which age, sex, the presence of vaccination, types of influenza viruses, hours between the first clinical symptom and the pharmacy visit, the use of antipyretic analgesics and an antitussive expectorant used for covariates were used as background factors. Based on the results, we confirmed that the baloxavir marboxil-treated group based on the oseltamivir-treated group was associated with a low risk for revisit (hazard ratio (HR) 0.28, 95% confidence interval (CI) 0.11–0.70, \( p = 0.006 \) (Table 3). On the other hand, there was no difference between baloxavir marboxil- and laninamivir-treated groups (HR 0.52, 95%CI 0.24–1.13, \( p = 0.10 \) (Table 4)).

**DISCUSSION**

In this study, we investigated the frequency of obtaining prescriptions for baloxavir marboxil and neuraminidase inhibitors, and compared the number and frequency of pharmacy revisits between pediatric patients with influenza who were taking each agent. The results indicated that oseltamivir, laninamivir and baloxavir marboxil were mainly administered with approximately the same frequency to the pediatric patients included in this study. Moreover, the pharmacy revisits for the baloxavir marboxil-treated group were decreased in comparison to that of the oseltamivir-treated group in a multivariable model using PS. On the other hand, there was no difference in the number of revisits between the baloxavir marboxil- and the laninamivir-treated groups. When we checked prescription contents at the pharmacy revisit, the number of antipyretic analgesics was low in all groups (baloxavir marboxil \( n = 3 \), oseltamivir \( n = 3 \), laninamivir \( n = 6 \)). This result suggests that febrile symptoms were substantially recovered. However, antitussive expectorants were prescribed for more than half in all groups at the pharmacy revisit (baloxavir marboxil \( n = 6 \), oseltamivir \( n = 36 \), laninamivir \( n = 14 \)). The prescription frequency for the oseltamivir-treated group at the pharmacy revisit was at a particularly high rate of ninety percent (baloxavir marboxil 50, oseltamivir 90, laninamivir 70%). This result indicates that the symptoms associated with respiratory tract infections persisted longer in the patients who were using oseltamivir compared with the patients using baloxavir marboxil or laninamivir. Because the patients needed to take oseltamivir for five days in a row, they might fail to take this medication regularly for some reason, thus possibly leading to the symptoms to persist. Otherwise, the dosage form may also result in prolonged respiratory tract infections. In Japan, oseltamivir is available for pediatric patients in only two dosage forms, capsules and dry syrup. In general, pediatric patients are able to take the tablet form at the age of six.\(^{22} \) However, in reality, it has been reported that oral solutions such as a dry syrup are prescribed with a high frequency compared with the tablet form for six year old patients, and the prescription frequency was the same level at seven years of age.\(^{22} \) In addition, the result of a questionnaire survey by a Japanese pediatrician also indicated similar results.\(^{21} \) These reports suggest that pediatric patients prefer a dry syrup and oral solutions and not tablets. Actually, the dosage form of oseltamivir in our study was nearly always a dry syrup regardless of age. Because a dry syrup usually needs to be dissolve in water, there is a risk that patients could spill the solution or might not be able to take the required amount of the drug.\(^{23} \) Therefore, it is possible that the dry syrup form of oseltamivir could prolong respiratory tract infections and the clinical symptoms would be associated with a pharmacy revisit.

Finally, it was possibility that the effect of anti-influenza agents for pediatric patients depended on the administration period and dosage form. Therefore, when pediatric patients are able to take the tablet form, baloxavir marboxil may be more effective for treating influenza compared to oseltamivir. Meanwhile, there was no difference in the frequency of revisits between the baloxavir marboxil- and laninamivir-treated group. However, the effect of laninamivir also depends on the degree of inhalation.\(^{19} \) It has been reported that laninamivir, which includes lactose hydrate could cause a patient to develop a lactose hypersensitivity, resulting in an anaphylactic reaction.\(^{24} \) Therefore, the selection for baloxavir marboxil or laninamivir corresponding to the pediatric patient’s state needs to be considered.

In this regard, there is a risk that baloxavir marboxil could induce the generation of baloxavir marboxil-resistant influ-

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Table 1. The Characteristics of the Influenza Patients Examined in This Study

|                     | Baloxavir marboxil | Oseltamivir | Laninamivir | \( p \)-Value |
|---------------------|------------------|-------------|-------------|----------------|
| Age (year), median, IQR | \( n = 149 \) 10.00 (8.00, 12.00) | \( n = 161 \) 4.00 (3.00, 6.00) | \( n = 162 \) 9.00 (7.25, 11.00) | <0.001         |
| Male/female, \( n \) | 74/75              | 71/90       | 89/73       | 0.15           |
| Vaccine            |                   |             |             |                |
| Vaccination (no/yes/unknown), \( n \) | 100/43/6          | 82/56/23    | 76/55/31     | <0.001         |
| Times (0/1/2/unknown), \( n \) | 100/26/17/6       | 82/23/33/23 | 76/25/30/31  | 0.001          |
| Types (A/B/unknown), \( n \) | 149/0/0           | 157/2/2     | 153/0/9      | 0.08           |
| Time (hour) between first clinical symptom and pharmacy visit, IQR | 13.0 (4.0, 24.0) | 19.0 (4.0, 28.0) | 20.0 (6.0, 28.0) | 0.08 |
| Prescription       |                   |             |             |                |
| Antipyretic analgesic, \( n \) | 115               | 107         | 138         | <0.001         |
| Antitussive expectorant, \( n \) | 113               | 121         | 124         | 0.90           |

*IQR, interquartile range.*

Table 2. The Relation between the Number of Pharmacy Revisits and Each Anti-influenza Drug

|                     | Pharmacy revisit negative | Pharmacy revisit positive |
|---------------------|---------------------------|---------------------------|
| Baloxavir marboxil  | 137                       | 12                        |
| Oseltamivir         | 121                       | 40                        |
| Laninamivir         | 142                       | 20                        |
enza A virus in pediatric patients. However, according to a report from the National Institute of Infectious Disease, the frequency of detection of resistant strains from baloxavir marboxil between 2019 and 2020 was few (0.14%) and this frequency was lower than that for oseltamivir and peramivir. It is thought that one possible reason for this is the fact that the frequency of use of baloxavir marboxil has decreased based on recommendations of the Japan Pediatric Society and The Japanese Association for Infectious Diseases. Actually, in one of the pharmacies of our study, the frequency of use of baloxavir marboxil was decreased in comparison to that of the 2018–2019 influenza season. In addition, it is also possible that the recommendation induced the appropriate use of baloxavir marboxil, and, as a result, the appearance of resistant strains was decreased. Therefore, although the effectiveness of baloxavir marboxil could be assured, we need to pay attention to the emergence of resistant virus and the appropriate use of this medication.

Based on the above results, pharmacists in pharmacies should act as follows: when pediatric patients visit the pharmacy for some reason, pharmacists should confirm and list the dosage forms that pediatric patients are able to take.

Next, pharmacists should actively conduct patient-compliance instructions according to the dosage forms. For instance, if pharmacists judge that a pediatric patient is not able to sufficiently inhale laninamivir using the practice tool of the drug, they should suggest the use of other anti-influenza drugs such as oseltamivir or baloxavir marboxil. In another example, to reduce bitter and rough sensation of the oseltamivir dry syrup, pharmacists are advised to carefully explain the use of the jelly dedicated for taking the drug to a pediatric patient and the parents. When a pediatric patient with a high fever or vomiting experiences difficulty in taking a drug internally, pharmacists should recommend the use of peramivir to the medical doctor and the parents. Furthermore, pharmacists should regularly perform advice such as those described above, and make an effort to increase the appropriate use of anti-influenza drugs in pediatric patients. Actually, the pharmacy of the first author in our study already initiated some of these efforts.
ventive measures for dealing with influenza infection to visitors by a bulletin board presentation at the pharmacy. Moreover, they should suggest the selection of anti-influenza agents corresponding to the state of a pediatric patient based on the above information to medical doctors as necessary. Apart from that, our study revealed that the number of pediatric patients who were fully vaccinated against the influenza virus was low. Therefore, pharmacists in pharmacies should provide positive information stating that two times of vaccination will greatly reduce the risk of children contracting an influenza infection.3,4)

Our study has some limitations. First, the number of pediatric patients was limited. Second, our study evaluated the frequency of revisits to pharmacies as an indicator of the clinical efficacy of each anti-influenza drug. However, when clinical symptoms are minimal on the 7th day after the first visit, some pediatric patients may not revisit because they might assume that they will get better soon. Thus, the clinical efficacy of each anti-influenza drug and the frequency of revisits will not exactly match. Third, because we did not set up the criteria that advised pediatric patients to visit the same pharmacy at a revisit, there is a slight possibility that some cases may have visited another pharmacy. Fourth, if the information regarding clinical findings of each pediatric patient in the first pharmacy visit was used as a background factor to generate PS, we would be able to more accurately evaluate the situation at the revisit for each anti-influenza agent-treat group. However, it was difficult to acquire this information at pharmacies.

CONCLUSION

Our study suggests that baloxavir marboxil may be useful for pediatric patients in outpatient clinics. It is hoped that this result will help to promote appropriate therapy for influenza by considering various factors such as the frequency of resistant strains and societal trends (Japan Pediatric Society and The Japan Association for Infectious Diseases).

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Conflict of Interest Yu Norikoshi and Kodai Sasahara are directors of Tour de medication Co., Ltd.

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